UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2021

or

☐ TRANSITION REPORT UNDER SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____

Commission file number: **01-39834**

CLENE INC.

(Exact name of registrant as specified in its charter)

Delaware	**85-2828339**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
6550 South Millrock Drive, Suite G50 Salt Lake City, Utah	**84121**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(801) 676 9695**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value	CLNN	The Nasdaq Capital Market
Warrants, to acquire one-half of one share of Common Stock for $11.50 per share	CLNNW	The Nasdaq Capital Market

Securities registered pursuant to Section 12(g) of the Act: **None.**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
		Emerging Growth Company	☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's common stock held by non-affiliates as of June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $359.6 million, based on the closing price of the registrant's common stock on the Nasdaq Capital Market of $11.24 per share.

The number of shares outstanding of the Registrant's shares of common stock as of March 8, 2022 was 63,138,351.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement relating to its 2022 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. The definitive proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of fiscal year to which this report relates.

CLENE INC.
Annual Report on Form 10-K for the Year Ended December 31, 2021

PART I

Throughout this Annual Report on Form 10-K (the "Annual Report"), the "Company," and references to "we," "us," or similar such references should be understood to be references to Clene Inc. and its consolidated subsidiaries.

CAUTIONARY NOTE REGARDING FORWARD LOOKING STATEMENTS

Certain statements in this Annual Report may constitute "forward-looking statements" for purposes of the federal securities laws. Our forward-looking statements include, but are not limited to, statements regarding our or our management team's expectations, hopes, beliefs, intentions or strategies regarding our future operations. In addition, any statements that refer to projections, forecasts or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking statements. The words "anticipate," "believe," "contemplate," "continue," "could," "estimate," "expect," "intends," "may," "might," "plan," "possible," "potential," "predict," "project," "should," "will," "would" and similar expressions may identify forward-looking statements, but the absence of these words does not mean that a statement is not forward-looking. Forward-looking statements in this Annual Report may include, for example, statements about:

- our future financial performance;
- the clinical results of our drug candidates;
- the likelihood of commercial success for our drug candidates;
- our plans and strategies to obtain and maintain regulatory approvals of our drug candidates;
- the size and growth potential of the markets for our drug candidates, and our ability to serve those markets, either alone or in combination with others;
- changes in the market for our products;
- expansion plans and opportunities; and
- other factors detailed under the section entitled "Risk Factors."

These forward-looking statements represent our views as of the date of this Annual Report and involve a number of judgments, risks and uncertainties. We anticipate that subsequent events and developments will cause our views to change. We undertake no obligation to update forward-looking statements to reflect events or circumstances after the date they were made, whether as a result of new information, future events or otherwise, except as may be required under applicable securities laws. Accordingly, forward-looking statements should not be relied upon as representing our views as of any subsequent date.

As a result of a number of known and unknown risks and uncertainties, our actual results or performance may be materially different from those expressed or implied by these forward-looking statements. Some factors that could cause actual results to differ include:

- our substantial dependence on the successful commercialization of our drug candidates, if approved, in the future;
- our inability to maintain the listing of our common stock, $0.0001 par value ("Common Stock") on the Nasdaq Stock Market LLC ("Nasdaq");
- our significant net losses and net operating cash outflows;
- our ability to demonstrate the efficacy and safety of our drug candidates;
- the clinical results for our drug candidates, which may not support further development or marketing approval;
- actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials and marketing approval;
- our ability to achieve commercial success for our marketed products and drug candidates, if approved;
- our ability to obtain and maintain protection of intellectual property for our technology and drugs;
- our reliance on third parties to conduct drug development, manufacturing and other services;
- our limited operating history and our ability to obtain additional funding for operations and to complete the licensing or development and commercialization of our drug candidates;
- the impact of the COVID-19 pandemic on our clinical development, commercial and other operations;
- changes in applicable laws or regulations;

- the effects of inflation;
- the effects of staffing and materials shortages;
- the possibility that we may be adversely affected by other economic, business and/or competitive factors; and
- other risks and uncertainties set forth in the section entitled “Risk Factors.”

In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this Annual Report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and you are cautioned not to rely unduly upon these statements.

SUMMARY OF MATERIAL RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous material and other risks that you should be aware of before making an investment decision. These risks are discussed more fully in the section entitled “Risk Factors.” These risks include, among others, the following:

- We depend substantially on the successful commercialization of our drug candidates in the future, which may fail to materialize or may experience significant delays.
- We currently do not generate any revenue from the commercial sales of drug candidates and we may not become profitable when expected, or at all.
- We have incurred significant net losses since our inception and expect to continue to incur significant net losses for the foreseeable future.
- Our ability to continue as a going concern requires that we obtain sufficient funding to finance our operations, which may not be available on acceptable terms, or at all. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our drug development or commercialization efforts.
- We have a limited operating history, which may make it difficult to evaluate our current business and predict our future performance.
- We may encounter difficulties in managing our growth and expanding our operations successfully, which could adversely affect our business, financial condition, results of operations and prospects.
- Changes in government regulation or in practices relating to the pharmaceutical and biotechnology industries, including potential healthcare reform, could decrease the need for our drug candidates, or make it more difficult to obtain regulatory approvals for our drug candidates and commercialize them.
- If we, or any contract research organization (“CRO”) we may engage, fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business, financial conditions, results of operations and prospects.
- Our internal computer systems, or those used by any CROs or other third-party contractors or consultants we may engage, may fail or suffer security breaches.
- We manufacture all of our drug candidates ourselves, and intend to manufacture most, if not all, of any approved drugs ourselves as well, which could have a material adverse effect on our business, financial condition, results of operations and prospects.
- Delays in completing and receiving regulatory approvals for our manufacturing facilities could delay our development plans or commercialization efforts, which could harm our business.
- We may fail to get regulatory approval for our products, or such approval could be significantly delayed.
- Damage to, destruction of or interruption of production at our manufacturing facilities would negatively affect our business and prospects.
- Significant inflation could adversely affect our business, financial condition and results of operations.
- Our future success depends on our ability to retain key executives and to attract, train, retain and motivate qualified and highly skilled personnel.

Item 1. Business

Overview

We are a clinical-stage pharmaceutical company pioneering the discovery, development, and commercialization of novel clean-surfaced nanotechnology ("CSN®") therapeutics. CSN® therapeutics are comprised of atoms of transition elements that when assembled in nanocrystal form, possess unusually high, unique catalytic activities not present in those same elements in bulk form. These catalytic activities drive, support, and maintain beneficial metabolic and energetic cellular reactions within diseased, stressed, and damaged cells.

Our patent-protected, proprietary position affords us the potential to develop a broad and deep pipeline of novel CSN® therapeutics to address a range of diseases with high impact on human health. We began in 2013 by innovating an electro-crystal-chemistry drug development platform that draws from advances in nanotechnology, plasma and quantum physics, material science, and biochemistry. Our platform process results in nanocrystals with faceted surfaces that are free of the chemical surface modifications that accompany other production methods. Many traditional methods of nanoparticle synthesis involve the unavoidable deposition of potentially toxic organic residues and stabilizing surfactants on the particle surfaces. Synthesizing stable nanocrystals that are both nontoxic and highly catalytic has overcome this significant hurdle in harnessing transition metal catalytic activity for therapeutic use.

Our clean-surfaced nanocrystals exhibit catalytic activities many-fold higher than other commercially available nanoparticles, produced using various techniques, that we have comparatively evaluated. We have multiple drug candidates with potential applications in neurology, infectious disease, and oncology. Our efforts are currently focused on addressing the high unmet medical needs in two areas: first, those related to central nervous system disorders including Amyotrophic Lateral Sclerosis ("ALS"), Multiple Sclerosis ("MS"), and Parkinson's Disease ("PD"); and second, those related to COVID-19, a highly infectious viral respiratory disease with serious and sometimes fatal co-morbidities.

The Clene Approach

The Clene approach to drug development is *innovation focused* and *scientifically driven*.

- *Innovation focused*—There are a significant number of diseases with high impact on human health that have proven exceedingly challenging for traditional small-molecule or biologic drug development approaches. Our approach involves the innovation of highly catalytically-active therapeutic nanocrystals with novel mechanisms of action that result from proprietary advances in nanotechnology, plasma and quantum physics, biochemistry, and materials science. This platform affords us the ability to make new drug modalities targeting a wide range of diseases that have eluded intervention using traditional small molecule or monoclonal antibody approaches.
- *Scientifically driven*—Clear scientific rationale and sound experimental design drive our discoveries, from basic science to clinical trials. We believe we have established ourselves as an industry leader in position for the development of therapeutic catalytic nanocrystals. We have deep knowledge of the chemical properties, safety profiles, and catalytic abilities of transitional metal nanocrystals and have proven abilities to produce concentrated, stable, highly active, clean-surfaced nanocrystal suspensions using efficient, "green," scalable processes. In so doing, we are establishing new classes of nanotherapeutics with the potential to address some of the most serious diseases affecting human health.

Strategy and Leadership

Our management team is key to the successful execution of this strategic plan and fulfillment of our business model. Our exceptional team brings extensive expertise and industry experience to their roles in leading the Company skillfully and effectively. The members of the executive team have established track records in scientific innovation, early and late-stage pharmaceutical development, commercialization, marketing, and the generation and protection of intellectual property.

Our innovation of CSN® therapeutic candidates places us at the forefront of novel drug development for a host of high impact, high unmet need human diseases. As we lead the development of CSN® therapeutics, our business strategy can be encapsulated by the following:

- *First mover advantage*—We believe that our proprietary knowledge of the processes needed to manufacture clean-surfaced, highly faceted, catalytically active nanocrystals, and of the resulting toxicological and physicochemical properties associated with these nanocrystals, places us in a leadership position in the innovation and development of new candidate therapeutics for diseases that have proven to be extremely difficult to target using traditional methods.
- *Wide range of applicability*—Energy metabolism is a fundamental mechanism in all living cells, and CSN® therapeutics that improve cellular energetic production and utilization have the potential to be applied to many different disease states and cell types. An advantage of this approach is that a single drug candidate can be developed to hit multiple targets in

multiple diseased cell types, presently being investigated across multiple clinical trials with our lead asset, CNM-Au8®, a catalytically-active gold nanocrystal suspension. We continue to explore ways in which the unique mechanisms of action of CSN® therapeutics can be applied across different diseases.

- *Flexibility and tunability*—Catalytic activities are determined by the shape, faceting, size, and chemical composition of nanocrystals. Our CSN® platform has demonstrated flexibility in its ability to make, for instance, both pure gold and gold-platinum nanocrystals of consistent and reproducible shapes and sizes, in addition to making solutions of ionic zinc and silver. Because of the ease with which new single elemental and composite nanocrystals can be made of varying shapes and sizes using our proprietary techniques, we plan to continue developing a wide range of CSN® therapeutics to generate a deep pipeline of drug candidates to treat a host of different diseases.

Intellectual Property, Trade Secrets and Manufacturing

We are the sole inventors of our manufacturing processes, devices, and drugs. These inventions are protected by a comprehensive intellectual property portfolio of over 150 patents issued worldwide, with approximately 20 additional patents pending. See "—Intellectual Property" for more details. The patents relate to (1) the devices that manufacture our CSN® therapeutic drug candidates, (2) the processes involved in the use of these devices, (3) the drug candidates manufactured in these devices, and (4) methods of use for the drug candidates. In addition to filings for United States ("U.S.") and foreign patents, we will continue to protect and maintain our proprietary position by the use of trademarks, trade secrets, copyright protection, and continued technological innovation. For example, years of intensive research and development were invested in fine-tuning our production and delivery processes to the point where we expect to be able to consistently, reliably, and affordably produce our drug candidates, including CNM-Au8®, to meet large scale needs. We believe that any attempts to reverse engineer or otherwise replicate our discoveries would be extraordinarily challenging for potential competitors without violating our intellectual property protections.

We are also focused on building out a robust and relevant trade secret portfolio. Our trade secret portfolio largely relates to the liquid handling and processing of our water-based products from start to finish. In the case of our lead asset, CNM-Au8®, highly purified water containing at least one processing enhancer enters the production device where it is exposed to a plasma-conditioning step. The exact nature of the plasma conditioning affects additional constituents that can become part of the flowing water thus affecting the subsequent crystal growth processes. Likewise, many details of the electrode design, configuration and operation also affect the electrochemical crystal growth processes that occur at each electrode set. Similarly, many design and operational aspects of each trough device directly affect the electrochemical crystal growth processes that occur at each electrode set. Finally, various aspects of liquid handling subsequent to crystal growth, such as concentration and filling, are critical so as not to introduce any contaminants into the liquid, which could alter the surfaces of the nanocrystals, thus adding toxicity and/or adversely affecting efficacy of the biological catalysis processes. We continue to explore additional ways to expand our trade secret portfolio in various aspects of the design, production, control and manufacture of our products.

Our manufacturing facility meets rigorous international Good Manufacturing Processes ("GMP") standards in producing our CSN® therapeutics. Furthermore, we are currently engaged in increasing our manufacturing facility space in order to meet expected commercial demand should one of our drug candidates be approved for commercial sale. We have the expertise to expand and scale up production as we continue to meet anticipated future demand for our products.

Products

Our CSN® therapeutic candidates aim to address high unmet medical needs in several disease areas including:

(1) disease modification of **central nervous system disorders**, including ALS, MS, and PD;

(2) the treatment of **infectious diseases**, including COVID-19;

(3) accelerated **wound healing and scar formation**; and

(4) the treatment of **selected cancer types**.

In addition to the development of catalytically-active, faceted, clean-surfaced nanocrystals, our electro-crystal-chemistry platform can produce ionic solutions of various transition elements including silver, zinc, and others—elements which have proven historical utility in the treatment of disease.

- **CNM-Au8®**, our lead asset, is a highly concentrated aqueous suspension of catalytically-active, clean-surfaced, faceted gold nanocrystals. CNM-Au8®'s catalytic mechanisms target the energetic deficits, oxidative stress, and accumulation of misfolded proteins that are common to many neurodegenerative diseases. CNM-Au8® is hypothesized to act as a neuroprotective and remyelinating therapy in neurodegenerative disease states in order to: (1) drive, support, and maintain beneficial metabolic and energetic cellular reactions within diseased, stressed, and/or damaged cells, (2) directly catalyze

the reduction of harmful, reactive oxygen species ("ROS"), and (3) promote protein homeostasis via activation of the heat shock factor-1 pathway, recognized to dampen the cytotoxicity caused by misfolded and denatured proteins, which are known to occur ubiquitously in neurodegenerative diseases. We believe that CNM-Au8® is the only drug candidate in development with these unique catalytic mechanisms of action using nanocrystals. Nonclinical toxicology studies have demonstrated no adverse effect levels ("NOAELs") even up to maximum feasible dosing levels for oral administration. *In vitro* and *in vivo* pharmacology studies have demonstrated that CNM-Au8® treatment enhances remyelination and neuroprotection in numerous models of MS, PD, and ALS. A Phase 1 First-In-Human study did not reveal safety or tolerability concerns for CNM-Au8® in healthy human volunteers dosed in accordance with the study protocol. A Phase 2 study in ALS suggested efficacy signals without any significant safety findings. Phase 2 brain imaging studies in MS and PD demonstrated target engagement with CNM-Au8® treatment impacting brain energy metabolites. Our ongoing and completed clinical trials and Expanded Access Programs ("EAPs") are discussed in detail below.

- **CNM-ZnAg** is a broad-spectrum antiviral, antibacterial agent comprised of zinc (Zn^{2+}) and silver (Ag^{+}) ions under development to treat infectious disease, such as COVID-19, and to provide immune support for symptom resolution. Zn^{2+} and Ag^{+} ions are produced in aqueous solutions using our electrochemistry manufacturing platform; combining Zn^{2+} and Ag^{+} ions made in this manner leads to enhanced bioavailability of the ions and potentially, synergistic immune system effects. We have one clinical trial presently underway which commenced in February 2021 in Brazil, to determine CNM-ZnAg efficacy for the treatment of symptomatic subjects with COVID-19 to prevent hospitalization and improve time to symptom resolution.
- **CNM-AgZn17** is a gel polymer suspension of Zn^{2+} and Ag^{+} under development for treatment of infectious diseases and to support wound healing. We have demonstrated in *in vitro* assays that CNM-AgZn17 has broad-based anti-viral and anti-bacterial activity against common and antibiotic resistant pathogens such as Methicillin-resistant *Staphylococcus aureus*. We have also shown enhanced wound healing benefits in animal models of diabetic wound healing and decreased scar formation following burns. We anticipate filing an Investigational New Drug ("IND") application with the U.S. Food and Drug Administration ("FDA") and subsequently plan to initiate a Phase 1 dermal First-In-Human safety study with CNM-AgZn17 in 2023.
- **CNM-PtAu7** is a gold-platinum combination nanocrystal with the potential to be an effective treatment for oncology indications. We have demonstrated *in vitro* up-regulation of pro-apoptotic and down-regulation of anti-apoptotic genes in the human breast cancer cell lines EFM-19 and MT-3 using CNM-PtAu7. We have further demonstrated down-regulation of genes associated with the electron transport chain activity which may relate to changes in tumorigenesis activity. We anticipate initiating standard animal toxicology programs in 2023 with an IND filing planned in 2024, subject to evaluation of the safety and efficacy learnings from the preclinical oncology assays and toxicology findings.

Supplements

Our patented electrochemistry manufacturing platform further enables us to develop very low concentration dietary supplements to advance the health and well-being of broad populations. These dietary supplements can vary greatly and include nanocrystals of varying composition, shapes and sizes as well as ionic solutions with diverse metallic constituents.

Dietary supplements are marketed and distributed through our wholly owned subsidiary, dOrbital, Inc. ("dOrbital"), or through an exclusive license with 4Life Research LLC ("4Life"), a stockholder and related party. These include:

- **rMetx™** (ZnAg Immune Boost) by dOrbital; rMetx™ is an aqueous zinc-silver ion dietary (mineral) supplement made using our electrochemistry manufacturing platform with bioactive immune-supporting properties. rMetx™ is sold through dOrbital, and a substantially similar product under the tradename, Zinc Factor™, is sold by 4Life, an international supplier of health supplements and a related party, under a supply agreement.
- **KHC46** (Gold Factor™) by 4Life: KHC46 is an aqueous gold dietary (mineral) supplement of very low-concentration Au nanoparticles produced using our electrochemistry manufacturing platform. KHC46 has different production methods and uses different devices resulting in different physiochemical properties from our lead drug candidate, CNM-Au8®. KHC46 is licensed exclusively to 4Life for worldwide marketing and distribution.

Clinical Development Pipeline

CNM-Au8®: We have one Phase 2/3 registrational clinical trial, the Healey ALS Platform Trial, which is currently ongoing to establish the safety and efficacy of CNM-Au8® in patients with ALS. We completed RESCUE-ALS, a Phase 2 proof of concept clinical trial to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8® in patients with early symptomatic ALS. We also completed REPAIR-PD and the first dosing cohort of REPAIR-MS, two open-label, investigator blinded Phase 2 clinical trials which demonstrated target engagement of CNM-Au8® on the brain's energy metabolites. REPAIR-MS will continue with the initiation

of a second dosing cohort. In addition, we have a Phase 2 clinical trial, VISIONARY-MS, for the treatment of visual pathway deficits in chronic optic neuropathy to assess the efficacy, safety, tolerability, and pharmacokinetics of CNM-Au8® for remyelination in stable relapsing MS. We support two EAPs for patients with ALS. The initial EAP was launched in partnership with the Sean M. Healey & AMG Center ("Healey Center") for ALS at Massachusetts General Hospital in September 2019, which is closed to new enrollment, but remains ongoing for current participants. A second EAP was implemented in conjunction with the Healey ALS Platform Trial at three participating clinical sites. Finally, we anticipate launching RESCUE-PD, a Phase 2 clinical trial for the treatment of patients with PD, in mid-2022.

CNM-ZnAg: We have one Phase 2 clinical trial presently underway to establish the efficacy and safety of ZnAg liquid solution for the treatment of COVID-19.

The chart below reflects the respective stages of our main drug candidates.

Our CSN® Therapeutics Platform

We have developed a new pharmaceutical technology, CSN® therapeutics. By uniting concepts from electrochemistry, nanotechnology, plasma and quantum physics, material science, and biochemistry, we have created and refined a proprietary electrocrystallization method that results in a single component or multiple components in nanocrystals of the transition elements that are clean-surfaced, highly faceted, and biologically catalytically active. These nanocrystals can be concentrated as aqueous suspensions and orally administered. We are further able to produce ionic solutions of various transitions elements utilizing our electrochemistry manufacturing platform. Once in the gastrointestinal system, nanocrystals pass into the blood stream, and accumulate in organs such as the liver, kidneys, and spleen, with lower amounts crossing the blood brain barrier and reaching the brain, spinal cord, and cerebrospinal fluid. Nanocrystals can remain active within the body for days before they are eliminated via the hepatobiliary-fecal system as well as via the urinary system.

Once inside the body, CSN® therapeutics cross cellular membranes and enter cells where they directly donate and receive electrons within biological systems. In this way, each nanocrystal acts as a potent catalyst which can drive, support, and maintain beneficial metabolic and energetic cellular reactions within diseased, stressed, and damaged cells. We believe these catalytic, nanocrystal-based therapeutic drugs represent an entirely new approach to drug development, substantially differing from the standard paradigm of small-molecule drugs and large-molecule biologics. Unlike traditional pharmacological approaches, which are limited to single targets or specific signaling pathways, our technology platform has produced metallic nanocrystals that are beneficial through multi-modal activities in multiple cell types across multiple diseases. By utilizing cellular catalysts to support energetic reactions within cells, we believe this technology represents a revolutionary advance in the treatment of the underlying pathophysiology of neurodegeneration and related diseases associated with energetic failure.

Figure 1 below shows examples of the kinds of nanocrystals that can be produced using our CSN® therapeutic platform.

Figure 1. Representative CSN® Therapeutic Nanocrystals

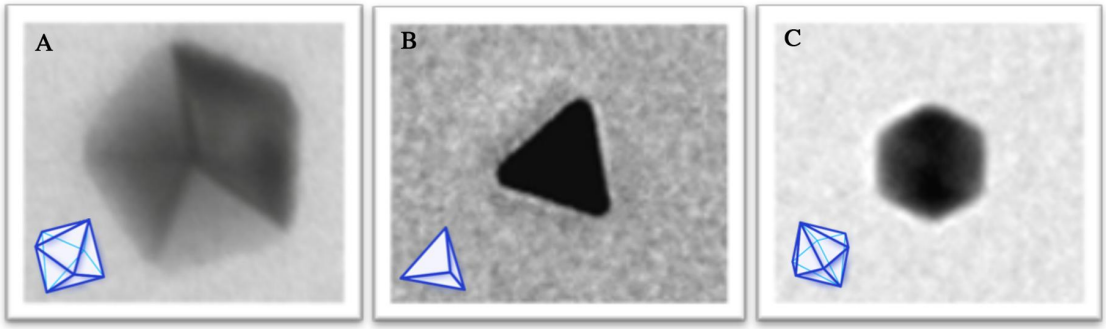


Figure 1. Representative transmission electron micrographs of the commonly observed crystalline shapes of gold nanocrystals (CNM-Au8®) resulting from our CSN® therapeutic platform. Insets are wireframes illustrating each classic shape: A, pentagonal bipyramid; B, tetrahedron; and C, hexagonal bipyramid. These nanocrystals are 10-13 nm in diameter.

Catalytically-Active Nanocrystals

A catalyst lowers the activation energy of a chemical reaction in such a way as to accelerate the rate of the reaction, without being consumed in the reaction. In doing so, it does not change the equilibrium of the substrates and products, and it can catalyze both forward and reverse reactions until homeostasis, or a balance of substrates and products, has been achieved.

Several industrial uses of metal nanocrystals have been discovered, but to our knowledge, we believe we are the only company currently developing catalytically-active nanocrystals to directly modulate biological systems as therapeutic drug candidates. Prior to our invention of the CSN® therapeutic platform, the methods employed to make stable nanoparticles required the use of organic solvents or capping agents, which would contaminate the surfaces of the nanoparticles and were substantially difficult to remove. There are multiple conflicting reports in the literature regarding the toxicity of these nanoparticles, ranging from reportedly non-toxic to highly toxic to living organisms. We believe this lack of consistency may have been due to the varying degrees to which different nanoparticle preparations were contaminated with organic reagents, leading to observed toxic effects. Because our electrocrystal chemistry method does not involve the use of any organic solvents or reduction chemicals, we have observed that our nanocrystals possess substantially higher catalytic activity in living organisms than those reported for nanoparticles made using other methods. All of the toxicology studies completed with our lead asset, CNM-Au8®, have resulted in NOAEL findings.

Transition metal nanocrystals are surface catalysts. Unlike enzymes, which are protein catalysts that lower activation energies using active site binding pockets, metal nanocrystals carry out their catalytic activities on their surfaces, where they act as exceptionally efficient electron donors and receivers. For this reason, unmodified, clean surfaces that are free of contaminating chemicals are extremely important for catalytic activity. The facets and vertices of the nanocrystals serve as the surface areas where electron exchange can take place. Metal nanocrystals have been shown to have a variety of different catalytic activities, including superoxide dismutase, peroxidase, and catalase-like activities for reducing ROS, to reactions involving the oxidation of glucose, ascorbic acid, or the energetic metabolite, nicotinamide adenine dinucleotide (“NAD”). Figure 2 is an illustration of catalysis, showing a single gold nanocrystal converting molecules of nicotinamide adenine dinucleotide hydride (“NADH”) in the background into NAD in the foreground. Gold nanocrystals have been described as electron reservoirs because their surfaces can readily accept as well as donate thousands of electrons per second in order to catalyze biochemical reactions, allowing them to accelerate reaction rates to extraordinarily high levels. For example, the conversion of NADH to NAD is usually very slow at room temperature. Upon addition of our gold nanocrystal suspension CNM-Au8®, we have observed the very rapid conversion of NADH into NAD. Importantly, the NAD reaction drives adenosine triphosphate (“ATP”) production in both the mitochondrion as well as in the cytoplasm, via a reaction called glycolysis. ATP is the universal currency of energy in all living things; without the ability to convert NADH to NAD and vice versa, cells would be quickly depleted of ATP energy stores and die. CSN® therapeutics capture the natural, extraordinary catalytic activities of faceted, clean-surfaced nanocrystals to produce metabolites of high energetic or protective value to the cell.

Figure 2. Catalytically-Active Nanocrystal Mechanism Representation

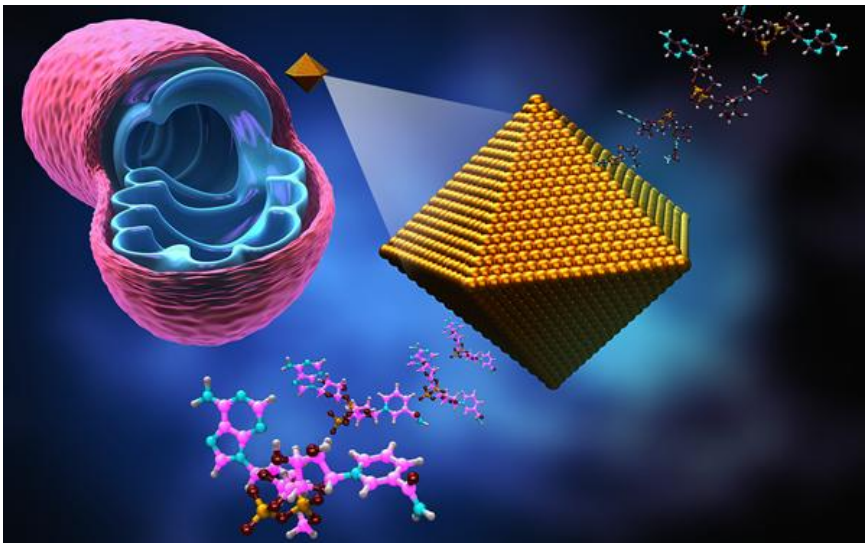


Figure 2. Illustration of catalytic activity (Not to scale). A pentagonal bipyramidal gold nanocrystal is shown with its electron cloud to represent the ability of the nanocrystal to rapidly exchange electrons with substrates interacting with its surface. In the background, NADH molecules drawn as dark chemical ball-and-stick figures are catalytically converted into NAD in the foreground as bright pink ball-and-stick figures. A pink and blue mitochondrion on the left can use available NAD for the generation of ATP (Illustrated by Ella Maru).

Our Focus on Central Nervous System Disorders

Over the past several decades, traditional small molecule and biologic drug development approaches have suffered serious setbacks in the attempts to address nervous system disorders. A likely contributor to these setbacks is the multifactorial mechanisms underlying these diseases themselves, which are sufficiently complex they may not be amenable to “one drug-one target” disease modification. In the face of these failures, we believe our new paradigm of nanocrystal drug development, producing novel drugs with unique catalytic, multi-modal mechanisms of action, is advantageous.

Multiple lines of evidence now point to energetic failure as a key contributor to neurodegenerative disease. Neurons, and their associated support cells, in particular oligodendrocytes (“OLs”), are amongst the highest energy-consuming cells in the body: the brain represents only two percent of human body weight, yet it consumes over twenty-percent of the body’s metabolic energy. As humans age, our cell’s ability to convert food into energy in the form of ATP becomes less efficient. Eventually, the nervous system’s demand for ATP surpasses the cells’ ability to supply it, and as a consequence, neurons begin to fail and subsequently die. Genetic and environmental factors determine which neuronal types are most susceptible to energetic failure in any individual. In PD, dopaminergic and other neuronal cell types manifest mitochondrial failure, leading to impaired energy production. In ALS, mitochondrial dysfunction is considered a hallmark of both sporadic and familial ALS, and several genetic causal variants of ALS have been linked to dysregulated neuronal energy metabolism. In MS, the cells capable of remyelinating damaged axons have been shown to be under metabolic stress, rendering them incapable of undergoing the energetically demanding process of repairing damaged myelin.

Preclinical work has shown that CNM-Au8® nanocrystals cross the blood brain barrier to potentially protect multiple central nervous system cell types. In multiple preclinical studies, we have demonstrated these central nervous system cells may benefit from catalytically-active nanocrystals in several ways: OLs receive an energetic boost sufficient to drive myelin production; dopaminergic, hippocampal, and cortical neurons improve energy production and utilization sufficient to enhance survival and maintain function in response to multiple disease-relevant stressors. Human astrocytes derived from patients with ALS have the capacity to kill motor neurons when grown in a co-culture, and these motor neurons exhibit markedly reduced toxicity when co-cultures are treated with CNM-Au8®. By their very nature, faceted, clean-surfaced nanocrystals with catalytic capabilities circumvent many of the challenges that have plagued the central nervous system pharmaceutical drug development field in the past. Importantly, the catalytic mechanism by which they act produces several useful energetic metabolites while reducing the presence of harmful ones. These mechanisms are well suited to address the complex failures that occur in neurodegenerative diseases on multiple levels and within multiple central nervous system cell types.

The innovation of CSN® therapeutics is that we believe we are positioned to address the most significant challenge posed by numerous central nervous system diseases. Unlike the "one drug—one target" model, faceted clean-surfaced nanocrystals act by multiple mechanisms to enhance the cellular energetic state, while simultaneously and independently reducing oxidative stress and stimulating protein homeostasis inside central nervous system cells. Each nanocrystal is capable of exchanging thousands of electrons per second, potentially addressing deficits in diseased central nervous system cells in a manner that does not further deplete the cells of their internal energy stores. We believe our data demonstrates that CSN® therapeutics thereby supports cells and replenishes cellular energetic deficiencies. In other words, our studies show that CSN® therapeutics supports the cells of the central nervous system with the basic building blocks of energy they require to function normally.

Market Potential of CSN® Therapeutics for Neurodegenerative Diseases

Despite the urgent demand for treatments and the tremendous market opportunities for neurodegenerative disease therapeutics, effective treatments are limited. The current FDA-approved therapeutic agents for ALS have very limited disease-modifying effects. We estimate that global ALS sales will be greater than $1 billion by 2029. Additionally, there were approximately 2.2 million MS patients globally as of 2016, and we estimate the market size to be approximately $23 billion. Currently, there are no existing therapies that either promote remyelination or have been demonstrated to improve function in people with non-active, progressive MS. People with non-active, progressive MS account for approximately one-third of all MS cases and they suffer progressive loss of function, severely reduced quality of life and shortened life spans. Finally, there are no currently available disease-modifying therapies for PD. All of the existing PD therapies are limited to symptomatic improvement and none have been shown to prevent or slow the loss of dopaminergic neurons. There were approximately 6.1 million PD patients globally as of 2016, and we estimate the market will be approximately $6 billion by 2026. If the clinical trials presently underway provide evidence of remyelination or demonstrate improved neurological function, CSN® therapeutics will have significant commercial sales potential in treating ALS, MS, or PD.

Not a single approved MS drug worldwide has been shown to have an effect on remyelination and neuroprotection. CNM-Au8®'s mechanism of action targeting remyelination and neuroprotection for central nervous system disorders, together with the urgent market demand for safe and effective treatments, provides us with what we believe is a first-mover-advantage with significant market potential for the treatment of central nervous system diseases. Our most advanced CSN® therapeutic candidate, CNM-Au8®, has been developed to address the significant unmet medical needs in the treatment of the central nervous system disorders, ALS, MS, and PD. ALS, MS, and PD each severely impact healthspan and lifespan of those who suffer from these disorders, resulting in significant demand for disease-modifying treatments.

CNM-Au8® and Restoration of Energetic Metabolism in ALS, MS, and PD

Overview

CNM-Au8® is a concentrated, orally-delivered suspension of pure gold nanocrystals in pharmaceutical grade water buffered with sodium bicarbonate. A single 60 milliliter dose at 30 milligrams contains over one hundred trillion nanocrystals. The median feret diameter of CNM-Au8® nanocrystals is approximately 13 nanometers with each nanocrystal consisting, on average, of an estimated 70,000 gold atoms. CNM-Au8®'s catalytic mechanism, directly donating and/or receiving electrons, enhances cellular energetic reaction rates without requiring associated energetic investment from cells, thus increasing cells' net energetic capacity. CNM-Au8® treatment results in improved energetic metabolism within cells of the central nervous system. Through this mechanism, CNM-Au8® may protect multiple neuronal and glial populations including OLs and/or neurons from oxidative, inflammatory, hypoxic, and excitotoxic insults, potentially resulting in enhanced myelination and improved neuronal survival while preserving neurite processes and synapse integrity.

Standard ICH M3(R2) toxicology studies were conducted on CNM-Au8® in four animal species, which yielded no toxicity findings resulting in NOAEL findings up to maximum feasible dosing. A First-in-Humans Phase 1 Clinical Trial of orally administered single and multiple ascending doses of CNM-Au8® was then carried out in 86 healthy human volunteers. All doses (up to 90 mg/day) of CNM-Au8® were well-tolerated. Safety was investigated as part of the Phase 2 RESCUE-ALS trial with no significant adverse findings. Treatment emergent adverse events were predominantly rated as mild to moderate severity and transient. No serious adverse events ("SAEs") were assessed as related to active drug treatment.

CNM-Au8® has received regulatory approval to proceed to Phase 2 clinical trials designed to assess the safety and efficacy of CNM-Au8® for brain metabolite target engagement and functional and physiologic improvements indicative of remyelination and neuroprotection. Details for each clinical trial of CNM-Au8® are given below in the "Clinical Development Plan of CNM-Au8® as a Disease-Modifying Drug" section for each indication.

Mechanism of Action

CNM-Au8® acts through catalysis to improve energetics, reduce harmful ROS, and induce protein homeostasis, via the heat shock protein-1 pathway in nervous system cells. These unique mechanisms of action lead to a cascade of beneficial effects as summarized in Figure 3.

Figure 3. Catalytic Biological Mechanism of Action

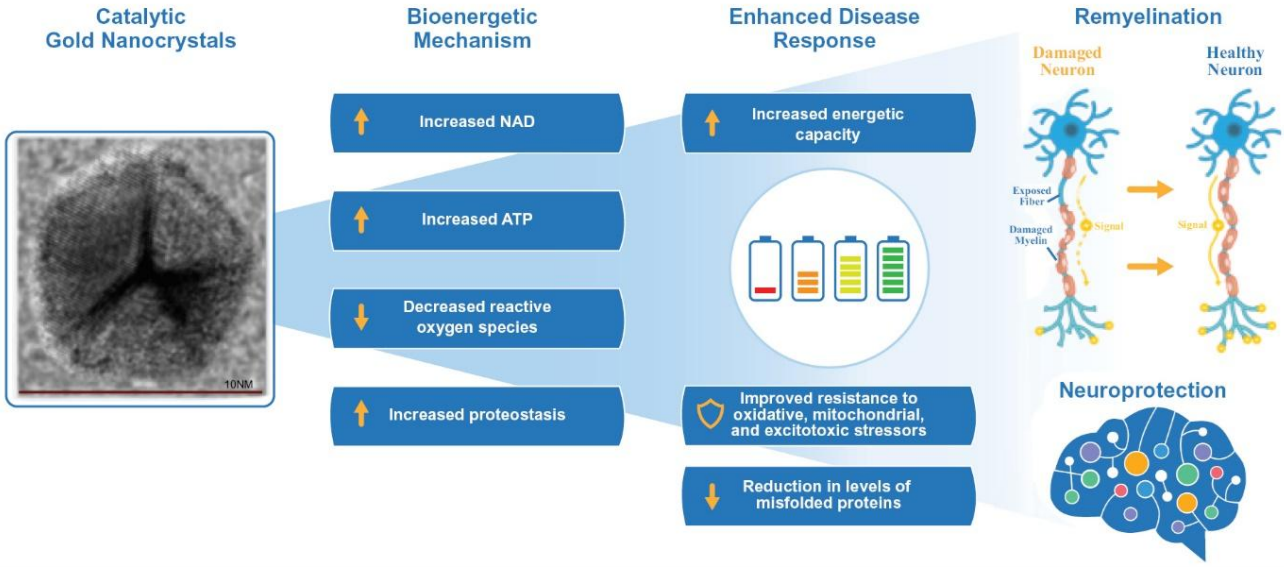


Figure 3. CNM-Au8® mediated catalysis enhances cellular energetic capacity and decreases oxidative stress, resulting in increased NAD and ATP production as well as increased proteostatic activity via the heat shock factor 1 pathway. Together, these activities lead to a cascade of enhanced disease responses in neurons, OLs, and astrocytes, cell types that are most vulnerable to energetic deficiencies. CNM-Au8® thereby mediates remyelination and neuroprotective effects in neurodegenerative diseases such as ALS, MS, and PD.

One of the key metabolites catalyzed by CNM-Au8® is the oxidized form of nicotinamide adenine dinucleotide ("NAD^+") (Fig. 4). NAD^+ and its reduced partner NADH are vital for driving cellular energy ATP-generating reactions in living cells (Fig. 4A). Brain imaging studies have shown the ratio of NAD^+ to NADH typically decreases with aging. Lowered NAD^+ levels in both the blood and brain have been associated with neurological diseases such as schizophrenia, MS, PD, and Huntington's disease. Boosting NAD^+ activity in neurodegenerative disease preclinical models has consistently demonstrated beneficial anti-aging and neuroprotective effects. CNM-Au8® exhibits higher catalytic activity for directly oxidizing NADH into NAD than any other commercially available gold nanoparticle we have tested (Fig. 4C, D). We have shown that treating cultured nervous system cells with CNM-Au8® increases their cellular pools of NAD^+ and ATP, demonstrating that CNM-Au8® increases the energetic capacity of central nervous system cells (Fig. 4E, F). This optimization of ATP (Fig. 4F) allows OLs to increase myelin production, as well as help numerous other types of central nervous system cells resist environmental and disease-related stressors that would otherwise cause them to die.

The statistical analyses shown in Figure 4 were conducted by one-way analysis of variance ("ANOVA") to compare means of each treatment group to mean of the vehicle control (corrected for multiple comparisons). The p-value (Fig. 4E, F) represents the probability of obtaining test results at least as extreme as the results observed in the assay, under the general assumption that there is no difference between the groups (the null hypothesis). The lower (smaller) the p-value, the greater the statistical significance of the observation, and the less likely the null hypothesis is true. The scientific community and regulatory authorities, such as the FDA, conventionally regard p-values of 0.05 or less to be significant when replicated in independent clinical trials. Consistently statistically significant preclinical results, such as those described here, are used to support investigative New Drug Applications ("NDAs") to investigate the clinical effects of an investigational product.

One significant stressor shared by many neurodegenerative diseases is the accumulation of harmful ROS within neurons as their energetic demands begin to exceed their ability to produce enough ATP to carry out normal functions. Chronic oxidative stress, caused by accumulation of ROS, can overwhelm the mitochondrial systems that normally tightly regulate ROS levels. Accumulation of excess ROS damages cell membranes, allows calcium ion imbalances, and eventually leads to cell death.

Figure 4. NAD Oxidation and Biological Effects on ATP and NAD⁺

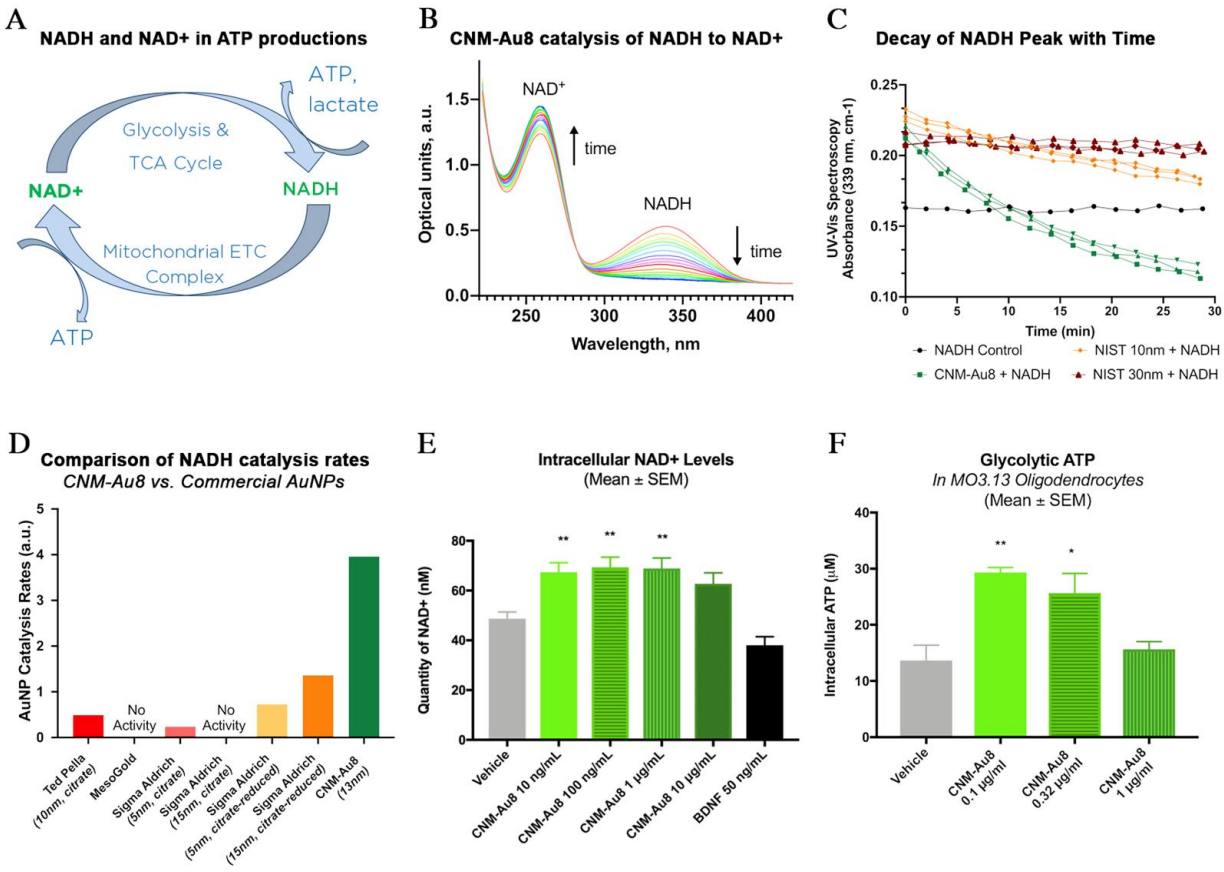


*Figure 4. Energetic catalysis by CNM-Au8®. A, The NAD-NADH reduction-oxidation couple plays a key role in both ATP-generating reactions, glycolysis and mitochondrial electron transport chain oxidative phosphorylation. B, Ultraviolet-visible light spectroscopy was used to show the catalytic activity of CNM-Au8® with time. As the reaction progresses, NADH is consumed, as demonstrated by the decrease in the NADH absorbance peak at 340 nm, while NAD⁺ is generated, as shown by the corresponding increase in the NAD⁺ absorbance peak at 260 nm. C, the rate of decay of the NADH absorbance peak is greater for CNM-Au8® than it is for citrate-reduced gold, nanoparticles of 10 nm (orange) and 30 nm (red) diameters (purchased from the National Institute of Standards and Technology), indicating that CNM-Au8® has a catalytic rate at least three-fold higher than National Institute of Standards and Technology comparators under the same reaction conditions. D, Catalytic rate of CNM-Au8® is demonstrably superior to several commercially available gold nanoparticles. Sigma Aldrich provides reactant-free, "citrate reduced" gold nanoparticles, in which extra procedures are used to clean the surfaces of reactants. "Citrate" gold nanoparticles may still have residual reactants present in the suspensions. E, Cellular NAD⁺ levels increase in response to CNM-Au8® treatment in primary rodent neuron-glial co-cultures. F, Cellular ATP levels increase in primary rodent OL cultures in response to CNM-Au8® treatment. Panels E-F, quantities shown are group means +/− SEM. One-way ANOVA, corrected for multiple comparisons, was used to compare the mean of each treatment group to the mean of the vehicle control; a statistically significant difference between treatment and vehicle is denoted by asterisks: *p < 0.05; **p < 0.01.*

In addition to boosting NAD⁺ levels inside nervous system cells, CNM-Au8® directly acts to reduce ROS by directly catalyzing their reduction (Fig. 5). CNM-Au8® possesses anti-oxidative catalytic activity and has been demonstrated to directly reduce oxygen radicals in a superoxide dismutase-like manner, as well as convert hydrogen peroxide ("H_2O_2") into water and oxygen in a catalase-like manner (Fig. 5A, B). Anti-oxidative activity for CNM-Au8® has been demonstrated in primary mouse OL cultures, in which basal levels of ROS were reduced with treatment (Fig. 5C). In a PD *in vitro* model, ROS generated by treating primary rodent dopaminergic cells with the neurotoxin 1-methyl-4-phenylpyridinium ("MPP") was lowered in response to CNM-Au8® treatment in the presence of MPP (Fig. 5D). The statistical analyses shown in Figure 5 were conducted by one-way ANOVA to compare means of each treatment group to the mean of the vehicle control (corrected for multiple comparisons). The p-value (Fig. 5C, D) represents the probability of obtaining

test results at least as extreme as the results observed in the assay, under the general assumption that there is no difference between the groups (the null hypothesis).

Previous drug development efforts for neurodegenerative diseases have included numerous antioxidants, all of which failed to show disease-modifying effects. We believe CNM-Au8® remains in a different class from standard antioxidants because, to our knowledge, no other antioxidant demonstrates catalytic ability to increase energetic metabolites NAD^+ and ATP, while independently catalytically decreasing ROS.

Figure 5. Reduction of Reactive Oxygen Species

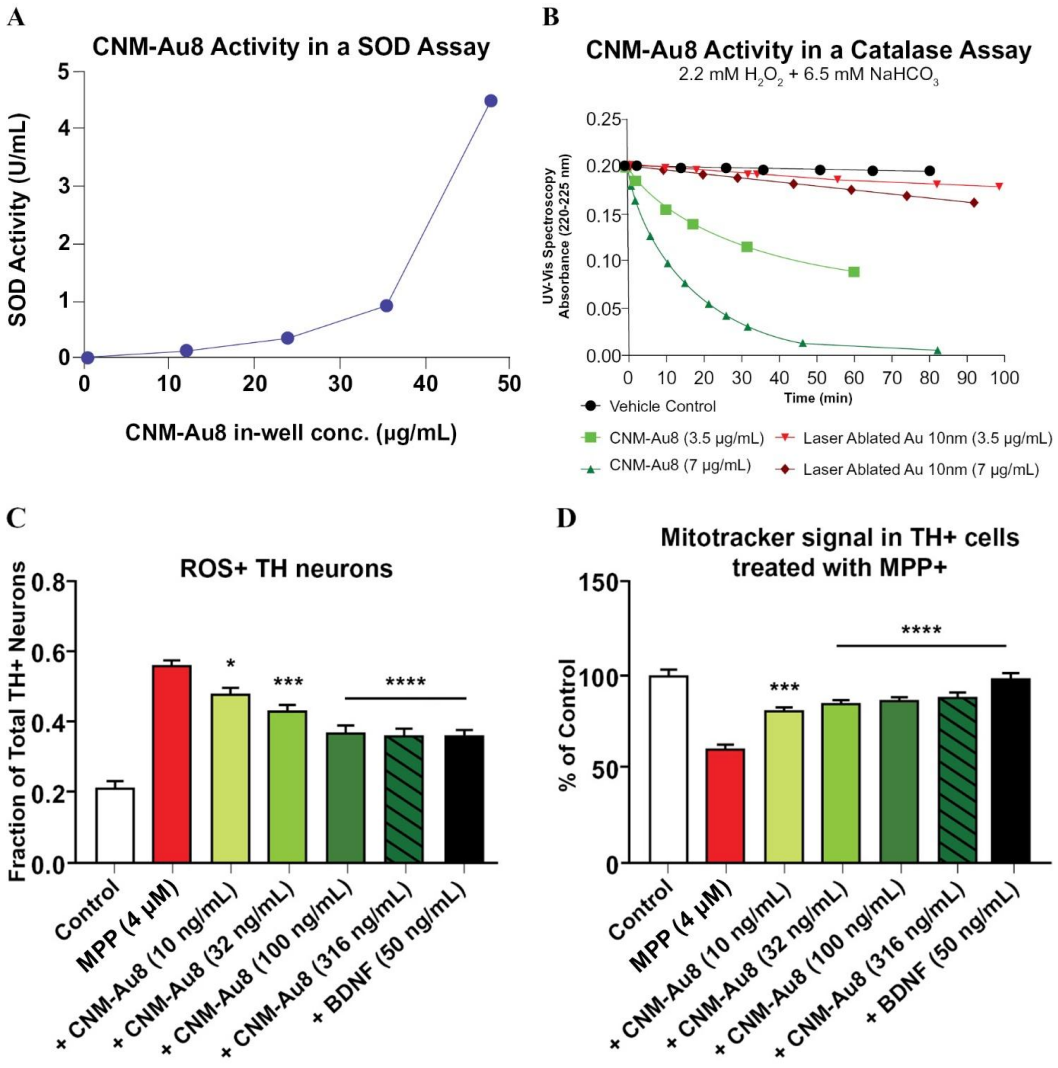


Figure 5. CNM-Au8® is a catalytically active antioxidant. A, SOD-like activity of CNM-Au8® on superoxide radicals was measured using a colorimetric SOD assay kit (Cayman Chemical). B, Decay of the absorbance peak of H_2O_2 as the dismutation of H_2O_2 takes place in the presence of CNM-Au8® (green) or comparator AuNPs of similar diameter (red) or no gold (black). C,D, Neurotoxin (MPP^+) induced mitochondrial stress and death of dopaminergic neurons in primary E15 rat co-cultures is prevented by CNM-Au8® (green), as determined by TH^+ cell number (not shown), reduction of ROS as measured as by the fraction of dopaminergic ("TH") cells fluorescing with CELLROX Green signal, a marker of cytosolic oxidizing environment (C), and increased mitochondrial membrane potential (Mitotracker Red CMXRos) (D). Panels C-D, quantities shown are group means +/− SEM. One-way ANOVA, corrected for multiple comparisons was used to compare the mean of each treatment group of MPP with CNM-Au8® treatment to the mean of the MPP (4µM) alone treatment group; a statistically significant difference between each CNM-Au8® treatment group and MPP alone is

*denoted by asterisks: *p < 0.05; **p < 0.01, ***p < 0.001; ****p < 0.000. Untreated "Control" group is included to demonstrate the significant effect of MPP treatment to increase levels of ROS in TH neurons in Panel C and reduce mitochondrial membrane potential in Panel D, which was not included in the ANOVA analysis.*

Previous drug development efforts in the neurodegenerative disease space have targeted misfolded protein aggregates as toxic drivers of disease; for example, alpha-synuclein in PD, amyloid beta in Alzheimer's Disease, and TAR DNA binding protein 43 ("TDP-43") in ALS. An important component of the mechanism of action of CNM-Au8® is its ability to dose-dependently reduce aggregated alpha-synuclein and TDP-43 in cellular models of PD and ALS, respectively (Fig. 6). We believe this activity is, at least in part, attributable to the robust induction of twenty gene transcripts of the Heat Shock Factor 1 pathway, which we observed in OLs in response to CNM-Au8® treatment (Robinson, et al. Nanocatalytic activity of clean-surfaced, faceted nanocrystalline gold enhances remyelination in animal models of MS. Sci Rep 10, 1936 (2020)) as well as due to an indirect cellular response to NAD upregulation, which has been shown to activate autophagic and proteostatic responses.

In summary, CNM-Au8® exhibits a novel mechanism of action via its catalytic activities, involving:

(1) enhancement of energetic metabolism via increased production of NAD^+ and ATP;

(2) reduction of oxidative stress; and

(3) enhancement of proteostatic, autophagic responses that reduce accumulation of toxic protein aggregates that are hallmarks of neurodegenerative diseases.

Figure 6. Reduction in Misfolded Protein Aggregates

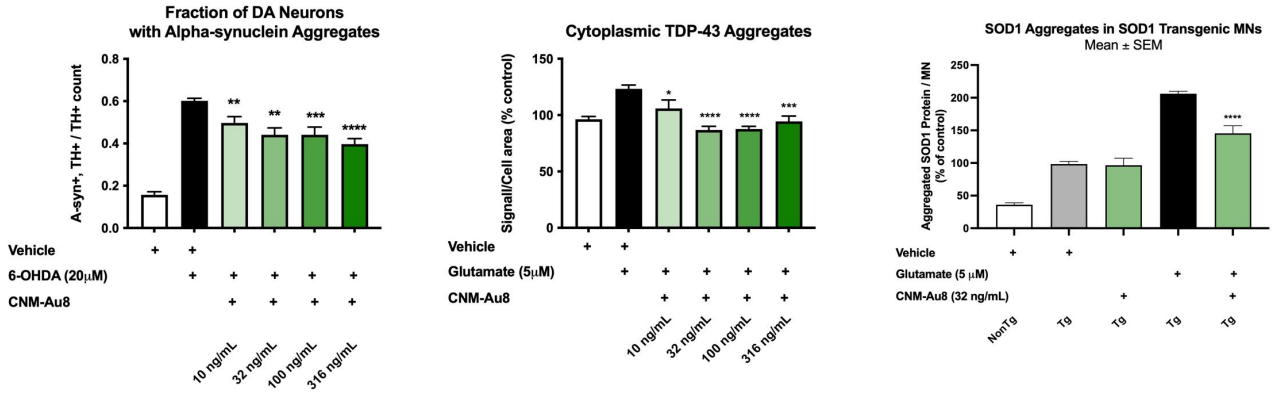


*Figure 6. shows the dose-dependent reduction of three different types of protein aggregates in dopaminergic and spinal motor neurons that are typically found in PD (Figure 6A), sporadic and familial ALS cases (Figure 6B), and familial SOD1 ALS cases (Figure 6C). In each of these assays, there was a concomitant dose-dependent increase in neuron survival and preservation of neurite network with CNM-Au8® treatment. These results demonstrate that CNM-Au8® reduces the quantity of toxic protein aggregates in in vitro models representing different neurodegenerative diseases. Group means plotted +/- SEM. * p <0.05; ** p < 0.01; *** p < 0.001; **** p< 0.0001; treatment vs. vehicle, one-way ANOVA corrected for multiple comparisons.*

Safety and Tolerability of CNM-Au8®

We completed a Phase 1 First-In-Human study of CNM-Au8® in 2016 to demonstrate it was safe for further clinical development, and to assess the pharmacokinetic profile at different dosing concentrations.

Trial design. The Phase 1 First-In-Human study of CNM-Au8® was a randomized, placebo-controlled, double-blind, escalating single- and multiple-dose study to evaluate the safety, tolerability, and pharmacokinetics of CNM-Au8® in healthy male and female volunteers. There were two phases to this study: a single-ascending dose ("SAD") phase and a multiple-ascending dose ("MAD") phase. The SAD phase was conducted first followed by the MAD phase of the study.

- Single Ascending Dose: 40 subjects were randomized to CNM-Au8® (n=30) or placebo (n=10) at a 3:1 ratio in single dose escalating cohorts who received CNM-Au8® at 15 mg, 30 mg, 60 mg, or 90 mg with follow-up study duration for each subject of 17 days.

- Multiple Ascending Dose: 46 subjects were randomized to CNM-Au8® (n=35) or placebo (n=11) in multiple dose cohorts who received CNM-Au8® at 15 mg, 30 mg, 60 mg, and 90 mg with the duration of treatment at 21 days and follow-up of each subject was up to 50 days.

Safety. Safety assessments revealed no significant findings. All doses used in this study were determined to be well-tolerated based on the frequency of reported treatment emergent adverse events ("TEAEs"). TEAEs occurred more frequently on placebo (86%) than in the CNM-Au8® dosing groups in both the SAD and MAD phases combined (75%). No subjects discontinued the study due to TEAEs and no SAEs were reported across any treatment group. The most frequently reported TEAEs were almost entirely of Grade 1 (mild) severity and transient. The most frequently reported TEAEs consisted of headaches, somnolence, fatigue, abdominal pain, diarrhea, nausea, and dizziness.

Pharmacokinetics. Pharmacokinetics analyses from the MAD phase showed that at the end of 21 days, the maximum concentration of gold in blood was determined to be 1.53 ng/mL, 1.98 ng/mL, 2.35 ng/mL, and 3.33 ng/mL for each group dosed with 15, 30, 60, or 90 mg respectively. Pharmacokinetics analyses demonstrated that CNM-Au8® has a half-life of 14-21 days. The end-of-study drug exposure levels in humans either matched or exceeded the equivalent exposure that demonstrated neuroprotection and remyelination efficacy in animal models.

Conclusion. The First-In-Human safety results demonstrated no safety signals following dosing with CNM-Au8® at or above clinically used doses and drug exposure levels in humans either matched or exceeded the equivalent exposure that demonstrated neuroprotection and remyelination efficacy in animal models.

After successful completion of Phase 1 studies of CNM-Au8®, we progressed CNM-Au8® into multiple Phase 2 clinical trials designed to test the efficacy of CNM-Au8® in specific disease indications. Based on the safety findings and the strength of our preclinical remyelination and neuroprotection data, we have initiated one Phase 2/3 registrational clinical trial, the Healey ALS Platform Trial, which is currently ongoing to establish the safety and efficacy of CNM-Au8® in patients with ALS. We completed RESCUE-ALS, a Phase 2 proof of concept clinical trial to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8® in patients with early symptomatic ALS. We also completed REPAIR-PD and the first dosing cohort of REPAIR-MS, two open-label, investigator blinded Phase 2 clinical trials which demonstrated target engagement of CNM-Au8® on the brain's energy metabolites. REPAIR-MS will continue with the initiation of a second dosing cohort. In addition, we have an ongoing Phase 2 clinical trial, VISIONARY-MS, for the treatment of visual pathway deficits in chronic optic neuropathy to assess the efficacy, safety, tolerability, and pharmacokinetics of CNM-Au8® for remyelination in stable relapsing MS. We support two EAPs for patients with ALS. The initial EAP was launched in partnership with the Healey Center for ALS at Massachusetts General Hospital in September 2019. A second EAP was implemented in conjunction with the Healey ALS Platform Trial at three participating clinical sites. We are accumulating increasing human safety exposure in our ongoing Phase 2 and Phase 2/3 clinical trials and our EAPs. To date, on a blinded basis we have seen no concerning or dose-limiting safety signals, and two independent data safety monitoring boards overseeing our randomized double-blind placebo-controlled trials have recommended continuing the conduct of the trials following unblinded evaluation of the safety data.

Amyotrophic Lateral Sclerosis

ALS Market Opportunities

ALS is an adult-onset, progressive, and fatal neurodegenerative disorder of the neuromuscular system resulting in muscle weakness and paralysis leading to death as early as three to five years after initial diagnosis. ALS affects more than 15,000 patients in the U.S. and is the most prevalent adult-onset progressive motor neuron disease. ALS involves the progressive degeneration of motor neurons in the spinal cord and the brain, which are responsible for controlling voluntary muscle movement. In ALS, this progressive loss of motor neurons leads to muscle weakness, loss of muscle mass, and inability to control movement. Although there are two FDA approved drugs for ALS, riluzole and edaravone, neither treatment substantially halts nor reverses the progressive nature of this disease. The onset of disease for the majority of individuals with ALS occurs between 40 and 60 years old and is more common in men. After the age of 65, the difference in incidence between males and females decreases.

ALS Current Therapies and Limitations

Current ALS treatment therapies are largely palliative, aiming only to provide temporary relief from symptoms without addressing the underlying disease progression. For example, one approach to the loss of respiratory function, which is the most common cause of ALS-related death, is non-invasive ventilation. Despite the great need for an effective disease-modifying treatment, and significant research efforts by the pharmaceutical industry to meet this need, there have been limited clinical successes and no curative therapies approved to date. There are two FDA-approved therapeutic agents for the treatment of ALS: riluzole, an anti-glutamatergic agent, and edaravone, a free-radical scavenger. However, both of these treatments are acknowledged to have limited disease-modifying effects, as riluzole extends participant lifespans by an average of only two to three months, while edaravone slows the decline of the ALSFRS-R

score, a clinical measure of functional decline, in only a small subset of participants who are at an early stage of disease. Additionally, the FDA has granted Priority Review for an NDA submission by Amylyx Pharmaceuticals, Inc. related to its drug AMX0035 based on a Phase 2 clinical trial in which AMX0035 demonstrated a statistically significant reduction in clinical decline at the end of the 6-month randomized phase as measured by the ALSFRS-R score. The European Medicines Agency ("EMA") is also currently reviewing AMX0035 for potential commercialization. There is clearly an urgent unmet need for the development of safe and effective disease-modifying therapeutics for ALS.

Potential Advantages of CNM-Au8® for ALS

We believe that CNM-Au8® has the potential to be a first-in-class disease modifying nanotherapeutic drug for ALS. In a human induced pluripotent stem cell ("iPSC") model of ALS, CNM-Au8® demonstrated clearly superior human motor neuron protection compared to riluzole. Furthermore, oral delivery of CNM-Au8® to ALS model mice extended the median lifespan of these animals by over three times the lifespan extension attributed to edaravone or riluzole treatment reported in the literature. While the mechanism of action of edaravone shares one similar component with CNM-Au8®, namely, reduction of oxidative stress, we believe the important difference in activity lies in CNM-Au8®'s demonstrated potential to enhance energetic activity in diseased neurons as well as to significantly reduce oxidative stress. Furthermore, we believe the complex nature of many of the neurodegenerative diseases, including ALS, calls for a therapeutic drug with multimodal activity that can act to enhance the energetic profile of multiple central nervous system cell types; for this, CNM-Au8® may be uniquely suited to address the therapeutic challenges posed by such complicated and devastating diseases.

Summary of Nonclinical Pharmacology Neuroprotection Studies for ALS

Motor neurons progressively degenerate during the course of ALS. To demonstrate neuroprotection of motor neurons by CNM-Au8®, *in vitro* neuroprotection assays were first used. Rat motor neurons were challenged with glutamate to induce excitotoxicity, or with amyloid beta 1-42 peptide ("A-beta"), which is toxic to motor neurons. In Alzheimer's Disease, A-beta aggregates participate in the formation of amyloid plaques. CNM-Au8® treatment of motor neurons challenged with glutamate or with A-beta increased numbers of surviving motor neurons and preserved neurite networks in a dose-dependent manner.

Aggregation of misfolded proteins that display neurotoxic properties is a hallmark of many neurodegenerative diseases, including ALS. Accumulation of mis-localized, cytoplasmic TDP-43 in motor neurons is associated with over 90% of ALS cases, and TDP-43 aggregates have been shown to disrupt cellular functions in motor neurons. In neuron-glial co-culture assays, application of glutamate or A-beta to rat motor neurons causes TDP-43 aggregates to accumulate in the cytoplasm of motor neurons. Treatment of the glutamate- or A-beta-challenged motor neurons with CNM-Au8® significantly reduced the accumulation of TDP-43 aggregates in a dose-dependent manner.

In addition to animal models, iPSCs have emerged as a new technique for neurodegenerative disease modeling using human-derived cells. iPSCs can be generated from a human skin or blood samples, and then differentiated in vitro into astrocytes and motor neurons. Using this technique, ALS patient-derived astrocytes were shown to be toxic to normal healthy human motor neurons. Introduction of CNM-Au8® to these toxic ALS patient astrocyte-motor neuron co-cultures resulted in a significant, dose-dependent rescue of human motor neurons and preservation of motor neuron neurite networks. Collectively, these results indicated that CNM-Au8® exerts motor neuron protection effects in several different models, including in response to excitotoxic stress, A-beta toxicity, and toxic astrocytes.

To investigate the efficacy of CNM-Au8® in an *in vivo* model of ALS, two studies were conducted in separate transgenic (SOD^{1G93A}) mouse model strains that model the human SOD1 familial form of ALS. In a study using rapidly progressing SOD^{1G93A} animals, CNM-Au8® treated animals showed significant reduction of brainstem atrophy and brainstem vacuolization normally seen in untreated SOD^{1G93A} mice. In the study using slower-progressing SOD^{1G93A} animals, CNM-Au8® treated animals showed significant treatment effects in a number of behavioral and functional tests, including overall clinical score, weights hold, static rod orientation time, and average wheel-running velocity. Median survival of CNM-Au8® treated animals significantly exceeded vehicle-treated controls by 23 days (approximately 20% of the animal's expected life-span).

Clinical Development of CNM-Au8® as a Disease-Modifying Drug for ALS

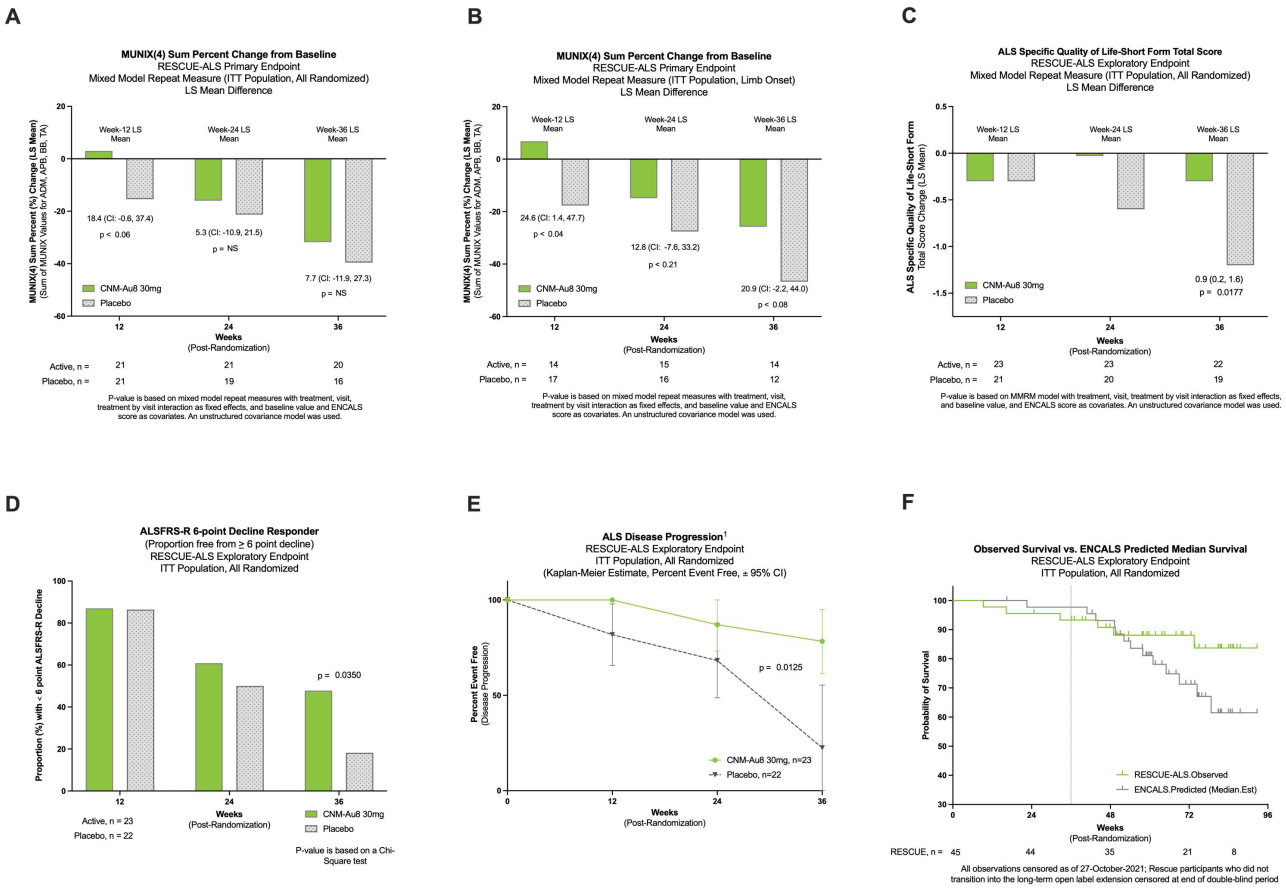
Orphan Drug Status for ALS

The FDA granted orphan drug designation to CNM-Au8® for the treatment of ALS in May 2019. Following FDA orphan drug designation, sponsors may qualify for seven-year FDA-administered Orphan Drug Exclusivity, partial tax credits for research and development expenses, potential research and development grants, waived FDA fees, and protocol assistance from the FDA.

RESCUE-ALS

RESCUE-ALS was a Phase 2, randomized, double-blind, placebo-controlled trial of the efficacy, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8® in early ALS patients. The trial was conducted over 36 weeks in 45 enrolled participants. The trial randomized participants 1:1 to treatment with CNM-Au8® at 30 mg daily or matching placebo on top of standard of care (riluzole). The primary endpoint of the trial was the percent change of the sum of Motor Unit Number Index ("MUNIX") from baseline to week 36. Secondary endpoints were the change in forced vital capacity ("FVC") and the absolute change in MUNIX values to week 36. Exploratory endpoints included multiple clinically relevant measures of ALS disease progression, ALS Functional Rating Scale Revised ("ALSFRS-R") 6-point decline, ALS Specific Quality of Life ("ALSSQOL-SF"), and additional clinical and neurophysiology endpoints. On November 2, 2021, we announced the top-line results of the RESCUE-ALS trial. While the trial did not meet the primary or secondary endpoints of MUNIX and FVC at week 36, an efficacy signal was observed for the MUNIX endpoint at week 12 (Fig. 10A, p=0.057). Furthermore, in a pre-specified analysis in the subset of limb onset ALS, CNM-Au8® demonstrated a significant treatment effect in MUNIX at week 12 (p=0.0385) and a trend for improvement at week 36 (p=0.0741) (Fig. 7B). Limb onset ALS accounts for approximately 70% of the ALS population. MUNIX is a neurophysiological biomarker that estimates the number of functioning lower motor neurons serving selected muscles. Clinically relevant exploratory endpoints through trial week 36 demonstrated significant benefits with CNM-Au8® treatment, including, slowing ALS disease progression (Fig. 7E, p=0.0125), decreasing the proportion of participants with an ALSFRS-R 6-point decline (Fig. 7D, p=0.035), and improving quality of life as measured by ALSSQOL-SF (Fig. 7C, p=0.018). Summary data are displayed in the figure below. In addition, CNM-Au8® treated participants consistently showed directional benefits (i.e., less decline) across measures of respiratory function and the motor function, albeit non-significantly. The long-term extension of the RESCUE-ALS trial showed evidence for a potential survival benefit when compared to the expected survival for the overall trial population using the validated ENCALS predictive model (Fig. 7F; Westeneng et al. Lancet Neurol. 2018 May;17(5):423-433). CNM-Au8® was found to be well-tolerated through 36 weeks of oral daily dosing. There were no reported SAEs related to CNM-Au8® treatment. Treatment-emergent adverse events were predominantly mild-to-moderate in severity. The most frequently reported adverse events associated with CNM-Au8® treatment included aspiration pneumonia (n=3) and transient gastrointestinal distress (n=2). In summary, we believe these data suggest an acceptable risk-benefit ratio in favor of CNM-Au8® and demonstrated signs of slowing disease progression in people with ALS.

Figure 7. Results of RESCUE-ALS



RESCUE-ALS was substantially funded by FightMND, which provided us with a grant of AUD1.4 million. In general, the grant terms from Fight MND include repayment of funds received in the event of commercialization of CNM-Au8® for the treatment of ALS in Australia from future net sales proceeds up to a mid-single-digit multiplier of the original grant amount of AUD1.4 million. Funding is disbursed based on the achievement of performance milestones related to patient enrollment targets. All intellectual property rights from the clinical trial activities are owned by us.

Healey ALS Platform Trial

In September of 2019, the Healey Center for ALS at Massachusetts General Hospital selected CNM-Au8® as one of the first three drugs for inclusion in the first Platform Trial for the treatment of ALS. The Healey ALS Platform Trial will test promising experimental therapeutics with a design that allows for the testing of multiple drugs simultaneously in order to rapidly identify and accelerate the development of novel therapies for ALS, while offering the advantages of reduced trial time, reduced costs and increased patient participation. The trial includes substantial financial support from philanthropic donors and the Healey Center, and provides access to 54 expert ALS clinical trial sites across the U.S. from the Northeast Amyotrophic Lateral Sclerosis consortium.

The trial is a Phase 2/3, multicenter, double-blind, placebo-controlled registrational clinical trial to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of CNM-Au8® in treating ALS. Participants were randomized 3:1 between active treatment and placebo with active treatment equally distributed between low dose (30 mg) CNM-Au8® and high dose (60 mg) CNM-Au8®. The primary endpoint is rate of change in ALSFRS-R score from baseline to week 24, with planned secondary endpoints of changes in slow vital capacity and hand-held dynamometry measurements. Exploratory endpoints include a combined joint-rank score based on survival and change in ALSFRS-R score from baseline to week 24, voice pathology measurements, and biofluid-based pharmacodynamic and metabolic markers.

We contribute a direct fee to the Healey Center toward the clinical conduct of this trial; there will be no additional licensing fees or milestone requirements. The IND for the Healey ALS Platform Trial is held by Massachusetts General Hospital. We own all CNM-Au8® data while placebo data will be shared across the different treatment regimens within the platform trial. Enrollment was completed in November 2021 and top-line results for CNM-Au8® are anticipated in the second half of 2022.

Expanded Access Programs

Based on interest in the potential of CNM-Au8® to delay disease progression in ALS patients, clinical experts at Massachusetts General Hospital requested to use CNM-Au8® in two EAPs. An EAP is a pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. To qualify for an EAP within the U.S. the following should apply: (i) a patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition, (ii) there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition, (iii) patient enrollment in a clinical trial is not possible, (iv) potential patient benefit justifies the potential risks of treatment, and (v) providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication. The EAPs are conducted under study protocols filed with the FDA and commenced in September 2019 and September 2021. The EAPs will collect safety and pharmacokinetic data in ALS patients not otherwise eligible for clinical trials due to standard inclusion and exclusion criteria.

As of February 18, 2022, 56 participants had been enrolled in the EAP that commenced in September 2019 with exposure up to 125 weeks. Currently, 33 participants are active under the protocol. As of February 18, 2022, 14 participants had been enrolled in the EAP that commenced in September 2021 with exposure up to approximately 20 weeks. Currently, all 14 participants are active under the protocol. An EAP provides additional safety data for FDA review and will be considered as part of the safety data package for CNM-Au8®, and may provide supportive long-term safety data with respect to an NDA submission should the Healey ALS Platform Trial result in a statistically significant treatment benefit.

Multiple Sclerosis

MS Market Opportunity

MS is an inflammatory and degenerative disorder of the central nervous system involving immune-mediated destruction of the brain, optic nerves, and spinal cord. MS results from autoimmune attacks on the myelin sheath, the protective covering wrapping the axons of neurons. When myelin is destroyed by autoinflammatory immune attacks, neurons become damaged and can ultimately die, leading to motor symptoms, cognitive disability, visual impairment and other neurological impairments.

MS typically begins between the ages from 20 to 40, and it is the leading cause of non-traumatic disability in young adults. Women are affected approximately three-times as often as men, except in individuals with the less common, primary-progressive form of the disease, where there is no gender preponderance. MS is the most common inflammatory demyelinating disease, with a prevalence that varies considerably, from high levels in North America and Europe to low rates in Eastern Asia and sub-Saharan Africa. A recent study led by the National MS Society estimates that approximately 800,000 people are living with MS in the U.S. Despite currently available disease-modifying therapies, approximately 26% of people with MS have developed a non-active, progressive form of the disease, for which there are limited approved, effective therapies, leading to significant loss of quality of life.

The diagnosis of MS is predominantly a clinical one that is aided by radiological tests (e.g., magnetic resonance imaging). Other diagnostic methods include blood tests, evoked potential tests, lumbar puncture, and optical coherence tomography, which is a new technology for examining the effects of MS on the health of nerve cells and axons in the retina. Utilizing magnetic resonance imaging, a new diagnostic classification for MS—clinically isolated syndrome has been included in the updated 2017 International (McDonald) Criteria. Ongoing improvements in diagnostic technologies may increase the number of patients diagnosed with MS.

MS Current Therapies and Limitations

All of the currently available drugs for treating MS either treat the symptoms caused by MS or act to reduce the degree of autoimmune-mediated inflammation. These drugs are typically referred to as disease-modifying therapies ("DMTs"). Nearly all of the current approved DMTs are approved for the treatment of relapsing forms of MS ("RMS"). They commonly act via immunosuppression or via immunomodulation, and thereby act to minimize autoimmune-associated attacks on myelin. Immunomodulatory DMTs reduce the risk of having an inflammatory attack, referred to as a "relapse", and can slow the development of disability in those patients having attacks (i.e., "active" patients). As a corollary, DMTs may possibly diminish the risk of conversion of RMS to secondary progressive MS. The newer DMTs have been shown to substantially reduce autoimmune-mediated attacks and to delay the progression of the disease in active patients. However, there are no drugs available which can reduce the ongoing loss of function (i.e., disease progression) in

non-active (those no longer having attacks) MS patients. None of the approved DMTs have been shown to clinically improve remyelination of damaged and demyelinated axons in MS lesions. Currently available DMTs for the treatment of MS include: *Injectable medications*, Avonex (interferon beta-1a), Betaseron (interferon beta-1b), Extavia (interferon beta-1b), Copaxone (glatiramer acetate), Plegridy (peginterferon beta-1a), Rebif (interferon beta-1a), Glatiramer acetate generic equivalent (Glatiramer Acetate Injection, Glatopa (glatiramer acetate); *Oral medications*, Aubagio (teriflunomide), Gilenya (fingolimod), Tecfidera (dimethyl fumarate), Mavenclad (cladribine), Mayzent (siponimod); *Infusion medications*, Lemtrada (alemtuzumab), Novantrone (mitoxantrone), Ocrevus (ocrelizumab), and Tysabri (natalizumab). Advances in MS treatment with new B-cell depleting therapies, including ocrelizumab, have largely ameliorated inflammatory disease activity as measured by the reduction in risk of having relapses and the lack of occurrence of new gadolinium enhancing (inflammatory) lesions, as detected by MRI. However, despite the stabilization of MS disease activity in active MS patients by these agents for these MS patients, significant improvement in overall function has not been shown. Importantly, for the DMTs that have been approved to date, efficacy and safety are generally inversely correlated.

There is an increasing demand for better treatment strategies. Although current drugs for MS can reduce the risk of an inflammatory attack and slow down the progression of the disease in some MS patients, patients' responses to drugs can be variable and suboptimal. For non-active MS patients, there is no available DMT that can substantially alter their progressive worsening. Also, the side effects of current MS drugs range from mild to serious, which may lead to reduced patient adherence.

Potential Advantages of CNM-Au8® for MS

We believe that CNM-Au8® has the potential to be a global first-in-class remyelinating and neuroprotective disease-modifying nanotherapeutic drug for MS. CNM-Au8® supports neurologic functions by enhancing energetic activities in neurons and OLs that have been attacked by the disease. Unlike the current immunomodulating MS DMTs, CNM-Au8® is thought to act to directly support neuroprotection and remyelination by improving energetics, reducing harmful ROS and inducing protective heat shock protein mechanisms. CNM-Au8® is administered orally, penetrates the blood brain barrier, and to date has a favorable safety, tolerability, and toxicology profile. Used alternately or in conjunction with standard immunomodulatory DMTs, CNM-Au8® treatment may improve patients' quality of life and potentially reverse disease progression because of its enhancing energetic activities in neurons and OLs that have been attacked by the disease, even in patients whose inflammatory attacks are well-controlled.

Summary of Nonclinical Pharmacology Myelination Studies for MS

Myelination is a complex process resulting in the wrapping of axons by OL membranes containing specialized proteins and lipids. The resulting myelin sheath provides metabolic support to the axon and facilitates axonal electrical conduction, which in turn allows for central nervous system processing of motor, sensory, and higher order cognitive functions. During active myelination, OLs synthesize on the order of 100,000 proteins per minute and several thousand new lipid molecules per second, reflecting the significant energetic investment needed for biomass generation, and making this cell type among the most energetically demanding in the body. In MS, myelin is destroyed by autoimmune-mediated inflammatory attacks, and neurons whose axons were once protected and supported by myelin become damaged and can ultimately die. OL precursor cells are known to be present near MS lesions and can play a role in remyelination, but studies have shown that these cells are energetically compromised and remyelination is suboptimal in most central nervous system lesions.

Energetic deficits have been noted in the brains of living patients with MS using ^{31}Phosphorus magnetic resonance spectroscopy ("^{31}P-MRS"). In autopsied brains from MS patients, OL precursor cells near MS lesions displayed impaired mitochondrial complex activity and other energetic deficits. These energetic deficits play key roles in MS disease progression. CNM-Au8® is uniquely designed to directly address these important pathophysiological mechanisms.

We investigated the ability of CNM-Au8® to address OL energetic deficits, to induce remyelination and to restore functional activities and motor behaviors in a comprehensive remyelination preclinical program involving multiple *in vitro* and *in vivo* assays to determine CNM-Au8® efficacy. This work has been published as a peer-reviewed publication in Scientific Reports and is briefly summarized here.

In vitro experiments on primary OL precursor cells demonstrated robust induction of myelin production by CNM-Au8®. RNASeq analyses of CNM-Au8® treated OL precursors cells demonstrated that multiple transcripts for known myelination genes are upregulated, and that glycolytic activity and ATP production are also increased. Several in vivo experiments were also conducted to demonstrate that orally delivered CNM-Au8® results in increased remyelination in the brains and spinal cords of animals treated with cuprizone or lysolecithin, two agents that are known to strip neurons of myelin via different mechanisms (Robinson et al. *Sci Rep.* 2020 Feb 11;10(1):1936). As fully described in the peer-reviewed publication by Robinson et al. both orally delivered cuprizone, or stereotactically injected lysolecithin are commonly used techniques to cause demyelination of the corpus callosum or spinal cord, respectively. Cuprizone, which is administered to rodents by including this agent in their chow, is a copper chelating agent that specifically causes mature OL death within multiple brain regions, including the corpus callosum. Maximal demyelination due to cuprizone feeding

typically occurs within five weeks, which can be visually monitored and quantified using transmission electron microscopy. Lysolecithin injection results in the rapid degradation of myelin within a localized area of the spinal cord, observable using Luxol Fast Blue or toluidine staining for myelin with light microscopy, or also with transmission electron microscopy of the lesion, within a day of injury, allowing for the observation of remyelination within the induced lesion within the following weeks. Remyelination of the corpus callosum or spinal cord using either technique requires the migration of surviving OL precursor cells to the sites of demyelination, differentiation of these cells into mature myelinating OLs, and rapid generation of specialized proteins and lipids for formation of new myelin membrane wraps around axons in this energetically demanding process. Multiple independent *in vivo* remyelination assays, using either cuprizone or lysolecithin as demyelination agents, were performed to demonstrate the remyelinating ability of CNM-Au8®. For example, CNM-Au8® was provided either prophylactically, at the same time as the start of cuprizone feeding, or only after two weeks of cuprizone feeding, therapeutically, in order to allow demyelination to start to take place prior to administration of CNM-Au8®. In both contexts, CNM-Au8® demonstrated greater recovery of myelin in affected brain areas than vehicle-treated controls. Furthermore, animals that were provided with CNM-Au8® only after full demyelination (five complete weeks of cuprizone treatment) had taken place displayed evidence of higher levels of mature myelin marker expression in their brains than vehicle controls, indicating that CNM-Au8® was not blocking the action of cuprizone but rather inducing recovery by stimulating the differentiation of OLs. Similar results were confirmed by the lysolecithin experiments, which indicated that myelin destroyed by a completely different mechanism could be recovered with the daily oral administration of CNM-Au8® for one or two weeks after focal demyelination by lysolecithin. Treatment with CNM-Au8® significantly improved not only the quantifiable detection of myelinated axons in the brains of experimental animals, but also mouse behaviors and functional movements in the open field test and kinematic assays. For example, quantitation of the number of myelinated versus unmyelinated axons in 587 transmission electron microscope images, averaging 84 images per treatment group (with 15 mice per treatment group, seven treatment groups total), demonstrated a statistically significant ($p < 0.0001$ using one-way ANOVA corrected for multiple comparisons) recovery of remyelinated axons in therapeutically treated animals who were dosed with CNM-Au8® by gavage compared to vehicle treated, cuprizone-fed controls. In independent demyelination model studies using lysolecithin, lesioned animals treated with CNM-Au8® exhibited a 43% mean increase in myelinated axons within lesions post-LPC injection compared to vehicle controls ($p = 0.15$, unpaired t-test comparing CNM-Au8® treated rats to vehicle treated controls). Finally, in a cuprizone-mediated demyelination model study of both gross and fine motor behaviors, the group of animals receiving therapeutically delivered CNM-Au8® displayed detectable improvements in behaviors in both open field and fine motor kinetics assessments. Principal component analysis of gait metrics showed no statistical difference ($p = 0.47$) between CNM-Au8® treated, cuprizone-fed animals compared to the sham treated group, whereas there was a detectable difference in vehicle-treated, cuprizone-fed animals and sham controls ($p = 0.032$; two-way ANOVA) by the end of study at week 6.

Figure 8 shows examples of the observed induction of myelination by CNM-Au8® from selected *in vitro* and *in vivo* experiments reported in Robinson et al. These studies were fully funded by us and were the result of collaborations among academic researchers from Northwestern University, George Washington University, and various other academic consultants and our employees.

Figure 8. Remyelination Summary

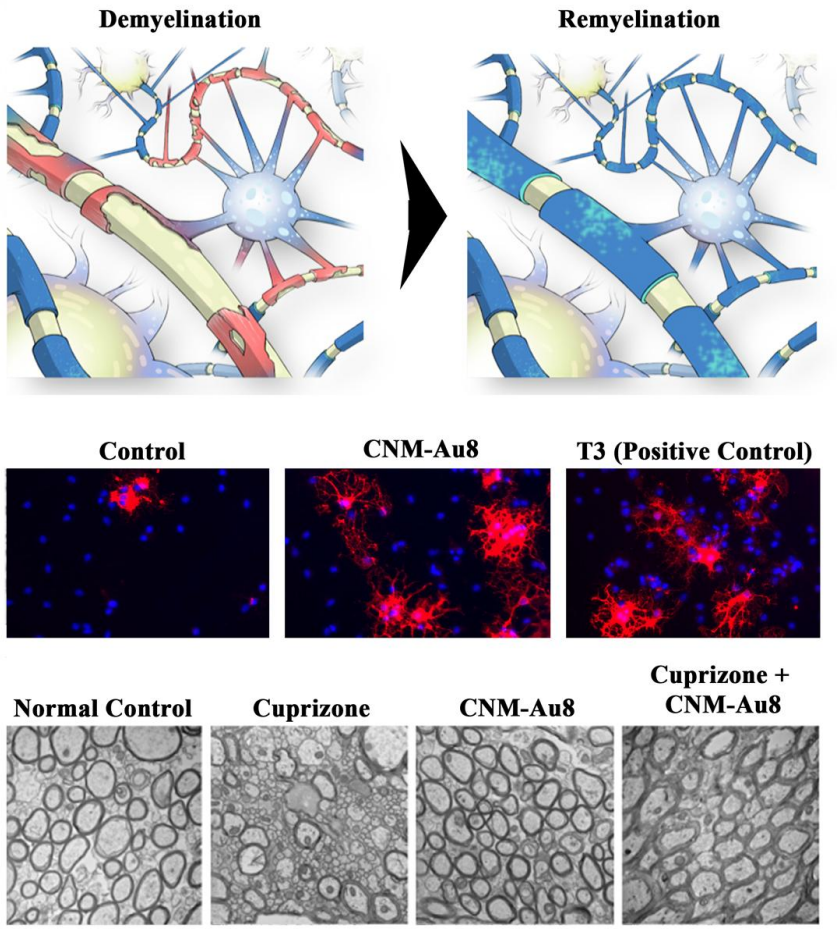


Figure 8. A summary of myelinating activities of CNM-Au8®. Top row, Left: illustration of the demyelination (red) of a neuron's axon (yellow) that occurs in MS. Right: Illustration of restored myelination along the axon (blue) provided by the OL (blue cell). Middle row: isolated primary mouse OL precursors treated with vehicle control (left), 3 µg/mL CNM-Au8®, or positive control and myelin-inducing agent tri-iodothyronine. Cells are fixed and stained for Myelin Basic Protein ("MBP"), a marker of mature myelin in red, and the nuclear stain DAPI in blue, to reveal the presence of all OL precursor cells in the field of view. Many more cells expressing MBP are seen in the CNM-Au8® treated cells compared to vehicle-treated cells. Bottom row: transmission electron images of slices of corpus callosum of mice treated with, left to right: no cuprizone, cuprizone for five weeks, CNM-Au8® for five weeks, or cuprizone for five weeks and CNM-Au8® for the last three of the five weeks. Myelin can be seen as dark rings in each micrograph. Cuprizone treatment destroys myelin, while CNM-Au8® treatment alone does not change myelin. CNM-Au8® treatment of cuprizone-treated animals results in the recovery of myelin in the brains of these animals.

Clinical Development of CNM-Au8® as a Disease-Modifying Drug for MS

Based on safety findings in our Phase 1 clinical trial of CNM-Au8® and our robust preclinical remyelination data, we have launched two Phase 2 clinical trials to investigate the effects of CNM-Au8® in MS patients.

VISIONARY-MS

The VISIONARY-MS clinical trial, launched in December 2018, is an ongoing double-blind, randomized, placebo-controlled Phase 2 trial evaluating the efficacy and safety of two doses of CNM-Au8® as a remyelinating and neuroprotective treatment in people who have stable RMS with chronic visual impairment. Enrolled participants must have chronic optic neuropathy, defined as visual impairment with no episodes of acute optic neuritis within the six months prior to enrollment, and stable (non-active) disease, defined

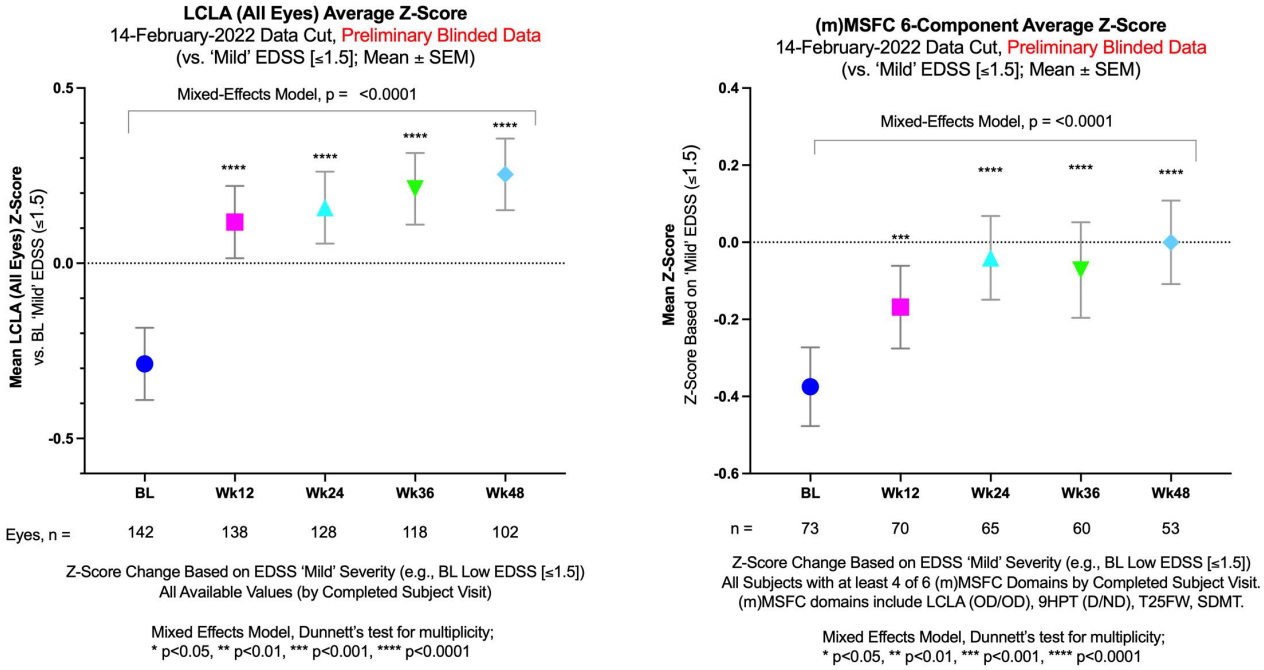
as no MS relapses within the three months prior to entry. Concomitant immunomodulatory MS DMTs are allowed. Participants are randomized to low-dose CNM-Au8® (15 mg/day), high-dose CNM-Au8® (30 mg/day), or matching placebo. The primary endpoint is improvement in low contrast letter acuity ("LCLA") from baseline to week 24. Exploratory endpoints include OCT, multi-focal VEP amplitude & latency, full field-VEP amplitude & latency, MRI endpoints, visual function (high contrast) and QOL/Expanded Disability Status Scale ("EDSS").

Contrast is the quantity of lightness or darkness contained by an object in comparison to its background. The smallest difference in contrast distinguished by the eye is known as the contrast threshold, usually reported as its reciprocal value, which is also known as contrast sensitivity (1/contrast threshold). Therefore, if a large amount of contrast is necessary for a patient to identify an object, they have poor contrast sensitivity and will have a low numerical value for this measurement. Contrast sensitivity can be thought of as a spectrum, in that black letters on a white background will be easier for any individual to discern than lower-contrast grey on white letters, regardless of whether or not visual impairment is present. The contrast threshold is the minimum amount of contrast necessary for an individual to discern an object from its background, and for people with MS the contrast threshold has been found to be higher than that of healthy individuals, even when visual acuity (measured at high contrast) is equal between the two groups. Contrast sensitivity is on a spectrum and may elicit more subtle changes in an individual's contrast threshold that are missed by high contrast visual acuity. LCLA tests low-contrast vision at various spatial frequencies that may be particularly affected by damage to specific inter-neural connections in an individual's complex visual pathway.

In the VISIONARY-MS trial, all participants remain in the double-blind, placebo-controlled treatment period through week 48, until the last participant completes week 24. In this way, double-blind, placebo-controlled data will be generated for most patients in the trial through week 48, improving the trial's ability to assess the long-term effects of CNM-Au8® on clinical endpoints. The TGA, Health Canada, and the FDA have all approved conduct of the trial. As of February 1, 2022, 73 participants were enrolled in the VISIONARY-MS trial with exposure to the investigational product for up to 48-weeks in the double-blind period. Long-term treatment from randomization through open-label extension exceeds 117 weeks.

Preliminary, interim, blinded efficacy results from VISIONARY-MS were recently reported as a poster at the American Committee for Treatment and Research in Multiple Sclerosis ("ACTRIMS") Forum 2022 held February 24-26, 2022. Results from the first 73 enrolled participants, including 53 participants with trial duration up to 48 weeks, demonstrated clinically-relevant, exposure-related mean standardized improvements in LCLA, as well as an integrated composite of the other remaining modified Multiple Sclerosis Functional Composite sub-scales ("(m)MSFC"), including Symbol Digit Modalities Test (SDMT, cognition), 9-Hole Peg Test (9HPT, upper extremity function), and Timed 25-foot Walk (T25FWT, gait) in the population, as a whole. These blinded interim analyses compared changes in (m)MSFC scores over the trial treatment period to the baseline values of trial participants with mild disease, as defined by Baseline EDSS scores of 1.5 or less. The baseline scores for these participants were chosen as a comparator because they demonstrate less neurological impairment than those of the overall trial population, providing a valid comparator group to evaluate change over time in the total trial population. Changes in the four MSFC sub-scales (LCLA, SDMT, 9HPT, and T25FW) were compared to baseline scores of this comparator group with mild disease from baseline to week 48. These comparisons were performed at each trial time-point (Weeks 12, 24, 36, and 48). At each visit, the overall trial population (randomized 2:1 active CNM-Au8® to placebo) showed notable, exposure-related improvements in mean in overall MSFC scores and key MSFC sub-scales compared to the comparator group (mixed-effects model; $p<0.0001$ vs. baseline). We believe these data support CNM-Au8®'s potential to drive meaningful neurological improvements in MS patients. Further, we believe these observations are notable given the expected long-term decline in LCLA, SDMT, 9HPT, and T25FW amongst MS patients reported from data sets including from the MS Outcome Assessments Consortium ("MSOAC") (Goldman et al. *Neurology.* 2019 Nov 19;93(21):e1921-e1931). MSOAC includes prospectively acquired RMS patient-level data from fourteen separate MS clinical trials including over 12,776 participants combined into a single database and followed for up to 24-months. When LCLA, SDMT, 9HPT, and T25FW were analyzed as a multidimensional measure rather than individually, progression on any one of these performance measures was more sensitive than the commonly used MS EDSS, and demonstrated long-term declines in RMS patients. The increasing mean improvements observed across the entire trial population (CNM-Au8® and placebo) may suggest a positive clinical effect for CNM-Au8® when contrasted with the anticipated decline reported in publications from the MSOAC data. Figure 9 represents a summary of the observed average change of LCLA and an integrated MSFC average 6-component Z-score of the change from Baseline by each 12-week interval across all trial participants in VISIONARY-MS (e.g., low dose, high dose, placebo) for all visits recorded as of February 14, 2022 and indicates continuing improvement over the course of the trial.

Figure 9. VISIONARY-MS Mean Standardized LCLA and Integrated (m)MSFC Z-Score Change vs. Baseline



R. Glanzman, MD, FAAN, H. Beadnall MBBS FRACP, A. Klistorner PhD, M. Barnett, MBBS FRACP PhD, R. Sergott MD, A. Rynders, K. Ho, PhD, M. Hotchkin. Holladay, UT/United States of America, Camperdown, NSW/Australia, Philadelphia, PA/United States of America, Holladay/United States of America. "VISIONARY-MS: Update to a Phase 2 Clinical Trial of CNM-Au8, Catalytically Active Gold Nanocrystals Suspension, for the Treatment of Chronic Optic Neuropathy" presented at the ACTRIMS Forum 2022 held February 24-26, 2022.

Available blinded safety data from VISIONARY-MS indicate that CNM-Au8® is well-tolerated with most adverse events characterized as mild in severity. No SAEs related to the investigational product (e.g., placebo, CNM-Au8®) have been reported to date. The most frequently reported adverse events include headache, upper respiratory infection, and sore throat. The VISIONARY-MS trial will conclude early due to COVID pandemic-related challenges. After an orderly wind down of the VISIONARY-MS trial, the full unblinded results from the trial are anticipated in the second half of 2022.

REPAIR-MS and REPAIR-PD

Two Phase 2, central nervous system imaging clinical trials, REPAIR-MS and REPAIR-PD, were initiated to demonstrate central nervous system target engagement by measuring the effects of orally delivered CNM-Au8 on brain energy metabolites in patients with MS and PD *in vivo*. These energetic metabolites are measured non-invasively and semi-quantitatively by utilizing ^{31}P-MRS imaging with a 7 Tesla ("7T") MRI scanner. The REPAIR trials are being conducted at the University of Texas Southwestern, a center with specialized capabilities for conducting and analyzing 7T ^{31}P-MRS imaging studies. Both REPAIR trials were approved for clinical conduct by the FDA and commenced in December 2019 (REPAIR-PD)/January 2020 (REPAIR-MS) with full data presented in August 2021 for both REPAIR-PD and the first dosing cohort of REPAIR-MS. We enrolled 13 participants in the REPAIR-PD trial with exposure to CNM-Au8® up to 21-weeks and 13 relapsing MS participants in the REPAIR-MS trial with exposure to CNM-Au8® up to 18-weeks. REPAIR-MS and REPAIR-PD were single-center, active-only, sequential group studies examining the brain metabolic effects, safety, pharmacokinetics and pharmacodynamics of CNM-Au8® in patients who have been diagnosed with MS within 15 years of screening or in patients with PD who have been diagnosed within three years of screening. REPAIR-PD has completed with the first dosing cohort and a planned second cohort will not be enrolled due to institutional limitations. REPAIR-MS will continue with the initiation of a second dosing cohort of up to 15 participants with non-active progressive MS.

In the REPAIR program, a full volume head coil was used to collect whole brain spectral waveforms in ~600 voxels with a spatial resolution of 2 cm^3 for the following metabolites: NAD pool (both NAD^+ and NADH together), ATP-α, ATP-ß, ATP-γ, phosphocreatine, extracellular and cellular inorganic phosphate, uridine diphosphate glucose, phosphocholine ("PC"), phosphoethanolamine,

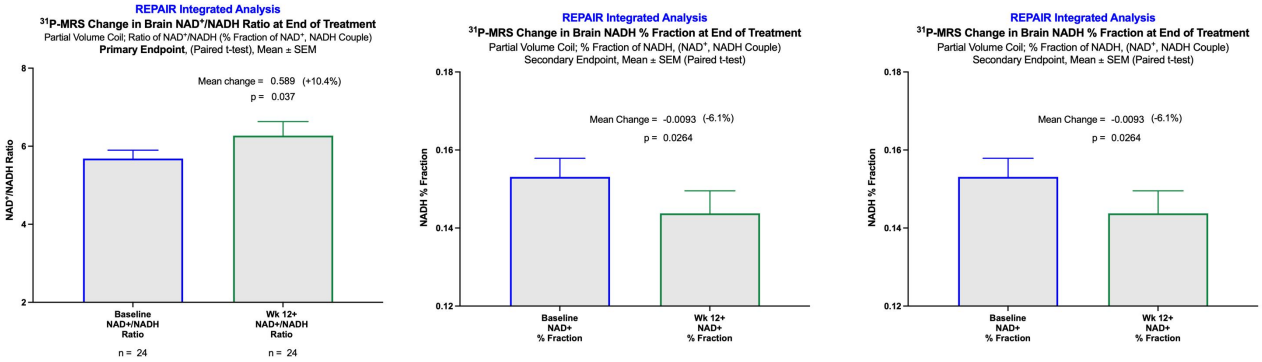
glycerophosphocholine, and glycerophosphoethanolamine. A partial volume head coil was used in the same patient cohort to measure occipito-parietal levels of individual NAD^+ and NADH phosphorous metabolites to determine the ratio of NAD^+/NADH.

Pre-specified integrated analyses of the first two completed dosing cohorts across REPAIR-MS and REPAIR-PD were announced on August 5, 2021, and were presented at the MDS Virtual Congress 2021 held on September 17-22, 2021 in an oral presentation. The results for the primary endpoint, the mean change in the brain NAD^+/NADH ratio (the ratio of the oxidized to reduced form of NAD), demonstrated a statistically significant increase by an average of 0.589 units (10.4%) following 12-weeks of treatment with CNM-Au8® (p=0.037, paired t-test), in the pre-specified integrated analysis of the REPAIR-PD and REPAIR-MS trials. Key secondary endpoints, mean change from baseline in the NAD^+ fraction and NADH fraction of the total NAD pool, were concordant with the primary endpoint, demonstrating the NAD^+ fraction increased (p=0.026), while the NADH fraction decreased (p=0.026). The individual results for these sister trials demonstrated consistent statistical trends toward improvement in the NAD^+/NADH ratio with results of p=0.11 and p=0.14, for REPAIR-PD and REPAIR-MS, respectively.

Analyses of pre-specified exploratory endpoints demonstrated that homeostatic equilibrium was achieved across essential energetic metabolites, including ATP, cellular phosphorous ("$Pi^{(in)}$"), PC, and phosphorylation potential index ("ATP-ß/ADP*$Pi^{(in)}$"). For these metabolites and indices, the percent change from baseline to the week 12 end-of-treatment was significantly inversely correlated with baseline levels, such that participants with relatively lower baseline levels demonstrated increases, and subjects with relatively higher baseline levels demonstrated a re- balancing effect with levels decreased to the baseline population mean. This relationship was observed both on an integrated basis across the two trials, and independently in both REPAIR-PD and REPAIR-MS, respectively, for: ATP-ß ($r^2 = 0.82$, $p < 0.0001$; $r^2 = 0.71$, $p = 0.0011$), phosphorylation potential ($r^2 = 0.72$, $p = 0.0002$; $r^2 = 0.68$, $p = 0.0019$), PC ($r^2 = 0.78$, $p < 0.0001$; $r^2 = 0.54$, $p = 0.0095$), and $Pi^{(in)}$ ($r^2 = 0.42$, $p = 0.017$; $r^2 = 0.48$, $p = 0.018$).

Figure 10 below illustrates the changes in NAD/NADH ratio via the partial volume coil assay (primary endpoint) and the changes in the key secondary endpoints from the combined integrated analyses.

Figure 10. Integrated Results of REPAIR-MS and REPAIR-PD



Parkinson's Disease

PD Market Opportunities

PD is a chronic, progressive neurodegenerative disorder involving the progressive loss of dopaminergic neurons in the *substantia nigra* area of the midbrain. The degeneration of dopaminergic neurons leads to resting tremor, bradykinesia, limb rigidity, and gait and balance problems as well as increasingly recognized cognitive loss and behavioral changes due to more generalized neuronal loss. Both genetic and environmental factors are thought to contribute to the development of PD in addition to aging, which is the most significant risk factor for developing the disease. Approximately one in one hundred individuals over the age of 60 is affected by PD.

PD Current Therapies and Limitations

While there are a number of approved PD therapies, such as dopamine agonists, COMT and MAO-B inhibitors, and deep brain stimulation, these treatments are limited to symptomatic improvement. No treatment is currently available to prevent the destruction of dopaminergic neurons. The inexorable progression of loss of dopaminergic innervation leads to progressively worsening symptoms with "on" (dyskinesias) and "off" (rigidity) symptoms that become increasingly difficult to manage. In addition, long-term use of levodopa, a commonly-prescribed dopamine precursor used to treat Parkinsonian symptoms, often results in dyskinesia that in itself becomes

disabling. Despite an enormous effort over the past several decades, no disease-modifying or neuroprotective therapeutic for PD is available. A therapeutic that alters or slows the clinical progression, and thus improves PD healthspan and lifespan, would address a very significant unmet need.

Neuronal energetic failure underlies PD, as evidenced by the observed impaired mitochondrial and lysosomal functioning, neuronal sensitivity to glutamate toxicity, accumulation of oxidative stress, autophagic failure in clearing misfolded proteins, and loss of synapse integrity associated with this disease. As such, improvement of cellular energetic efficiency, as is possible with CNM-Au8®, represents an important and previously unaddressed therapeutic target for this disease.

Potential Advantages of CNM-Au8® for PD

We believe that CNM-Au8® has the potential to be a global first-in-class disease modifying nanotherapeutic drug for PD. While current therapies for PD are designed to stimulate surviving dopaminergic neurons in order to elicit partial functional effects, none of them prevent the inexorable degeneration of dopaminergic neurons to change the course of disease progression. Our nonclinical studies demonstrate that CNM-Au8® is robustly neuroprotective of dopaminergic neurons across a variety of disease-relevant insults created using a variety of toxins and stressors. In addition, CNM-Au8® may have a tolerability profile superior to existing approved products like commonly used drugs for PD, such as levodopa/carbidopa that result in risk of dyskinesias after long-term use.

Summary of Nonclinical Pharmacology and General Neuroprotection Studies for PD

Excitotoxic injury, oxidative stress, and the accumulation of misfolded alpha-synuclein are hallmarks of the failing energetic pathways associated with PD. In order to determine whether CNM-Au8® could act as a neuroprotective agent for PD, we conducted a series of *in vitro* and *in vivo* studies designed to test efficacy of CNM-Au8® in protecting various neuronal cell types from a variety of PD relevant disease-related stressors.

The potential of CNM-Au8® to confer neuroprotection in PD disease-specific cellular models was first demonstrated *in vitro*. Primary rat dopaminergic cells were challenged with 1-methyl-4-phenyl-1,2,3,6-tatrahydropyridine, ("MPTP," which is metabolized to its active form MPP^+) or alternatively with 6-hydroxydopamine ("6-OHDA"), which are both toxins specific to dopaminergic neurons. Treatment of primary neuronal-glial cocultures with CNM-Au8® increased the numbers of surviving dopaminergic neurons in response to either toxin in a dose-dependent manner, as well as affected overall improvement in neuronal health by a variety of metrics, including preservation of neurite network, reduction in oxidative stress, increase in mitochondrial staining, and reduction in alpha-synuclein aggregates. The activity of CNM-Au8® was then tested in the standard 6-OHDA-unilateral lesion model of PD. Lesioned rats, and a sham control group, were orally administered vehicle or CNM-Au8® for 4-weeks (2-weeks post-lesion) or 6-weeks (one-day post lesion) following the establishment of a lesion in the striatum. Significant functional improvements due to CNM-Au8® treatment was demonstrated in both the behavioral apomorphine-induced rotation and cylinder paw placement tests. In addition, larger numbers of surviving dopaminergic neurons were detected in the striatum of CNM-Au8®-treated lesioned animals compared to vehicle controls. These studies independently demonstrated that CNM-Au8® treatment has robust neuroprotective properties in preclinical models of PD.

Clinical Development of CNM-Au8® as a Disease-Modifying Drug for PD

REPAIR-PD

We initiated the Phase 2 REPAIR-PD clinical trial to determine CNS target engagement by measuring the effects of orally delivered CNM-Au8® on brain energy metabolites in patients with PD as discussed previously. The REPAIR-PD trial was conducted at the University of Texas Southwestern. The REPAIR-PD trial was approved for clinical conduct by the FDA and commenced in December 2019. The REPAIR-PD trial concluded with the completion of the first dosing cohort of 13 randomized participants. In the REPAIR program Phase 2 open-label trial, CNM-Au8® has demonstrated target engagement in the treatment of MS and PD.

The REPAIR-PD results were presented at the MDS Virtual Congress 2021 held on September 17-22, 2021. The results for the primary endpoint, the mean change in the brain NAD^+/NADH ratio (the ratio of the oxidized to reduced form of NAD), demonstrated a non-significant increase by an average of 0.386 units (6.8%) following 12-weeks of treatment with CNM-Au8® ($p=0.1077$, paired t-test). Key secondary endpoints, mean change from baseline in the NAD^+ fraction and NADH fraction of the total NAD pool, were concordant with the primary endpoint demonstrating the NAD^+ fraction increased ($p=0.1336$), while the NADH fraction decreased ($p=0.1336$). Exploratory endpoints, including the percent change from BL to the EOS visit demonstrated changes that highly correlated to BL levels for key energetic markers. On average, patients with energetic metabolite levels less than the BL mean significantly increased whole-brain metabolite levels at the EOS visit, while patients with BL levels greater than the mean normalized levels to the BL mean. Importantly, this relationship was observed for ATP-ß levels ($r^2 = 0.8158$; $p < 0.0001$), phosphorylation potential ($r^2 = 0.7218$; $p = 0.0002$), and several other ^{31}P metabolites, indicating a homeostatic effect of CNM-Au8® on brain energetics. TEAEs were rated as mild and transient. There were no SAEs and no participants experienced clinically significant laboratory abnormalities. These results

robustly demonstrate target engagement in the brains of PD patients, and provide the first clinical evidence demonstrating the catalytic effects of CNM-Au8® on brain energetic metabolites. For details, please see the "—REPAIR-MS and REPAIR-PD" section above.

RESCUE-PD

A second Phase 2 clinical trial is planned to investigate the effects of CNM-Au8® on slowing or preventing disease progression in PD patients. The RESCUE-PD trial will follow patients with PD to determine the effects of CNM-Au8® on stabilizing disease activity as a neuroprotective therapeutic. The RESCUE-PD trial is planned to commence in mid-2022, with results anticipated within 36 months following trial initiation.

Additional CSN® Therapeutics in the Pipeline

Three other drug candidates are at various IND-enabling stages of research. Utilizing our CSN® therapeutic drug development platform, we have developed additional drug candidates based on the transition elements silver and zinc (CNM-ZnAg) for anti-viral/anti-bacterial and wound healing applications (CNM-AgZn17), and gold and platinum (CNM-PtAu7) for oncology applications.

CNM-ZnAg, a Broad Spectrum Anti-viral and Anti-Bacterial agent in Development for Treatment of COVID-19

CNM-ZnAg was developed for use as an orally deliverable, broad-spectrum antiviral and antibacterial agent. It is formulated as an ionic solution of zinc (Zn^{+2}) and silver (Ag^{+}) with a limited presence (<1%) of silver Ag^{0} nanoparticles, all generated using the CSN® platform in a manner that does not involve traditional inorganic synthesis methods utilized to generate zinc and silver compounds. The rationale for integrating a zinc-silver ionic solution was premised on the recognized historical activity of both Zn and Ag (as independent entities) for antimicrobial and antiviral disease treatment. Initial development studies both internally as well as externally from other labs revealed that when Zn^{2+} and Ag^{+} are administered together, they exhibit synergistic antiviral and antibacterial properties that are not observed when Zn^{2+} or Ag^{+}, or Ag^{0} nanoparticles are administered singly.

In the human body, zinc is an essential structural component of <750 zinc finger transcription factors, and is a catalytic component of approximately 2,000 enzymes, encompassing all known enzyme classes. Most significantly, zinc is essential for the proper function of the immune system, and is specifically involved in multiple steps in the antiviral response. Zinc has demonstrated direct antiviral properties; in addition, zinc stimulates both innate and acquired antiviral responses. Thus, zinc-based treatments are hypothesized to support systemic immunity, while also acting to specifically inhibit viral replication, viral protein processing, and/or viral-infection-related symptoms. Silver has long been studied for its anti-infective activity. Silver's microbial-treatment properties have been documented for centuries, and silver has been the most extensively studied metal for the purpose of fighting infections and preventing food spoilage. Prophylaxis of silver nitrate against gonococcal ophthalmia neonatorum with silver ions was considered the standard of care in many countries until the end of the twentieth century, prior to the advent of antibiotics. Independent research had demonstrated silver nanoparticles have been shown to be active against several types of viruses including human immunodeficiency virus, hepatitis B virus, herpes simplex virus, respiratory syncytial virus, and monkey pox virus. Silver nanoparticles and silver ions reduce viral infectivity when added concomitantly with the virus inocula, possibly by blocking interaction of the virus with the host cell.

A standard toxicology program based on ICH M3(R2) guidelines has been completed for CNM-ZnAg. The toxicity of CNM-ZnAg was evaluated at high concentrations up to the maximum feasible dose administered via oral gavage up to four times daily for 28 days in rats and 7 days in canines. Across all studies, there were no deaths, no test-article-related clinical observations, and no effects on: body weight, food consumption, hematology endpoints, clinical pathology findings, blood coagulation times, urinalysis, or urine chemistry. Standard *in vivo* genotoxicity studies in rodents, including a 2-day COMET assay and a 28-day evaluation of micronucleated reticulocytes, revealed no test-article effects on genotoxicity.

A seven-day human tolerability study of the dietary supplement was previously conducted by an antecedent company to determine the safety and tolerability in 40 healthy human volunteers. There were no self-reported adverse events and laboratory assessments indicated no significant changes from baseline in body weight, blood pressure, heart rate, liver enzymes (AST/ALT), blood glucose, or blood lipids (total cholesterol, LDL/HDL, triglycerides). There were no safety findings associated with administration of the dietary supplement over the 7-day dosing period.

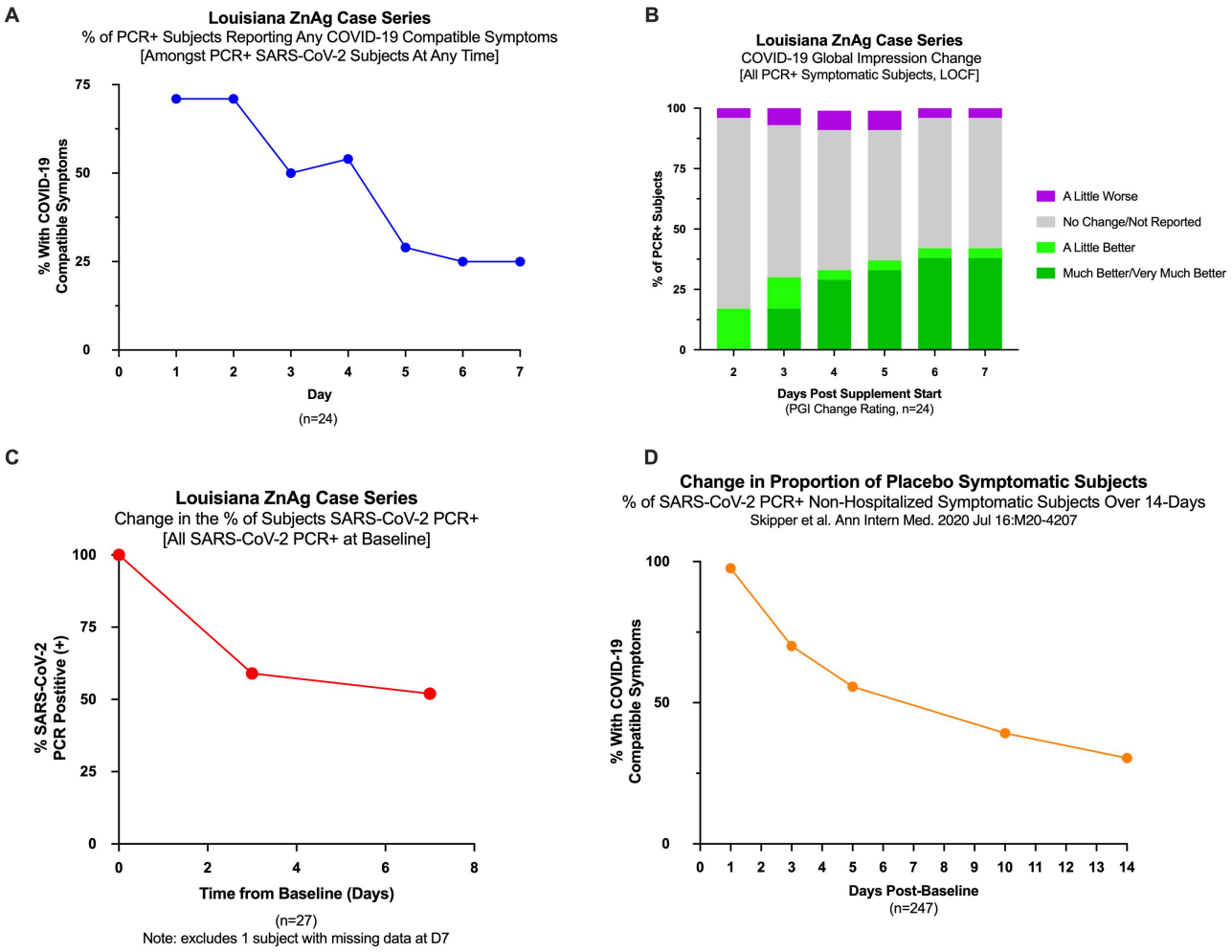
Clinical Development of CNM-ZnAg as a Therapeutic Treatment for COVID-19

COVID-19 is a rapidly emerging respiratory disease, resulting in substantial morbidity and mortality. Severe acute respiratory syndrome coronavirus 2 ("SARS-CoV-2") is the viral infection which causes COVID-19. Symptoms of COVID-19 are highly variable, with most infected individuals presenting with varying degrees of respiratory distress, fever, cough, sore throat, malaise, myalgias, nausea, diarrhea, anosmia, and ageusia. Due to the international infection rates and potentially serious nature of this disease,

COVID-19 was characterized as a pandemic by the World Health Organization on March 11, 2020. Therefore, there is a significant unmet medical need to urgently decrease the morbidity and improve time to recovery in COVID-19 infected individuals.

Because of exigent worldwide need, we determined to rapidly develop CNM-ZnAg as a candidate treatment for COVID-19 based on the hypothesis that CNM-ZnAg may provide immune support benefits. On a limited basis, a dietary supplement version of ZnAg has been provided to support immune health. Preliminary uncontrolled observational case series with the dietary supplement yielded results suggesting oral administration of ZnAg to individuals with PCR-confirmed, COVID-19 infections may improve subject well-being and limit the duration of the disease. Results from a large case-series study of a COVID-19 outbreak in a U.S.-based industrial food processing facility and its associated congregate housing are described below. Sixty-two company employees and managers voluntarily received the ZnAg dietary supplement orally daily (while in quarantine and in congregate housing), completed a standardized daily symptom survey, and underwent repeated SARS-CoV-2 PCR testing prior to ZnAg treatment initiation and again following 7 days of ZnAg supplement intake. The study population was of predominantly Hispanic ethnicity (74%). The mean age was 33.6 (10.8) years, with 84% male. Twenty-seven subjects were identified prior to supplement intake as SARS-CoV-2 positive by PCR testing. Amongst subjects with PCR+ confirmed SARS-CoV-2 at treatment start, 44% transitioned to PCR negative following 7-days of supplement administration (Fig. 11A). Amongst the 35 SARS-CoV-2 PCR negative subjects prior to treatment initiation, 88% remained SARS-CoV-2 negative by repeat PCR testing after 7-days of treatment. Amongst the 27 SARS-CoV-2 positive individuals, 24 reported symptoms consistent with COVID-19, generally self-reported as mild-to-moderate intensity. Symptom resolution (Fig. 11A), and PCR detected viral clearance (Fig. 11C) decreased rapidly following ZnAg treatment initiation consistent with a marked improvement in participants' global impression of change (Fig. 11B). The rate of symptomatic resolution (~75%) by Day 7 appears qualitatively greater than the placebo improvement rate (~50%) from a study completed in a comparable COVID-19 non-hospitalized symptomatic patient population (Fig. 11D, Skipper et al. *Ann Intern Me.* 2020 Jul 16;M20-4207).

Figure 11. PCR Status and Symptomatic Changes in Food Processing Facility Workers Infected with, or Exposed to, COVID-19



Given the potential for a clinical effect together with no identified safety signals from animal toxicology or initial human tolerability studies, we are investigating CNM-ZnAg in a randomized, placebo-controlled clinical trial to determine the efficacy and safety of CNM-ZnAg for symptomatic improvement of COVID-19. This clinical trial is being conducted in Brazil and as of February 2022 is fully enrolled with 276 subjects. Brazil represents a geography with a significant number of COVID-19 cases, robust clinical infrastructure and clinical trial experience, reasonable economic costs, and limited competition for participants for the enrollment of COVID-19 clinical research. The trial is a randomized double-blind placebo-controlled trial of CNM-ZnAg to decrease the incidence of hospitalization (primary endpoint) at Day 28 and improve the time to symptom resolution (secondary endpoint) in PCR confirmed SARS-CoV-19 subjects. The trial will evaluate two different doses of CNM-ZnAg, for which will be combined for analyses versus placebo. Trial results are anticipated in mid-2022.

CNM-AgZn17 for Wound-Healing and Burn Treatment

CNM-AgZn17 consists of an ionic solution of silver and zinc in a polymer gel formulation for topical application to the skin. We have demonstrated in in vitro assays that CNM-AgZn17 has broad-based anti-viral and anti-bacterial activity against common and antibiotic resistant pathogens such as Methicillin-resistant Staphylococcus aureus. We have also shown enhanced wound healing benefits in animal models of diabetic wound healing and less scar formation from during burn healing.

We are presently completing a standard toxicology program in animals to demonstrate safety in order to advance to first-in-human dosing studies. We have progressed to GLP dermal toxicity studies for topical applications expected to complete in 2023. Subject to

regulatory filings of these toxicology findings and other results, we anticipate initiating a standard Phase 1 dermal first-in-human safety study with CNM-AgZn17 with single-ascending dose and multiple-ascending dose cohorts by late 2023. The goal of this study will be to demonstrate safety sufficient to advance to Phase 2 clinical programs with CNM-AgZn17. Given the multiple preclinical benefits demonstrated to date with CNM-AgZn17, we envision a clinical program focused on healing burn and/or surgical wounds, which is anticipated to initiate in 2024.

CNM-PtAu7 — Our Oncology Targeted Nanotherapeutic

CNM-PtAu7 is a suspension of novel nanocrystals comprised of alloyed gold and platinum. We have demonstrated that treatment of human breast cancer cell lines EFM-19 and MT-3 with CNM-PtAu7 induces the expression of pro-apoptotic genes and represses the expression of anti-apoptotic genes, consistent with an anti-oncogenic effect. We have further demonstrated down-regulation of genes associated with the electron transport chain activity, which may also suppress tumorigenic activity. Further investigations related to the anti-tumor effects of CNM-PtAu7 are planned in additional malignant cell lines. CNM-PtAu7 has been patented in all major markets worldwide including the U.S., Europe, China, Singapore, and Japan.

Research and Development

Overview

We are deeply invested in our research and development program. Our research and development activities are essential to attaining and sustaining the position as a recognized global leader in the development of CSN® therapeutics. Our research and development plan is to continue the innovation of novel catalytically-active nanocrystals and ionic suspensions of metallic transition elements with recognized medicinal value and underexplored, or as yet undiscovered, physicochemical and catalytic properties.

We have developed in-house all of the technologies that are critical to our research and development processes, and guard those technologies with appropriate intellectual property protections, and will continue to do so. We conduct our research activities through an in-house research and development team at our facility in Maryland, and engage in external clinical research collaborations to support our research and development activities as well.

Internal Research and Development

Our internal, or in-house research and development activities are executed by a group of experienced research scientists, materials scientists, engineers, molecular biologists, medical doctors, clinical trial operational specialists, and a management team with deep expertise in the biopharmaceutical industry. Our in-house research and development team has a full range of capabilities ranging from drug discovery to preclinical development to and the design and implementation of clinical trials. We believe our in-house research and development team is experienced, qualified, and will enable us to achieve our long-term goal of developing and commercializing innovative CSN® therapeutics for patients worldwide. Our in-house research and development team operates functionally through four sub-teams: (1) research engineering team, (2) biological science discovery team, (3) nonclinical development team, and (4) clinical development team, which work collaboratively to ensure the success of our research and development efforts.

Our research engineering team is responsible for the development and optimization of new CSN® therapeutic candidates along with developing the technical processes and infrastructure to ensure reproducible chemistry, manufacturing, and controls (“CMC”) batch production of our CSN® therapeutic candidates. Members of our research engineering team have PhDs and/or master’s degrees in chemistry, material science and engineering, electrical engineering, and solid-state physics. Our research engineering team leader has a degree in electrical engineering and has been instrumental in the design of our electro-crystal-chemistry platform including the various continuous flows through apparatuses we use to produce our CSN® therapeutics.

Our biological science discovery team is responsible for the initial characterization of CSN® therapeutics, conducting biological assays, and assessing the activity and toxicity of drug candidates through in vitro and in vivo assays. Our biological discovery team assesses the CSN® therapeutic candidates once initial development has been completed by our research engineering team. This team is led by an experienced research scientist who is a medical doctor and has a PhD in molecular science. Our biological discovery team collaborates closely with our research engineering team to refine our CSN® candidate selection, for instance based on structural characteristics, in order to optimize the biological effects of our CSN® candidate therapeutics.

Our nonclinical development team is responsible for developing a complete dataset of nonclinical animal pharmacology, toxicology, and safety studies, which is sufficient to support regulatory filings with human research ethics committees (“HRECs”) and government regulatory authorities in order to obtain approval for use in human studies. Our nonclinical development team works collaboratively with our biological science discovery team and clinical development team to translate our findings into animals and prepare for eventual studies in patients. This team also leads our external collaboration research activities with universities and academic

experts. Our nonclinical development team is led by a research scientist with a PhD in Developmental Biology from Stanford University and a Master of Science degree in Genetics from the University of Cambridge where she was a Marshall Scholar. She is also an adjunct faculty member of the University of Utah School of Medicine.

Our clinical development team is led by our Chief Medical Officer, who is a board-certified neurologist and Fellow of the American Academy of Neurology. Once our CSN® therapeutic candidates have demonstrated sufficient safety and toxicology results to advance to human studies, the clinical development team designs, implements, and oversees the operational conduct of our clinical trials. The clinical trials are designed to prove our CSN® therapeutics are safe and effective in the treatment of diseases.

Outsourced Research and Development

In line with industry practice, we also outsource certain research and development to key academic partners, nonclinical research organizations, and to third-party CROs. We have collaborated with experts at key academic universities which have myelination and neuroprotection expertise. These university collaborators have conducted animal experiments to demonstrate the effects of CNM-Au8® treatment on remyelination and neuroprotection in animals and in cell-based in vitro assays. To support our research efforts, we have partnered with academic experts at The Johns Hopkins University in ALS, Cambridge University for myelination-related experiments, Northwestern University for myelination-related experiments, the George Washington University for myelination-related experiments, and the University of Edinburgh for myelination-related research. In general, we outsource the majority of toxicology, pharmacology, and toxicokinetic studies to expert nonclinical CROs.

To provide maximum flexibility and efficiency to operations, we engage industry-leading CROs to manage, conduct and support our clinical trials and to supplement our internal research and development capabilities. We apply a rigorous process to selecting CROs to conduct research studies for us; selection is based on the quality, reputation, and research experience in the field of central nervous system disorders. In addition to the scope, depth and quality of the service and product offerings of the CROs, for clinical trial management, we place emphasis on the ability of the CROs to facilitate optimal site selection, to recruit patients in a timely manner, and to conduct complex clinical trials efficiently. Our CROs are widely recognized within their functional areas of research.

We enter into separate agreements with CROs and our external partners for each clinical trial or nonclinical research project. All CROs and other external research collaborators were all independent third parties. Principal terms of the service agreements with our key CROs and external partners are summarized as follows:

- *Services.* The CRO, nonclinical research organization, or academic site implements and manages the study in accordance with the protocol designed by us as specified in the service agreement.
- *Term.* The CRO, nonclinical research organization, or academic site is required to support the clinical trial or nonclinical studies within the prescribed time limit until the end of the clinical trial.
- *Payments.* We are required to make payments to our partners in accordance with the payment schedule agreed by the parties.
- *Intellectual property rights.* We own intellectual property rights arising from the research activities related to our background intellectual property.
- *Risk allocation.* Each party indemnifies the other party for losses caused by its fault or gross negligence. We indemnify the CRO and external partners for theoretical risks related to CNM-Au8®.

We monitor and evaluate our CROs and external research partners with various activities including site visits, ongoing project team reviews, and/or assessments by third-party assessors. We strive to achieve clinical trial excellence by maintaining strong quality control measures. We perform core functions such as clinical development strategy formulation and protocol design in-house, and exercise control and oversight over key functions of clinical trial management. We conduct regular site visits to oversee site initiation, patient recruitment, and data quality monitoring, except when precluded by COVID-19 related research restrictions. We also engage third-party consultants to perform clinical trial audits. Data quality is further assessed by in-house data review, including medical review, document review, and monitoring report review. We will not work with a vendor who does not have processes established surrounding data privacy and safeguards to ensure compliance through the clinical trial. We have maintained a stable relationship with our CROs and other external research partners.

Clinical Trial Management

To support our clinical trials, our internal clinical trials team designs, implements, collects and analyzes data for our clinical trials. When additional services are required to support a clinical trial, we conduct a feasibility and qualification assessment for potential vendors and CROs. These vendors are vetted through review of their current operational structure and established procedures,

knowledge, and experience about the study, indication, or population, and past feedback from participating clinical sites. Our internal clinical development team supervises CROs on key clinical activities, such as patient eligibility review, medical data review, and SAE review, to ensure that the performance of these CROs complies with our protocols and applicable laws, which in turn protects the integrity and authenticity of the data from our clinical trials. Our internal clinical development team holds meetings with CROs to evaluate the CRO's performance by following up on clinical progress and resolving potential issues and risks.

Financial Grants

We have been awarded grants from various organizations, including the National Multiple Sclerosis Society, FightMND, a not-for-profit registered charity in Australia, and the Michael J. Fox Foundation, who together have issued us grants totaling approximately $2.3 million. We also receive indirect financial support for the Healey ALS Platform Trial, administered by Massachusetts General Hospital, which is conducting a platform trial of CNM-Au8® alongside other drugs at significantly lower costs than we would otherwise incur if we were to conduct a comparably designed study at reasonable market rates.

These grants include the following terms:

- *National Multiple Sclerosis Society*—a grant of $0.4 million was awarded to us in September 2019. The grant provides for biomarker analyses of the VISIONARY-MS clinical trial, and includes terms related to repayment of funds received in the event of commercialization of CNM-Au8® for the treatment of MS based on achievement of sales milestones up to a mid-single-digit multiplier of the original grant amount. Milestone funding is based on the achievement of analytical validation and reporting to the National Multiple Sclerosis Society. We will own all intellectual property rights from grant related activities.
- *FightMND*—a grant of AUD1.4 million was awarded to us in August 2019. The grant includes terms related to repayment of funds received in the event of commercialization of CNM-Au8® for the treatment of ALS in Australia from future net sales proceeds up to a mid-single-digit multiplier of the original grant amount. Milestone funding is based on patient enrollment targets. We will own all intellectual property rights from grant related activities.
- *The Michael J. Fox Foundation*—a grant of $0.5 million was awarded to us in January 2021. The grant provides for preclinical research for an *in vivo* rodent model with CNM-Au8® treatment in well characterized alpha-synuclein over-expression, and additional research in iPSC-derived neurons with commonly recognized Parkinson's genetic defects. Funding is milestone based. We will own all intellectual property rights from grant related activities.

In December 2019, we were awarded a grant from the U.S. Congressionally Directed Medical Research Program administered by the Department of Defense for $1.3 million, which we determined not to accept. We communicated our decision to the Department of Defense and the grant was terminated effective July 19, 2021. The grant was not recognized in the financial statements of any period and there was no impact to our financial position, results of operations, or cash flows for any period.

Manufacturing

We manufacture CSN® therapeutics at our own production facility based in North East, Maryland, USA (the "North East Facility"), based on novel manufacturing processes and devices that were entirely invented by us. The North East Facility is compliant with GMP where we operate an ISO8 level clean room that contains the specialized electro-crystal-chemistry devices, or continuous flow trough apparatuses, that we have invented and patented to produce our CSN® therapeutics from highly pure raw materials. At our present operating scale, we produce in-process gold nanocrystal suspension, the active pharmaceutical ingredient ("API") for our lead asset, CNM-Au8®, on an ongoing basis. We believe our current API production capabilities are fully sufficient to meet our needs for both research and development and supply for our ongoing Phase 2 and Phase 2/3 clinical trials, and we believe our processes can be scaled to achieve early commercially viable quantities.

We entered a lease commencing in September 2021 for a 74,210 square foot production facility in Elkton, Maryland, USA (the "Elkton Facility"), a few miles north of the North East Facility. The Elkton Facility is being redeveloped to support our unique manufacturing needs and will enable us to materially increase our manufacturing capacity preparatory to the expected data release in the second half of 2022 from the Phase 2/3 Healey ALS Platform Trial evaluating CNM-Au8® as a treatment for ALS. We also entered a lease commencing in February 2022 to expand our North East Facility to from approximately 21,000 square feet to 32,603 square feet to further increase our manufacturing capacity. We believe our technical expertise and capabilities are fully sufficient to expand capacity to support contemplated growth and anticipated commercialization. We also have developed a phased plan to significantly scale our production processes and capabilities as demand for our products increases to supply commercial marketing needs. We believe our current production environment has established us as the leading world-class manufacturer of CSN® therapeutics, and following the completion of our planned expansion, our facilities, equipment, and processes will comply with international practices and support our long-term strategic plans, taking into consideration quality, costs, manageability, expandability and controls.

Through years of intensive research and development we have fine-tuned our production and delivery processes to the point where we can consistently, reliably, and affordably produce our core drug candidates, including CNM-Au8®. We have also invested considerable time and substantial resources in perfecting the handling and storage systems in a manner that maintains stability and efficacy of our nanocrystal suspensions. In general, the manufacturing process for CSN® therapeutics involves the following steps:

- Sufficient quantities of processing enhancers (e.g., sodium bicarbonate, others) are dissolved in highly purified water. The resulting mixture is referred to as "process water."
- The process water is transferred to the conditioning portion of the trough apparatus at a constant nominal rate, where the process water is exposed to an atmospheric plasma in each trough apparatus, creating "conditioned water."
- The conditioned water then flows into the electrochemical crystal growth portion of the trough apparatus, at a constant rate, where the conditioned water is exposed to a series of pairs of wire electrodes. The flow of the conditioned water is controlled, and the electrodes are continuously monitored and controlled by computerized, automated controllers.
- The electrodes are slowly advanced at a nominal rate to ensure that the conditioned water is exposed to the same electrochemical processing conditions to ensure batch-to-batch reproducibility, thus maintaining consistent size and shapes of the nanocrystals in each nanocrystal suspension.
- In-process bulk product, API, containing elemental nanocrystals, is continuously produced. The in-process bulk product is collected into large containers.
- The nominal concentration of active drug ingredients is achieved by executing a concentration step where in-process API is treated by a proprietary concentration procedure.
- The concentrated product is verified to adhere to physiochemical release specifications.
- The concentrated bulk suspension is subsequently filtered during filling to remove any microbiological contaminants and volumetrically filled into single unit containers. The final drug candidate is assayed to ensure it meets release specifications.

License Arrangements

In 2018, we established a license agreement and an exclusive supply agreement with 4Life, an international supplier of health supplements and one of our stockholders.

Under this license agreement, we granted to 4Life an exclusive and royalty-bearing license in relation to products that are very low concentration silver, gold, and other similar very low-concentration non-pharmaceutical supplement products produced by our electro-crystal-chemistry technology platform. This exclusive license does not include ZnAg, for which 4Life has a non-exclusive right. 4Life is allowed to develop, make, manufacture, use, sell and commercialize the licensed products worldwide within the field of dietary supplements and certain non-pharmaceutical products for human use, internally or externally, which contain metallic-based constituents that are formed by our electrochemistry manufacturing techniques. 4Life will use its reasonably diligent commercial efforts to introduce the products to certain commercial markets following regulatory approval for their sale as nutritional mineral supplements. The initial term of this license agreement commenced on August 31, 2018 and will continue until five years after 4Life's introduction of the first nutritional supplement licensed product into the marketplace, which occurred on July 1, 2020. The license agreement may be renewed for additional five year periods by mutual agreement. Upon expiration of the license agreement the exclusive provisions in the agreement will convert to non-exclusive. The license agreement may only terminate by mutual agreement between the parties, or upon breach by either party that results in termination of the agreement under applicable law.

Under an exclusive supply agreement, 4Life will purchase the licensed products exclusively from us and we will sell the licensed products exclusively through 4Life, except for ZnAg which is not exclusively sold through 4Life. Upon the occurrence of certain future events, 4Life can achieve the right to exclusively manufacture the licensed products under the license agreement, other than ZnAg for which this right does not apply. The initial term of the exclusive supply agreement commenced on August 31, 2018 and will continue until five years after the minimum sales commencement date, which both parties have agreed was in April 2021. The exclusive supply agreement may be renewed for additional five year periods by mutual agreement. 4Life may terminate the exclusive supply agreement for cause, which is stated to include repudiation, uncured material breach, insolvency, bankruptcy, general assignment for benefit of creditors, failure to provide reasonable assurances of financial and operational capacity, prolonged unremedied force majeure, and failure to proper notify of change in control. We may terminate the exclusive supply agreement in the event of a repudiation, uncured material breach, insolvency, bankruptcy or general assignment for benefit of creditors by 4Life.

At the time of commercial sales, single-digit royalty payments are owed to us by 4Life based on the size of 4Life's basket of total product sales. Royalties are payable quarterly under the license agreement until termination of the license agreement. In addition, 4Life

will pay us our fully encumbered manufacturing expenses plus a guaranteed double-digit margin. We began supplying KHC46 (Gold Factor™) and a low dose zinc-silver solution (Zinc Factor™) during the first half of 2020 under this license agreement.

To date, we have not licensed our electro-crystal-chemistry platform, any CSN® therapeutics or any drug candidates to any other parties.

Sources and Availability of Raw Materials

Certain critical raw materials are available from a limited number of suppliers in the market. See "*Risk Factors - Our business depends on the use of raw materials, and a decrease in the supply or an increase in the cost of these raw materials or any quality issues in such raw materials could materially and adversely affect our business, financial condition, results of operations and prospects*" for further information.

Competition

While the treatment for central nervous system diseases is quite competitive and subject to frequent changes, there are currently no existing FDA-approved therapies that have mechanisms supporting remyelination and neuroprotection in patients. CNM-Au8®'s core effects of remyelination and neuroprotection provide us a globally unique first-mover-advantage for the treatment of central nervous system diseases. Together with our expanded intellectual property portfolio, we believe that it would be challenging for any potential competitors entering into the market of remyelination and neuroprotection focused therapeutics to replicate our efforts without violating our intellectual property protections.

Intellectual Property

Our intellectual property is protected through extensive global patents, institutional expertise and experience, and specialized technical know-how, which enable us to maintain our leading position in the development of CSN® therapeutics for high-medical need diseases.

As of December 31, 2021, we have over 150 issued patents worldwide and approximately 20 patents pending worldwide. We have world-wide rights to protect and thus commercialize our CSN® therapeutics and believe that our issued, and pending patents, provide sufficient protection to secure the future commercial potential of our CSN® therapeutics.

We have filed and obtained patents in the United States (U.S.); Australia (AU); Brazil (BR); Canada (CA); China (CN); European Patent Office (EP), including Belgium (BE), Switzerland (CH), Germany (DE), Denmark (DK), Finland (FI), France (FR), Great Britain (GB), Iceland (IS), Ireland (IE), Italy (IT), Hungary (HU), Netherlands (NL), Norway (NO), Poland (PL), Portugal (PT), Spain (ES), Sweden (SE), Slovenia (SI), and Turkey (TR); Egypt (EG); India (IN); Indonesia (ID); Israel (IL); Japan (JP); Korea (KR); Mexico (MX); New Zealand (NZ); Philippines (PH); Russia (RU); Seychelles (SC), Singapore (SG); and the United Arab Emirates (AE); with multiple fundamental patent families protecting our CSN® therapeutics. The following table lists the material granted patent families in connection with our CSN® therapeutics.

Description	Jurisdiction	Application Date (U.S.)	Grant Date (U.S.)
Continuous methods for treating liquids and manufacturing certain constituents (e.g., nanoparticles) in liquids, apparatuses and nanoparticles and nanoparticle/liquid solution(s) resulting therefrom (these patents relate to CNM-Au8® and ZnAg)	*Issued:* U.S. (4), AU (3), CA (2), CN, ID, IL, IN, JP (2), KR, MX, PH; BE, DK, ES, FI, FR, DE, HU, IE, IT, NL, NO, PL, PT, SE, SI, SC, CH, TR, GB *Granted:* *Pending:* U.S., EP	July 11, 2007	December 31, 2013 August 29, 2017 October 9, 2018 September 24, 2013 July 12, 2016 Expiration dates for these patents will occur in 2028 in the applicable foreign jurisdictions and in 2030 in the U.S.*

Continuous methods for treating liquids and manufacturing certain constituents (e.g., nanoparticles) in liquids, apparatuses and nanoparticles and nanoparticle/ liquid solution(s) therefrom	*Issued:* U.S. (3) *Pending:* U.S.	January 14, 2009	September 24, 2013 July 12, 2016 October 15, 2019
Continuous, semi-continuous and batch methods for treating liquids and manufacturing certain constituents (e.g., nanoparticles) in liquids, apparatuses and nanoparticles and nanoparticle/liquid solution(s) and colloids resulting therefrom (these patents relate to CNM-Au8® and ZnAg)	*Issued:* U.S. (3), AU, CA, CN, IN, IS, JP, KR; CH, DE, DK, FI, FR, IE, NL, NO, SE, GB *Allowed:* *Pending:* EP	January 15, 2009	June 30, 2015 July 31, 2018 May 18, 2021 Expiration dates for these patents will occur in 2030 in the U.S. and the applicable foreign jurisdictions*
Novel gold-based nanocrystals for medical treatments and electrochemical manufacturing processes therefor (these patents relate to CNM-Au8®)	*Issued:* U.S. (3), AE, AU (4), BR, CA, CN, ID, IN, IL, JP (4), KR (3), MX, PH, RU, SG (2); CH, DE, DK, ES, FI, FR, GB, IE, IT, NL, NO, SE *Allowed:* AE *Pending:* AU, MX, PH, SG, U.S. (2)	July 8, 2009	March 28, 2017 October 22, 2019 April 20, 2021 Expiration dates for these patents will occur in 2030 in the U.S. and the applicable foreign jurisdictions*
Novel gold-platinum based bi-metallic nanocrystal suspensions, electrochemical manufacturing processes therefor and uses for the same (these patents do not relate to any specifically named product candidates herein)	*Issued:* U.S., AE, AU, CA, CN, ID, IL, IN, JP, KR (2), MX, NZ, PH, RU, SG; CH, DE, DK, ES, FI, FR, GB, IE, IT, NL, NO, SE. *Pending:* BR, U.S.	March 30, 2011	July 12, 2016 Expiration dates for these patents will occur in 2030 in the U.S. and in 2032 in the applicable foreign jurisdictions*
Methods and treatment for certain demyelination and dysmyelination-based disorders and/or promoting remyelination (these patents relate to CNM-Au8®)	*Issued:* AU, ID, IL, JP, MX, NZ (2), PH, RU, SG (2); BE, DK, FI, FR, DE, HU, IE, IT, NL, NO, PT, SE, SI, CH, TR, GB *Granted:* *Allowed:* KR *Pending:* BR, CA, CN, IN, JP	NA	NA Expiration dates for these patents will occur in 2033 in the U.S. and the applicable foreign jurisdictions*

* Expiration dates do not include possible patent extensions for certain countries.

To date, we have not been involved in any proceedings in respect of, and we have not received notice of any claims of infringement of, any intellectual property rights that may be threatened or pending, in which we may be a claimant or a respondent.

Government Regulation

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling,

packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring, and post-approval reporting of drugs such as those we are developing. We, along with third-party contractors, are required to comply with the various preclinical, clinical, and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of CNM-Au8® or any future drug candidate.

FDA Drug Approval Process

In the U.S., the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act and implementing regulations and guidance. The process required by the FDA before drug candidates may be marketed in the U.S. generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's current Good Laboratory Practices regulations;
- submission to the FDA of an IND application, which must become effective before clinical trials may begin and must be updated annually or when significant changes are made;
- approval by an independent review board whose role is to review the research before the trial is commenced and continuously throughout the trial to assure the protection of the rights and welfare of the human subjects. These boards are often called "institutional review boards" ("IRBs");
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug candidate for its intended purpose;
- preparation of and submission to the FDA of an NDA after completion of all pivotal clinical trials that includes substantial evidence of safety and efficacy from results of nonclinical testing and clinical trials;
- a determination by the FDA within 60 days of its receipt of an NDA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with GMP and to assure that the facilities, methods, and controls are adequate to preserve the drug candidate's continued safety, purity and potency, and of selected clinical investigation sites to assess compliance with Good Clinical Practices ("GCP");
- satisfactory completion of an FDA Advisory Committee review, if applicable; and
- FDA review and approval of the NDA to permit commercial marketing of the product for particular indications for use in the U.S.

Preclinical and Clinical Development

Prior to beginning the first clinical trial with a drug candidate in the U.S., we must submit an IND application to the FDA. An IND application is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is the general investigational plan and the protocol(s) for clinical trials. The IND also includes results of animal and *in vitro* studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamic characteristics of the drug candidate; CMC information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises safety concerns or other questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold until the IND sponsor and the FDA resolve the outstanding concerns or questions. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCP and regulations governing the protection of human research subjects, including the requirement that all research subjects provide voluntary informed consent for their participation in any clinical trial. Clinical trials are conducted under clinical trial protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. For new indications, a separate new IND may be required. An IRB must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins and must monitor the trial until completed. Often each institution or clinical site has its own IRB. The IRB is responsible for ensuring that human subjects' rights and privacy are maintained. Regulatory authorities, the IRB, or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by a DSMB, an independent group of qualified experts organized by the clinical trial sponsor, which provides authorization for whether or not a clinical trial may move forward at designated check points based on access to certain data from the trial. The DSMB may halt the clinical trial if it determines that there is an

unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical trials and clinical trial results to public registries. For purposes of NDA approval, human clinical trials are typically conducted in three sequential phases (which may overlap or be combined):

- *Phase 1*—The investigational product is initially introduced into a small number of healthy human subjects or patients with the target disease or condition. These studies are generally designed to test the safety, dosage tolerance, absorption, metabolism, distribution, and elimination of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.
- *Phase 2*—The investigational product is administered to a larger, but still limited patient population with a specified disease or condition to evaluate the preliminary efficacy (usually based on a biomarker of disease), optimal dosages, and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger, confirmatory Phase 3 clinical trials.
- *Phase 3*—The investigational product is administered to an expanded patient population to provide statistically significant evidence of relevant clinical efficacy and to further test for safety, and potentially further evaluate different dosages, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval by health authorities.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These studies, termed Phase 4 studies, may be implemented as a condition of approval of the NDA. Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the drug candidate, and must finalize a process for manufacturing the product in commercial quantities in accordance with current GMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

Drug companies such as us are subject to legal requirements restricting, or imposing penalties for, the employment or use of individuals who have been debarred or excluded under various laws, including the provisions of 21 U.S.C. Section 335a, 335b, or 335c, 42 U.S.C. Section 1320a-7, in connection with making materially false or fraudulent statements to FDA, the offering or making of any prohibited payment, gratuity or other thing of value to personnel of the FDA or any other governmental entity, or other acts, statements, or omissions subject to FDA's policy titled "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities" set forth in 56 Fed. Reg. 46191 (September 10, 1991), Employment of such individuals, or the occurrence of such violations in the development and regulatory application process may prevent or delay any approval of an NDA.

NDA Submission, Review and Approval

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of nonclinical studies and clinical trials are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. The NDA must include all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's CMC, and proposed labeling, among other things. The submission of an NDA requires payment of a substantial application user fee to FDA (unless a waiver or exemption applies).

Once an NDA has been submitted, the FDA's goal is to review standard applications within ten months after it accepts the application for filing (a 60-day process), or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process can be significantly extended by FDA requests for additional information or clarification. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective and the facility in which it is manufactured, processed, packaged, or held meets standards designed to assure the product's continued safety and efficacy. The FDA may convene an advisory committee to provide clinical insight on application review questions. Before approving an NDA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with GMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs. If the FDA determines that the application, manufacturing processes, or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates an NDA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response Letter will describe all of the deficiencies that the FDA has identified in the NDA, except that, where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the Complete Response Letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the Complete Response Letter, the FDA may recommend actions that the applicant might undertake to resolve any findings and place the NDA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of an NDA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-market testing and surveillance to monitor safety or efficacy of a product.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the NDA with a Risk Evaluation and Mitigation Strategy ("REMS"), to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a product and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-market requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-market studies.

Expedited Development and Review Programs

A marketing application for a drug candidate submitted to the FDA for approval may be eligible for FDA programs intended to expedite the FDA review and approval process, such as priority review, fast track designation, breakthrough therapy, and accelerated approval.

A product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or to provide a significant improvement in the treatment, diagnosis or prevention of a serious disease or condition compared to marketed products. For products containing new molecular entities, priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date (compared with ten months under standard review).

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need by providing a therapy where none exists or a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. Fast track designation provides opportunities for more-frequent interactions with the FDA review team to expedite development and review of the product. The FDA may also review sections of the NDA for a fast track product on a rolling basis before the complete application is submitted, if the sponsor and FDA agree on a schedule for the submission of the application sections, and the sponsor pays any required user fees upon submission of the first section of the NDA. The review clock does not begin until the final section of the NDA is submitted.

In addition, under the provisions of the FDA Safety and Innovation Act enacted in July 2012, a sponsor can request designation of a drug candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Additionally, products studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-market clinical trials to verify and describe the anticipated

effect on irreversible morbidity or mortality or other clinical benefit. As a condition for accelerated approval, the FDA also currently requires pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of a product.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review and approval will not be shortened. Furthermore, priority review, fast track designation, breakthrough therapy designation, and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the U.S., or more than 200,000 individuals in the U.S. for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for this type of disease or condition will be recovered from sales in the U.S. for that drug. Orphan designation must be requested before submitting an NDA. After the FDA grants orphan designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. The orphan drug designation in and of itself does not convey any advantage in, or automatically shorten the duration of, the regulatory review or approval process. However, a drug granted orphan status allows the sponsor to receive tax credits and a user fee waiver.

If a product that has orphan designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full NDA, to market the same product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. Orphan drug exclusivity does not prevent FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. A designated orphan product may not receive orphan exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, exclusive marketing rights in the U.S. may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Post-Approval Requirements

Any products manufactured or distributed by us pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to quality control and quality assurance, record-keeping, reporting of adverse events, periodic reporting, product sampling, and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to FDA review and approval. There also are continuing user fee requirements, under which FDA assesses an annual program fee for each product identified in an approved NDA. Manufacturers and their subcontractors are required to register their establishments and list the drugs they manufacture with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with GMPs, which impose certain procedural and documentation requirements upon us. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from GMPs and impose reporting requirements upon us and any third-party manufacturers or packagers that it may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain compliance with GMP and other aspects of regulatory compliance.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of a product, mandated modification of promotional materials or issuance of corrective information, issuance by FDA or other regulatory authorities of safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product, or complete withdrawal of the product from the market or product recalls;
- fines, warning or untitled letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of existing product approvals;

- product seizure or detention, or refusal of the FDA to permit the import or export of products; or
- injunctions, consent decrees or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of drugs and biologics. A company can make only those claims relating to safety, efficacy, and conditions of use of the drug that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising, and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

Other U.S. Healthcare Laws and Compliance Requirements

In the U.S., our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare & Medicaid Services ("CMS"), which is part of the U.S. Department of Health and Human Services ("HHS"), as well as other divisions of HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice ("DOJ") and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs have to comply with the anti-fraud and abuse provisions of the Social Security Act (such as the Anti-Kickback Statute), the False Claims Act, the anti-fraud provisions of and the privacy and security provisions of regulations implementing the Health Insurance Portability and Accountability Act ("HIPAA"), the Drug Supply Chain Security Act ("DSCSA"), and similar state laws, each as amended, as applicable. Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patients, and customers may be subject to healthcare laws, regulations and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which we conduct our business. Such laws govern, without limitation, state and federal anti-kickback, fraud and abuse, patient brokering, false claims, privacy and security, price reporting, drug distribution, and physician sunshine laws. Some of our pre-commercial activities are subject to some of these laws.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity, from knowingly and willfully offering, paying, soliciting or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any item or service reimbursable, in whole or in part, under Medicare, Medicaid, or other federal healthcare programs. The term remuneration has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between therapeutic product manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting certain activities from prosecution. The exceptions and safe harbors are drawn narrowly and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchasing, or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor.

Additionally, the intent standard under the Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the "Affordable Care Act") to a stricter standard such provides that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Violations of the Anti-Kickback Statute can result in significant civil and criminal fines and penalties, imprisonment, and exclusion from federal healthcare programs. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act (discussed below). In addition, several states have similar state-level anti-kickback statutes.

The federal false claims and civil monetary penalty laws, including the False Claims Act, which imposes significant penalties and can be enforced by private citizens through civil qui tam actions, prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government, including federal healthcare programs, such as Medicare and Medicaid, knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. For instance, historically, pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal

programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved, off-label, and thus generally non-reimbursable, uses. Penalties for federal civil False Claims Act violations may include up to three times the actual damages sustained by the government, plus significant mandatory civil penalties, and exclusion from participation in federal healthcare programs.

HIPAA created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations or promises, any money or property owned by, or under the control or custody of, any healthcare benefit program, including private third-party payors, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up by trick, scheme or device, a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Like the Anti-Kickback Statute, the intent standard for certain healthcare fraud statutes under HIPAA does not require actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

We may be subject to data privacy and security regulations by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act ("HITECH"), and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to business associates, which are independent contractors or agents of covered entities that create, receive, maintain, or transmit protected health information in connection with providing a service on behalf of, to or for a covered entity as well as their covered subcontractors. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, many state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways, are often not pre-empted by HIPAA, and may have a more prohibitive effect than HIPAA, thus complicating compliance efforts.

Additionally, the federal Physician Payments Sunshine Act, and its implementing regulations, require that certain manufacturers of drugs, devices, biological and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) report annually to CMS information related to certain payments or other transfers of value made or distributed to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, or to entities or individuals at the request of, or designated on behalf of, the physicians and teaching hospitals and to report annually certain ownership and investment interests held by physicians and their immediate family members. Failure to report accurately could result in penalties. Beginning in 2022, applicable manufacturers also will be required to report such information regarding its payments and other transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives during the previous year. In addition, many states have similar statutes or regulations to the above federal laws that may be broader in scope and may apply regardless of payor. We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, and/or state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, drug pricing or marketing expenditures. These laws may differ from each other in significant ways further complicating compliance efforts. Additionally, to the extent that we have business operations in foreign countries or sell any of our products in foreign countries and jurisdictions, including Canada or the E.U., we may be subject to additional regulation.

We may someday develop products that, once approved, may be administered by a physician. Under currently applicable U.S. law, certain products not usually self-administered (including injectable drugs) may be eligible for coverage under Medicare through Medicare Part B. Medicare Part B is part of original Medicare, the federal healthcare program that provides healthcare benefits to the aged and disabled, and covers outpatient services and supplies, including certain biopharmaceutical products, which are medically necessary to treat a beneficiary's health condition. As a condition of receiving Medicare Part B reimbursement for a manufacturer's eligible drugs, the manufacturer is required to participate in other government healthcare programs, including the Medicaid Drug Rebate Program and the 340B Drug Pricing Program. The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of HHS as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. Under the 340B Drug Pricing Program, the manufacturer must extend discounts to entities that participate in the program.

In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. It is difficult to predict how Medicare coverage and reimbursement policies will be applied to our products in the future

and coverage and reimbursement under different federal healthcare programs are not always consistent. Medicare reimbursement rates may also reflect budgetary constraints placed on the Medicare program.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of drug products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. The federal government as well as some states also impose requirements on manufacturers and distributors to maintain records regarding the history of products in the chain of distribution. Federal law requires manufacturers to provide product tracing information to subsequent supply chain partners. The DSCSA governs the system of tracing certain prescription drugs as they are distributed in the U.S. A goal of the DSCSA is to protect consumers from drugs that may be counterfeit, contaminated, stolen, or adulterated. The law requires manufacturers to, prior to or at the time of each transfer of ownership of a drug, provide the subsequent owner with transaction history, transaction information, and a transaction statement. In the event of a recall or an inquiry regarding a potentially illegitimate product, manufacturers must be able to provide information regarding the transaction history and transaction information of their products. Violations of the DSCSA may result in fines or imprisonment. In addition, many states regulate manufacturers and enforce recordkeeping and licensure requirements.

Several states have enacted legislation requiring pharmaceutical and biotechnology companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical and biotechnology companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Ensuring business arrangements with third parties comply with applicable healthcare laws and regulations is a costly endeavor. If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other current or future governmental regulations that apply to us, we may be subject to penalties, including without limitation, civil, criminal and/or administrative significant penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private “qui tam” actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug candidates for which we may obtain regulatory approval. In the U.S. and in foreign markets, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products. In the U.S., third-party payors include federal and state healthcare programs, private managed care providers, health insurers and other organizations. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid in the U.S., and commercial payors are critical to new product acceptance.

Our ability to commercialize any products successfully also will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors, which decide which therapeutics they will pay for and establish reimbursement levels. Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor’s determination that use of a therapeutic is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

We cannot be sure that coverage or reimbursement will be available for any product that we commercialize and, if coverage and reimbursement are available, what the level of reimbursement will be. Coverage may also be more limited than the purposes for which the product is approved by the FDA or comparable foreign regulatory authorities. Reimbursement may impact the demand for, or the price of, any product for which we obtain regulatory approval.

Third-party payors are increasingly challenging the price, examining the medical necessity, and reviewing the cost-effectiveness, of medical products, therapies and services, in addition to questioning their safety and efficacy. Obtaining reimbursement for our products may be particularly difficult because of the higher prices often associated with branded drugs and drugs administered under the supervision of a physician. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Our drug candidates may not be considered medically necessary or cost-effective by payors. Obtaining coverage and reimbursement approval of a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical and cost-effectiveness data for the use of our product on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on its investment in product development. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize any drug candidate that we successfully develop.

Different pricing and reimbursement schemes exist in other countries. For example, in the E.U., governments influence the price of biopharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular drug candidate to currently available therapies. Other member states allow companies to establish their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any drug candidates for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. In addition, political and economic pressures as well as legislative changes in the U.S. have increased, and we expect will continue to increase, the pressure on drug pricing. The downward pressure on the rise in healthcare costs in general, particularly prescription medicines, medical devices and surgical procedures and other treatments, has become very intense. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Healthcare Reform

In the U.S. and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of drug candidates, restrict or regulate post-approval activities, and affect the ability to profitably sell drug candidates for which marketing approval is obtained. Among policy makers and payors in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been legal and political challenges to certain aspects of the Affordable Care Act. For example, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the Affordable Care Act will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Affordable Care Act. It is possible that the Affordable Care Act will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the Affordable Care Act and our business.

Further legislation or regulation could be passed that could harm our business, financial condition and results of operations. Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. For example, in August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect beginning on April 1, 2013 and will stay in effect through 2030 unless additional Congressional action is taken. However, COVID-19 relief legislation suspended the 2% Medicare sequester from May 1,

2020 through December 31, 2021. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024.

Additionally, there has been increasing legislative and enforcement interest in the U.S. with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Additionally, based on a recent executive order, the Biden administration expressed its intent to pursue certain policy initiatives to reduce drug prices. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. In addition, Congress is considering drug pricing as part of the budget reconciliation process.. Individual states in the U.S. have also become increasingly active in passing legislation and implementing regulations designed to control biopharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The Foreign Corrupt Practices Act also obligates companies whose securities are listed in the U.S. to comply with accounting provisions requiring us to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

JOBS Act

We qualify as an "emerging growth company" as defined in Section 2(a)(19) of the Securities Act, as modified by the JOBS Act. As such, we are eligible for and may take advantage of certain exemptions from various reporting requirements applicable to other public companies that are not emerging growth companies for as long as we continue to be an emerging growth company, including (i) the exemption from the auditor attestation requirements with respect to internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act, (ii) the exemptions from say-on-pay, say-on-frequency and say-on-golden parachute voting requirements, and (iii) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements.

We will remain an emerging growth company until the earlier of: (i) the last day of the fiscal year (a) following the fifth anniversary of the closing of the initial public offering of Tottenham Acquisition I Limited ("Tottenham"), (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a "large accelerated filer" under the Exchange Act of 1934, which would occur if the market value of the shares of our Common Stock held by non-affiliates exceeds $700 million as of the last business day of our most recently completed second fiscal quarter; or (ii) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this extended transition period and, as a result, we may adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-public companies instead of the dates required for other public companies. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

Smaller Reporting Company Status

We are also a "smaller reporting company" because the market value of our stock held by non-affiliates was less than $700 million as of June 30, 2021 and our annual revenue was less than $100 million during the fiscal year ended December 31, 2021. We may

continue to be a smaller reporting company in any given year if either (i) the market value of our stock held by non-affiliates is less than $250 million as of June 30 in the most recently completed fiscal year or (ii) our annual revenue is less than $100 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700 million as of June 30 in the most recently completed fiscal year. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

Additional Regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservation and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, and chemical substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

Other Regulations

We are also subject to numerous federal, state and local laws relating to such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control, and disposal of hazardous or potentially hazardous substances. We may incur significant costs to comply with such laws and regulations now or in the future.

Employees and Human Capital Resources

As of December 31, 2021, we had a total of 102 employees, 95 of which were full-time, primarily located in Utah and Maryland. The table below sets forth our employees by role:

Department	Count of Employees	Percent of Total
Manufacturing	37	35%
Clinical	11	11%
Quality Control & Bioanalytics	11	11%
Microbiology Lab	8	8%
Research and Development	7	7%
Senior Management	7	7%
Quality Assurance	8	8%
Finance	5	5%
Human Resources	4	4%
Information Technology	1	1%
Marketing	3	3%
Total	**102**	**100%**

None of our employees are represented by a labor union or are covered by a collective bargaining agreement, and we believe that we have good relations with our employees.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards and cash-based performance bonus awards.

Corporate Information

The mailing address for our principal executive office is 6550 South Millrock Drive, Suite G50, Salt Lake City, Utah 84121, and our telephone number is (801) 676-9695. Our website address is *https://clene.com*. The information contained in or accessible from our website is not incorporated into this Annual Report, and you should not consider it part of this Annual Report. We have included our website address in this Annual Report solely as an inactive textual reference.

Item 1A. Risk Factors

Investing in our securities involves a high degree of risk. You should carefully consider the risks and uncertainties described below, together with the other information in this Annual Report, including our consolidated financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding whether to invest in our securities. The occurrence of one or more of the events or circumstances described in these risk factors, alone or in combination with other events or circumstances, may have a material adverse effect on our business, reputation, revenue, financial condition, results of operations, and future prospects, in which event the market price of our Common Stock could decline, and you could lose part or all of your investment. The risks and uncertainties summarized above and described below are not intended to be exhaustive and are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations. This Annual Report also contains forward-looking statements that involve risks and uncertainties, refer to "Cautionary Note Regarding Forward-Looking Statements." Our actual results could differ materially and adversely from our anticipated results as a result of a number of factors, including the risks described below.

Risks Relating to Our Business and Industry

We depend substantially on the successful commercialization of our drug candidates in the future, which may fail to materialize or may experience significant delays.

As a new biopharmaceutical business, we currently do not have any drugs available for commercial sales nor do we have any drugs that have been approved for sale by the regulatory authorities. We have invested a significant portion of our efforts and financial resources in research and development of our leading drug candidate, CNM-Au8®, a catalytically-active gold nanocrystal suspension, which in early-stage studies has shown potential for the treatment of patients with ALS, MS, and PD. Our ability to generate revenue and become profitable in the future depends substantially on the future sales generated by CNM-Au8® and our drug candidates, which in turn depends on the successful research and development, regulatory approval, commercialization and sale of our drug candidates presently under clinical development for the treatment of patients with neurological disorders. We are also developing new drugs based on our technology that have not yet entered into human studies. The ultimate success of our drug candidates is subject to us achieving certain milestones, including without limitation:

- identifying, assessing, acquiring and obtaining evidence of biological activity of new drug candidates to treat certain diseases;
- obtaining satisfactory evidence of safety of these drug candidates in animal toxicology studies;
- obtaining regulatory approval for the conduct of, enrollment in, and completion of, clinical trials of our drug candidates;
- obtaining satisfactory proof of the clinical efficacy and safety of our drug candidates from these clinical trials;
- obtaining approvals and marketing authorizations from regulatory authorities for our drug candidates;
- developing sustainable and scalable manufacturing processes to produce these drug candidates;
- successfully expanding manufacturing processes to support global commercialization capacity of our drug candidates; and
- launching and commercializing any drug candidates for which we may obtain regulatory approvals and marketing authorizations, either directly or with a collaborator or distributor.

If we do not achieve one or more of these milestones in a timely manner, or at all, we could experience significant delays in our ability to obtain approval for and/or to successfully commercialize our drug candidates, which would materially harm our business and we may not be able to generate sufficient revenues and cash flows to continue our operations.

Even if we are able to generate revenues from any future sales of our drug candidates, we may not become profitable and may need to obtain additional funding to continue operations. Any required funding may not be available on favorable terms or at all. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and may be forced to reduce our operations. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease our value significantly and could impair our ability to raise capital, expand our business or continue our operations, which in turn may adversely affect our business, financial condition, and results of operations.

We currently do not generate any revenue from the commercial sales of drug candidates and we may not become profitable when expected, or at all.

Our main business is research and development, and if successful, sales of drug candidates. As all of our drug candidates are still in the research and development stage, we currently do not generate revenue from the sale of drug candidates, and we have recorded continued significant net losses. We generate an immaterial amount of revenue related to supply agreements for dietary (mineral) supplements; however, such revenue is not expected to be a material contributor to our revenue in the future. If we fail to commercialize our drug candidates as planned due to failures to complete clinical trials, obtain regulatory approval, conduct commercial scale manufacturing or for any other reason, we may experience significant delays or failure in generating revenue and realizing profit from the commercial sale of our drug candidates.

Further, we expect to incur significant costs in the future, in particular for research and development and the commercialization of our drug candidates. Research and development expenses totaled $28.4 million and $15.2 million for the years ended December 31, 2021 and 2020, respectively. As drug candidates presently undergoing preclinical research enter into the clinical trial stage, costs associated with such drug candidates may increase significantly. In the future, as we move more drug candidates into the clinical trial stage, conduct more clinical trials for commercialized products to broaden their use, and carry out commercial production of our drug candidates, the costs associated with such operations may increase significantly.

As we operate in the highly competitive pharmaceutical market, we compete to commercialize our drug candidates ahead of our competitors, putting us under pressure to incur research and development and other expenses with a potential negative impact on our profitability. On the other hand, our commercialized drug candidates, if any are approved, may fail to realize their sales potential due to competition, insufficient market demand, product defects, or any other reason. Therefore, even if we ever start to generate revenue from the sales of our commercialized drug candidates in the future, we may still not be profitable for an extended period of time or at all.

We have incurred significant net losses and net operating cash outflows since our inception and expect to continue to incur significant net losses for the foreseeable future.

Investment in biopharmaceutical drug development is highly speculative. It entails substantial upfront capital expenditures and significant risk that a drug candidate might fail to gain regulatory approval or become commercially viable. We continue to incur significant expenses related to our ongoing operations. We have incurred substantial losses since our inception. We recorded a loss from operations of $50.0 million and $20.2 million for the years ended December 31, 2021 and 2020, respectively, and a net loss of $9.7 million and $19.3 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $163.3 million. For details, see “Management’s Discussion and Analysis of Financial Condition and Results of Operations.” Substantially all of our operating losses have resulted from costs incurred in connection with our research and development programs and administrative expenses associated with our operations, and we expect that our research and development expenses will continue to increase in the future.

We expect to continue to incur losses for the foreseeable future, and we expect these losses to increase as we continue to expand our development of, and seek regulatory approvals for, our drug candidates, and we continue to build up our commercialization and sales workforce in anticipation of the potential future roll-out of our late-stage drug candidates. Typically, it takes many years to develop one new drug from the drug discovery stage to the time it is available for treating patients. In addition, we will continue to incur costs associated with operating as a public company and in support of our growth as a development-stage or commercial-stage pharmaceutical company. The size of our future net losses will depend, in part, on the number and scope of our drug development programs and the associated costs of those programs, the cost of commercializing any approved products, our ability to generate revenues and the timing and amount of milestones and other payments we make or receive through arrangements with third parties. If any of our drug candidates fails in clinical trials or does not gain regulatory approval, or if approved, fails to achieve market acceptance, we may never become profitable. Our failure to become and remain profitable would decrease our value significantly and impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

Our ability to continue as a going concern requires that we obtain sufficient funding to finance our operations, which may not be available on acceptable terms, or at all. A failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our drug development or commercialization efforts.

As of December 31, 2021, we had cash and restricted cash totaling $50.3 million and an accumulated deficit of $163.3 million. During the years ended December 31, 2021 and 2020, we used net cash in operating activities of $34.6 million and $18.9 million, respectively. We expect to continue to incur losses and use cash in operating activities for the foreseeable future. For details, please see “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources.” Our long-term operations require obtaining additional capital to fund our operations. As part of our ongoing business plans, we will continue seeking to raise additional capital through equity financing and may seek debt financing or other capital sources, and we may attempt

to collaborate with a third party for development and commercialization of our drug candidates. We may not be able to obtain capital on acceptable terms, or at all. The terms of any financing may adversely affect the holdings or rights of our stockholders. Depending on the results of our current business plans, we may need to implement cost-saving initiatives, including potentially delaying or reducing research and development programs and commercialization efforts beginning as early as the third quarter of 2022. Currently, without additional capital, we believe we have sufficient resources to fund our continuing operations into the second quarter of 2023. These factors, among others, may raise substantial doubt about our ability to continue as a going concern.

We have a limited operating history, which may make it difficult to evaluate our current business and predict our future performance.

We are a biopharmaceutical company formed in December 2012 focusing on the discovery and development of innovative drugs for the treatment of neurological diseases and other disorders. Our limited operating history, particularly in light of the rapidly evolving nanocrystal therapies field, may make it difficult to evaluate our current business and predict our future performance.

Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential drug candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval and become commercially viable. As a relatively new business, we have not yet demonstrated an ability to manufacture drugs at a commercial scale, to arrange for a third party to do so on our behalf, or to conduct sales and marketing activities necessary for successful commercialization. We have not had any product approved for commercial sale and have not generated any revenue from product sales. In addition, as a business with a limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and risks frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields. Consequently, any assessment you make about our current business or future success or viability may not be as accurate as it could be if we had a longer operating history and had been able to reduce some of the uncertainties as set out above. Further, our limited financial track record, without any revenue yet from our expected future principal business, may be of limited reference value for your assessment of our business.

We may encounter difficulties in managing our growth and expanding our operations successfully, which could adversely affect our business, financial condition, results of operations and prospects.

As we seek to advance our drug candidates through clinical trials, we will need to expand our development, regulatory, compliance, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Future growth will impose significant added responsibilities on members of our management. Our future financial performance and our ability to commercialize our drug candidates, if approved, and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional clinical, regulatory, manufacturing, financial, legal, managerial, administrative, and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successful growth and could harm our business, financial condition, results of operations and prospects.

Changes in government regulation or in practices relating to the pharmaceutical and biotechnology industries, including potential healthcare reform, could decrease the need for our drug candidates, or make it more difficult to obtain regulatory approvals for our drug candidates and commercialize them.

In recent years, the U.S. Congress, the President, executive branch agencies, and state legislatures have considered various types of healthcare reform to control growing healthcare costs. Similar reform movements have occurred in parts of Europe and Asia. Healthcare reform legislation could also increase the costs of drug development and commercialization or limit reimbursement for marketed drugs that could limit the profits to be made from the development of new drugs. This could adversely affect research and development expenditures by pharmaceutical and biotechnology companies, which could in turn decrease the business opportunities available to us in the U.S. and other countries. We are unable to predict what reform proposals will be adopted in the future, if any.

If we, or any CRO we may engage, fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on our business, financial condition, results of operations and prospects.

We and certain of the third parties we contract with, such as our third-party CROs, are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment, and disposal of hazardous materials and wastes. In addition, our future construction projects may necessitate that certain regulatory procedures be completed with the relevant administrative authorities in charge of environmental protection, health and safety before the project can be put into operation. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and

wastes. We cannot entirely eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources.

Although we maintain workers' compensation insurance to cover the costs and expenses we may incur due to injuries to our employees resulting from the use of or exposure to hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage, use or disposal of biological or hazardous materials.

In addition, the environmental, health and safety laws and regulations applicable to us and our third-party contractors may change and impose stricter requirements in the future. As a result, we may be required to incur substantial costs to comply with future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Our internal computer systems, or those used by any CROs or other third-party contractors or consultants we may engage, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses and unauthorized access. Although, to our knowledge, we have not experienced any material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and business operations.

In the ordinary course of our business, we collect and store sensitive data, including, among other things, legally protected patient health information, personally identifiable information about our employees, intellectual property, and proprietary business information. We manage and maintain our applications and data utilizing on-site systems and outsourced vendors. These applications and data encompass a wide variety of business-critical information including research and development information, commercial information, and business and financial information. Because information systems, networks and other technologies are critical to many of our operating activities, shutdowns or service disruptions of our systems or those of the vendors that provide information systems, networks or other services to us pose increasing risks. Such disruptions may be caused by events such as computer hacking, phishing attacks, ransomware, dissemination of computer viruses, worms and other destructive or disruptive software, denial-of-service attacks and other malicious activity, as well as security incidents from inadvertent or intentional actions (such as error or theft) by our employees, contractors, consultants, business partners, and/or other third parties, supply chain attacks, power outages, natural disasters (including extreme weather), terrorist attacks or other similar events. Such events could have an adverse impact on us and our business, including loss of data and damage to equipment and data. In addition, system redundancy may be ineffective or inadequate, and our disaster recovery planning may not be sufficient to cover all eventualities. Significant events could result in a disruption of our operations, damage to our reputation or a loss of revenues. In addition, we may not have adequate insurance coverage to compensate for any losses associated with such events.

We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in our information systems and networks and those of our vendors, including personal information of our employees and patients, and company and vendor confidential data. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our personnel or the personnel of our vendors to disclose sensitive information in order to gain access to our data and/or systems. Like other companies, we have on occasion experienced, and will continue to experience, threats to our data and systems, including malicious codes and viruses, phishing and other cyber-attacks. The number and complexity of these threats continue to increase over time. If a material breach of our information technology systems or those of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks.

Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely. As we outsource more of our information systems to vendors, engage in more electronic transactions with payors and patients and rely more on cloud-based information systems, the related security risks will increase and we will need to expend additional resources to protect our technology and information systems.

We may also be required to comply with laws, regulations, rules, industry standards, and other legal obligations that require us to maintain the security of personal data. We may also have contractual and other legal obligations to notify customers, collaborators, or other relevant stakeholders of security incidents. Failure to prevent or mitigate cyberattacks could result in unauthorized access to data, including proprietary and personal information. Most jurisdictions have enacted laws requiring companies to notify individuals, regulatory authorities, and others of security breaches involving certain types of data. Such disclosures are costly, could lead to negative

publicity, may cause our customer or collaborators or other relevant stakeholders to lose confidence in the effectiveness of our security measures and require us to expend significant capital and other resources to respond to and/or alleviate problems caused by the actual or perceived security incident. In addition, the costs to respond to a cybersecurity event or to mitigate any identified security vulnerabilities could be significant, including costs for remediating the effects of such an event, paying a ransom, restoring data from backups, and conducting data analysis to determine what data may have been affected by the breach. In addition, our efforts to contain or remediate a security incident or any vulnerability exploited to cause an incident may be unsuccessful, and efforts and any related failures to contain or remediate them could result in interruptions, delays, harm to our reputation, and increases to our insurance coverage.

In addition, regulatory response or litigation resulting from security breaches may adversely affect our business. Unauthorized access to our information technology systems could result in litigation with our customers, collaborators, or other relevant stakeholders, or regulatory actions by government entities. These proceedings could force us to spend money in defense or settlement, divert management's time and attention, increase our costs of doing business, or adversely affect our reputation. We could be required to fundamentally change our business activities and practices in response to such litigation, which could have an adverse effect on our business. If a security breach were to occur and the confidentiality, integrity or availability of our data or the data of our collaborators were disrupted, we could incur significant liability, which could negatively affect our business and damage our reputation.

Furthermore, our insurance may not be adequate to cover losses associated with such events, and in any case, such insurance may not cover all of the types of costs, expenses, or at all, and losses we could incur to respond to and remediate a security breach. The successful assertion of one or more large claims against us that exceeds our available insurance coverage, or results in changes to our insurance policies (including premium increases or the imposition of large deductible or co-insurance requirements), could have an adverse effect on our business. In addition, we cannot be sure that our existing insurance coverage and coverage for errors and omissions will continue to be available on acceptable terms or that our insurers will not deny coverage as to any future claim.

We manufacture all of our drug candidates ourselves, and intend to manufacture most, if not all, of any approved drugs ourselves as well, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We currently have manufacturing facilities in the U.S. and may build additional manufacturing facilities in other markets to expand our manufacturing capacity. These facilities may encounter unanticipated delays and expenses due to a number of factors, including regulatory requirements. If construction, regulatory evaluation, and/or approval of our new facilities is delayed, we may not be able to manufacture sufficient quantities of our drug candidates, if approved, which would limit our development and commercialization activities and our opportunities for growth. Cost overruns associated with constructing or maintaining our facilities could require us to raise additional funds from other sources, which may not be available on favorable terms or at all.

Much of the equipment used in our manufacturing process was developed and built by us, and it would be difficult or even impossible to purchase or create suitable replacements in a short period of time. Further, for much of this equipment we have an insufficient amount of or no spare parts available. Were certain equipment, some of which is critical to the production of our drug candidates, to become damaged, lost, or otherwise unusable, we would have to construct new parts, which could take a considerable amount of time, causing a temporary halt to at least a portion of our production operations. Additionally, we are constantly seeking to further fine-tune and develop our advanced manufacturing techniques and process controls to fully utilize our facilities. Advances in manufacturing techniques may render our facilities and equipment inadequate, in which case we may lose any competitive advantage.

To produce our drug candidates in the quantities that we believe will be required to meet anticipated market demand, if approved, we will need to increase or "scale up" the production process by a significant factor over current levels of production. A significant part of the scaling up process will include seeking ways to increase the automation and semi-automation of our production process, which will require additional research and development, investment, potential new regulatory approvals, and cooperation with third parties, some of which may not be successful. If we are unable or are delayed in scaling up, or if the cost of doing so is not economically feasible for us, we may not be able to produce our approved drug candidates in a sufficient quantity to meet any future demand.

Delays in completing and receiving regulatory approvals for our manufacturing facilities could delay our development plans or commercialization efforts, which could harm our business.

Our manufacturing facilities will be subject to ongoing, periodic inspection by various regulatory authorities, including the FDA, EMA, China's National Medical Products Administration ("NMPA"), Health Canada, and the Australian Therapeutics Goods Administration ("TGA") or other comparable regulatory agencies to ensure compliance with GMP. Our failure to follow and document our adherence to such GMP or other regulatory requirements may lead to significant delays in the availability of products for clinical or, if approved, commercial use, and may result in the termination of or a hold on a clinical trial, or may delay or prevent filing or approval of marketing applications for our drug candidates or the commercialization of our drugs, if approved. We also may encounter problems with the following:

- achieving adequate or clinical-grade materials that meet FDA, EMA, NMPA, Health Canada, TGA or other comparable regulatory agency standards or specifications with consistent and acceptable production yield and costs;
- shortages of qualified personnel, raw materials or key contractors; and
- ongoing compliance with GMP and other requirements of the FDA, EMA, NMPA, Health Canada, TGA or other comparable regulatory agencies.

Failure to comply with applicable regulations could also result in sanctions being imposed on us, including fines, injunctions, civil penalties, a requirement to suspend or put on hold one or more of our clinical trials, failure of regulatory authorities to grant marketing approval of our drug candidates, delays, suspension or withdrawal of approvals, supply disruptions, license revocation, seizures, or recalls of our drug candidates, operating restrictions and civil or criminal prosecutions, any of which could harm our business.

Damage to, destruction of or interruption of production at our manufacturing facilities would negatively affect our business and prospects.

If our manufacturing facilities or the equipment in them is damaged or destroyed, we may not be able to quickly or inexpensively replace our manufacturing capacity or replace it at all. In the event of a temporary or protracted loss of the facilities or equipment, we might not be able to transfer manufacturing to a third party. Even if we could transfer manufacturing to a third party, the shift would likely be expensive and time-consuming, particularly since the new facility would need to comply with the necessary regulatory requirements and we would need regulatory agency approval before selling any of our drugs, if approved, manufactured at that new facility. Such an event could delay our clinical trials or reduce our product sales if any of our drug candidates are approved and successfully commercialized. Any interruption in manufacturing operations at our manufacturing facilities could result in our inability to satisfy the demands of our clinical trials or commercialization. Any disruption that impedes our ability to manufacture our drug candidates in a timely manner could materially harm our business, financial condition, results of operations and prospects.

Currently, we maintain insurance coverage against damage to our property and equipment in amounts we believe are reasonable. However, our insurance coverage may not reimburse us, or may not be sufficient to reimburse us, for any expenses or losses we may suffer. We may be unable to meet the requirements for our drug candidates if there were a catastrophic event or failure of our manufacturing facilities or processes.

Significant inflation could adversely affect our business, financial condition and results of operations.

Inflation can adversely affect us by increasing our costs, including salary costs. Significant inflation is often accompanied by higher interest rates. Any significant increases in inflation and interest rates could have material adverse effect on our business, financial condition and results of operations.

Our future success depends on our ability to retain key executives and to attract, train, retain and motivate qualified and highly skilled personnel.

We are highly dependent on Mark Mortenson, our co-founder and Chief Science Officer, Rob Etherington, our Chief Executive Officer and President, and the other principal members of our management and scientific teams. We do not maintain “key person” insurance for any of our executives or other employees. The loss of the services of any of our executive officers, other key employees, and other scientific advisors, and our inability to find suitable replacements could result in delays in product development and harm our business.

Recruiting and retaining qualified scientific, technical, clinical, manufacturing, sales, and marketing personnel in the future will also be critical to our success. In addition, we rely on third-party consultants and advisors, including scientific and clinical advisors, to assist us in formulating our discovery, clinical development, operations, and commercialization strategy. The loss of the services of our executive officers or other key employees and consultants could impede the achievement of our research, development, and commercialization objectives and seriously harm our ability to successfully implement our business strategy.

We benefit from certain tax and financial incentives, the expiration of or changes to which could adversely affect our profitability.

We benefit from certain tax treatments, as well as tax concessions in relation to our research and development costs. We receive refundable tax credits through the research and development tax credits in the U.S., Australia, and the state of Maryland. In the U.S., the research and development credit is used to offset federal employment taxes on our U.S. payroll. In Australia, we receive a refundable tax offset of 43.5% of research and development deductions. In Maryland, we receive the Basic Research and Development Tax credit of 3% of the lesser of eligible research and development expenses and the Maryland Base Amount, which is used to offset state income

taxes and may be applied against following years' taxes until the credit is used or the credit may be carried forward for seven years. We also receive a tax exemption in Maryland for state personal property and sales tax, as well as the Maryland enterprise zone hiring and job creation tax credits.

In addition, current or future tax treatments, tax concessions, tax allowances and financial incentives applicable to us may be changed, terminated, or otherwise become unavailable due to many factors, including changes in government policy or administrative decisions by the relevant government authorities. Due to potential changes in government policies, we cannot be certain of the level of government grants we will receive in the future. Our post-tax profitability and cash flows may be adversely affected as a result of one or more of these or other factors.

Our ability to use net operating losses to offset future taxable income may be subject to certain limitations.

We have incurred substantial losses since inception and do not expect to become profitable in the near future, if ever. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any. As of December 31, 2021, we had U.S. federal net operating loss ("NOL") carryforwards of $110.1 million, which may be available to reduce future taxable income and have an indefinite carryforward period but are limited in their usage to an annual deduction equal to 80% of annual taxable income. In addition, as of December 31, 2021, we had state NOL carryforwards of $77.1 million, which may be available to reduce future taxable income, of which $64.2 million have an indefinite carryforward period while the remaining $12.9 million begin to expire after 2032. As of December 31, 2021, we also had research and development tax credit carryforwards of $2.6 million, which may be available to reduce future tax liabilities and expire at various dates beginning after 2032.

Under U.S. federal tax legislation commonly referred to as the Tax Cuts and Jobs Act ("TCJA"), as modified by the Coronavirus Aid, Relief and Economic Security Act, or the CARES Act, U.S. federal NOLs incurred in taxable years beginning after December 31, 2017 and in future taxable years may carry forward indefinitely, but the deductibility of such U.S. federal NOLs incurred in taxable years beginning after December 31, 2020 are limited. It is uncertain how various states will respond to the TCJA and CARES Act. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. Any future offerings of equity securities, together with other transactions that have occurred since our inception, may trigger such an ownership change pursuant to Section 382 of the Internal Revenue Code of 1986. We have not conducted a study to assess whether any such ownership changes have occurred. We may experience ownership changes as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our NOL carryforwards is materially limited, it would harm our financial condition and results of operations by effectively increasing our future tax obligations.

Changes in tax laws may adversely affect us, and the Internal Revenue Service or a court may disagree with tax positions taken by us, which may result in adverse effects in our financial condition or the value of our Common Stock.

The TCJA, enacted on December 22, 2017, significantly affected U.S. tax law, including by changing how the U.S. imposes tax on certain types of income of corporations and by reducing the U.S. federal corporate income tax rate to 21%. It also imposed new limitations on a number of tax benefits, including deductions or business interest, use of net operating loss carry forwards, taxation of foreign income and the foreign tax credit, among others.

The CARES Act, enacted on March 27, 2020, in response to the COVID-19 pandemic, further amended the Internal Revenue Code of 1986, including in respect of certain changes that were made by the TCJA, generally on a temporary basis. In addition, the Internal Revenue Service ("IRS") has yet to issue guidance on a number of important issues regarding the changes made by the TCJA and the CARES Act. In the absence of such guidance, we will take positions with respect to a number of unsettled issues. There is no assurance that the IRS or a court will agree with the positions taken by us, in which case tax penalties and interest may be imposed that could adversely affect our business, cash flows or financial performance.

Additionally, the current administration may propose significant changes to U.S. tax law, some or all of which may be enacted. The passage of such legislation, as well as changes or modifications in existing judicial decisions or in the current positions of the IRS, could substantially modify the tax treatment described in this Annual Report, possibly on a retroactive basis. We cannot predict whether the U.S. Congress or any other legislative body will enact new tax legislation or whether the IRS or any other tax authority will issue new regulations or other guidance, nor can we predict what effect such legislation or regulations might have on us or our financial condition. There can be no assurance that future tax law changes will not increase the rate of the corporate income tax significantly, impose new limitations on deductions, credits or other tax benefits, or make other changes that may adversely affect our business, cash flows or financial performance.

Our financial position and operations may be adversely affected by the COVID-19 pandemic.

An outbreak of the respiratory illness COVID-19 caused by a strain of novel coronavirus, SARS-Cov-2, has spread worldwide, causing many governments to implement measures to slow the spread of the outbreak through quarantines, strict travel restrictions, heightened border scrutiny, and other measures. The outbreak and government measures taken in response to the COVID-19 pandemic have had a significant impact, both direct and indirect, on businesses and commerce. The future progression of the COVID-19 pandemic and its effects on our business and operations are uncertain.

We, our CROs, clinical investigators, third-party vendors and clinical sites may experience disruptions in supply of drug candidates and/or procuring items that are essential for our research and development activities, including raw materials used in the manufacturing of our drug candidates, medical and laboratory supplies used in our clinical trials or preclinical studies or animals that are used for preclinical testing, in each case, for which there may be shortages because of ongoing efforts to address the COVID-19 pandemic. Any disruption in the supply chain from the COVID-19 pandemic, or any potential future outbreak, could have a material adverse effect on our clinical trial plans and business operations.

Additionally, we have enrolled, and will seek to enroll, patients in our clinical trials at sites located in many areas affected by the COVID-19 pandemic and, as a result, our trials have been impacted. In addition, even if sites are actively recruiting, we may face difficulties recruiting or retaining patients in our ongoing and planned clinical trials if patients are affected by the COVID-19 virus or are fearful of visiting or traveling to clinical trial sites because of the COVID-19 pandemic. Prolonged delays or closure to enrollment in our trials or patient discontinuations could have a material adverse impact on our clinical trial plans and timelines.

The response to the COVID-19 pandemic may redirect our resources with respect to regulatory and intellectual property matters in a way that would adversely affect our ability to obtain regulatory approvals and protect our intellectual property. In addition, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions.

Any negative impact that the COVID-19 pandemic has on the ability of our suppliers to provide materials for our drug candidates or on recruiting or retaining patients in our clinical trials or our ability to collect patient data could cause costly delays to clinical trial activities, which could adversely affect our ability to obtain regulatory approval for and, if approved, to commercialize our drug candidates, increase our operating expenses, and have a material adverse effect on our financial results.

The COVID-19 pandemic has significantly impacted economies worldwide. The extent to which the COVID-19 pandemic impacts our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread of the disease, the duration of the COVID-19 pandemic, travel restrictions and social distancing in the U.S. and other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and other countries to contain and treat the disease. The global outbreak of the COVID-19 pandemic continues to evolve and the conduct of our clinical trials may continue to be adversely affected, despite any efforts to mitigate this impact. The COVID-19 pandemic has the potential to adversely affect our business, financial condition, results of operations, and prospects. For details, please see “Management’s Discussion and Analysis of Financial Condition and Results of Operations—Impact of COVID-19 Pandemic.”

We have identified material weaknesses in our internal control over financial reporting. If we fail to remediate these material weaknesses, or if we experience additional material weaknesses in the future or otherwise fail to maintain an effective system of internal controls, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect investor confidence in us and, as a result, the value of our Common Stock.

Effective internal control over financial reporting is necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, is designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation, could cause us to fail to meet our reporting obligations. In addition, any testing by us, as and when required, conducted in connection with Section 404 of the Sarbanes-Oxley Act or any subsequent testing by our independent registered public accounting firm, as and when required, may reveal deficiencies in our internal control over financial reporting that are deemed to be significant deficiencies or material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our Common Stock.

In connection with the audit of our financial statements as of and for the years ended December 31, 2021 and 2020, our management identified material weaknesses in our internal control over financial reporting. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. The material weaknesses identified relate to the fact that we did not design or maintain an effective control environment commensurate with our financial reporting

requirements. This deficiency in our control environment contributed to the following additional material weaknesses related to control activities and information and communication within our internal control over financial reporting:

- we did not design and maintain controls over the preparation and review of account reconciliations and the review and segregation of duties over manual journal entries, including controls over the completeness and accuracy of information; and
- we did not design and maintain information technology ("IT") general controls for IT systems that are relevant to the preparation of the financial statements. Specifically, we did not design and maintain: (a) user access controls to ensure appropriate segregation of duties and that adequately restrict user and privileged access to financial applications, programs, and data to our appropriate personnel; (b) program change management controls to ensure that IT program and data changes affecting financial IT applications and underlying accounting records are identified, tested, authorized, and implemented appropriately; (c) computer operations controls to ensure that data backups are authorized and monitored; and (d) testing and approval controls for program development to ensure that new software development is aligned with business and IT requirements.

Each of the control deficiencies described above could result in a misstatement of one or more account balances or disclosures that would result in a material misstatement to the annual or interim consolidated financial statements that would not be prevented or detected. Accordingly, our management has determined that each of the control deficiencies described above constitute material weaknesses.

Although we have begun to implement measures to address the material weaknesses, the implementation of these measures may not fully address the material weaknesses and deficiencies in our internal control over financial reporting, and we cannot conclude that these matters have been fully remedied. As we continue to evaluate, and work to improve, our internal control over financial reporting, management may determine that additional or different measures to address control deficiencies or modifications to the remediation plan are necessary. Further, in the future we may determine that we have additional material weaknesses. Our failure to remediate the material weaknesses or failure to identify and address any other material weaknesses or control deficiencies could result in inaccuracies in our financial statements and could also impair our ability to comply with applicable financial reporting requirements and related regulatory filings on a timely basis, which could cause investors to lose confidence in our reported financial information, which may result in volatility in and a decline in the market price of our Common Stock.

Pursuant to Section 404, after the Reverse Recapitalization, we, as the surviving entity, are required to furnish a report by our management on the effectiveness of our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could adversely affect investor confidence in us and, as a result, the value of our Common Stock.

There is significant uncertainty associated with our drug candidates and their viability as a commercial product.

Metallic nanocrystal therapeutic candidates, such as our lead product, CNM-Au8®, are considered emerging and novel investigational products for the potential treatment of neurological diseases and other disorders. We are developing CNM-Au8® for the treatment of neurological disorders such as ALS, MS, and PD through remyelination and/or neuroprotection mechanisms related to catalysis of certain biological reactions. There are currently no approved remyelination therapies and the evidence for an effect of neuroprotection treatments on these indications is thus far limited. Since there is limited clinical trial data and precedent for the development of nanocrystal therapies that promote remyelination and neuroprotection to treat these indications, there is a substantial risk that the design or outcomes of our clinical trials will not be satisfactory to support regulatory approval. In addition, there are generally limited or no regulatory precedents concerning metallic nanocrystal drug marketing authorization, or a regulatory framework to appropriately differentiate approved nanocrystal product labeling. Our lead metallic nanocrystal drug candidate, CNM-Au8®, contains nanocrystals made entirely of high purity gold alone. It is unclear how regulatory authorities will identify or classify the active moiety of CNM-Au8®, including whether it is classified as a new chemical entity or comparable designation. The inability to obtain sufficiently differentiated active moiety classification from gold generically could potentially limit CNM-Au8® and our drug candidates from ever achieving profitability.

Moreover, the mechanisms of action for nanocrystal therapies are not thoroughly understood, and adverse events or side effects may be observed in clinical trials and reported by medical practitioners in connection with patient usage in the future. If those adverse events or side effects prove significant, they may hamper the ability of our drug candidates to pass through clinical trials or they may outweigh the benefits that patients derive from using our drug candidates, both of which could potentially prevent our drug candidates from ever achieving profitability.

Our drug candidates are not metabolized and may accumulate in the body following long-term usage, making the long-term effects of taking our drug candidates for substantial periods of time uncertain. While all of the current toxicology studies of our drug candidates have resulted in no-adverse-effect levels as of the date of this Annual Report, we have not completed reproductive or carcinogenicity studies, which we are required to complete in the future. Any negative results from these studies could materially and adversely affect our business, results of operations, financial condition and prospects.

Moreover, the results of clinical trials for nanocrystal therapies could reveal a high and unacceptable severity and prevalence of undesirable side effects. Any such side effects could adversely impact our ability to obtain regulatory approvals. For example, the FDA, NMPA, Health Canada, TGA, EMA or other comparable authorities could order us to suspend or terminate our studies or to cease further clinical development of or deny approval of our drug candidates. In addition, any adverse drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete trials or may result in potential product liability claims. Any of these occurrences may harm our business, financial condition, results of operations, and prospects significantly.

We have not previously obtained any regulatory approval for a drug candidate and we may be unable to obtain or may be delayed in obtaining regulatory approval for any of our drug candidates.

Our business is substantially dependent on our ability to complete the development of, obtain regulatory approval for and successfully commercialize drug candidates in a timely manner. We cannot commercialize drug candidates without obtaining regulatory approval to market each drug from the FDA, NMPA, Health Canada, TGA, EMA and other comparable regulatory authorities. The time required to obtain approval from regulatory authorities is unpredictable but typically takes years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a drug candidate's clinical development and may vary among jurisdictions.

Our drug candidates could fail to receive regulatory approval for many reasons, including:

- failure to begin or complete clinical trials due to disagreements with regulatory authorities;
- failure to begin or complete clinical trials due to inability to recruit sufficient numbers of study participants;
- failure to demonstrate that a drug candidate is safe and effective or is safe, pure and potent for our proposed indication;
- failure of clinical trial results to meet the level of statistical significance required for approval;
- data integrity issues related to our clinical trials;
- disagreement with our interpretation of data from preclinical studies or clinical trials;
- changes in approval policies or regulations that render our preclinical and clinical data insufficient for approval or require us to amend our clinical trial protocols;
- regulatory requests for additional analysis, reports, data, nonclinical studies and clinical trials, or questions regarding interpretations of data and results and the emergence of new information regarding our drug candidates;
- insufficient data from the clinical trials of our drug candidates to obtain regulatory approval;
- failure by us or our investigators to conduct a clinical trial in accordance with regulatory requirements or our clinical trial protocols; and
- clinical sites, investigators or other participants in our clinical trials deviating from a trial protocol, failing to conduct the trial in accordance with regulatory requirements, or dropping out of a trial.

The FDA, NMPA, TGA, Health Canada, EMA or a comparable regulatory authority may require more information, including additional preclinical or clinical data, to support approval, which may delay or prevent approval and our commercialization plans, or we may decide to abandon the development program.

New or unexpected adverse events, or changes in regulatory requirements and guidance may also occur, and we may need to amend clinical trial protocols submitted to applicable regulatory authorities to reflect these changes. Amendments may require us to resubmit clinical trial protocols to IRBs or HRECs for re-examination, which may impact the costs, timing or successful completion of a clinical trial.

If we experience delays in the completion of, or the termination of, a clinical trial of any of our drug candidates, the commercial prospects of that drug candidate will be harmed, and our ability to generate product sales revenues from any of those drug candidates will be delayed. In addition, any delays in completing our clinical trials will increase our costs, slow down our drug candidate development and approval process, and jeopardize our ability to commence product sales and generate related revenues for that product. Any of these occurrences may harm our business, financial condition, results of operations and prospects significantly. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our drug candidates.

We may not be able to successfully identify, discover, develop or in-license new drug candidates.

We cannot guarantee that we will be successful in identifying potential drug candidates for clinical development for a number of reasons. For example, our research methodology may be unsuccessful in identifying potential drug candidates or those we identify may be shown to have harmful side effects or other characteristics that make them unmarketable or unlikely to receive regulatory approval. We have devoted significant resources to discovery efforts through our proprietary electro-crystal-chemistry drug development platform, however, we cannot guarantee that we will be successful in identifying additional potential drug candidates, or that we will be able to successfully identify and in-license new drug candidates with high potential from other parties.

Research programs to pursue the development of our drug candidates for additional indications and to identify new drug candidates and drug targets require substantial technical, financial, and human resources. Our research programs may initially show promise in identifying potential indications and/or drug candidates, yet fail to yield results for clinical development for a number of reasons, including:

- the research methodology used may not be successful in identifying potential indications, and/or drug candidates;
- potential drug candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective drugs; or
- it may take greater human and financial resources to identify additional therapeutic opportunities for our drug candidates or to develop suitable potential drug candidates through internal research programs than we will possess, thereby limiting our ability to diversify and expand our drug portfolio.

Accordingly, there is no assurance that we will ever be able to identify additional therapeutic opportunities for our drug candidates or to develop suitable potential drug candidates through internal research programs, which could materially and adversely affect our future growth, business, financial condition, results of operations and prospects. We may focus our efforts and resources on potential drug candidates or other potential programs that ultimately prove to be unsuccessful.

Preclinical and clinical development of drug candidates involves a lengthy and expensive process with an uncertain outcome, and we are unable to predict if or when we will successfully develop or commercialize any of our drug candidates.

There is a risk of failure for each of our drug candidates. Before obtaining regulatory approval for the sale of any of our drug candidates, we must complete preclinical studies and then conduct extensive clinical trials to demonstrate the safety and efficacy of our drug candidates in humans. It is difficult to predict when or if any of our drug candidates will prove effective and safe in humans or receive regulatory approval. Our internal discovery programs for some of our drug candidates are at an early stage of development and will require significant investment and regulatory approvals prior to commercialization. We are not permitted to market or promote any of our drug candidates until we receive regulatory approval from the FDA, NMPA, TGA, Health Canada, EMA or comparable regulatory authorities, and we may never receive such regulatory approval for any of our drug candidates.

We could encounter regulatory delays if a clinical trial is suspended or terminated by us or, as applicable, by the IRBs or the ethics committees of the institutions in which such trials are being conducted, by the DSMB, which is an independent group of experts that is formed to monitor clinical trials while ongoing, or by the FDA, NMPA, TGA, Health Canada, EMA or other regulatory authorities. Such authorities may impose a suspension or termination due to a number of factors, including: (1) a failure to conduct the clinical trial in accordance with regulatory requirements or the applicable clinical protocols, (2) inspection of the clinical trial operations or trial site by the FDA, NMPA, TGA, Health Canada, EMA or other regulatory authorities that results in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, (3) failure to demonstrate a benefit from using a drug, (4) changes in governmental regulations or administrative actions, or (5) lack of adequate funding to continue the clinical trial. Many of the factors that cause a delay

in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our drug candidates. Further, the FDA, NMPA, TGA, Health Canada, EMA or other regulatory authorities may disagree with our clinical trial design or our interpretation of data from clinical trials, or may change the requirements for approval even after any regulatory authority has reviewed and commented on the design for our clinical trials.

Preclinical studies and clinical trials are expensive, difficult to design and implement, and can take many years to complete. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analysis, and many companies that have believed their drug candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain regulatory approval of their drug candidates. Future clinical trials of our drug candidates may not be successful.

Commencement of clinical trials is subject to finalizing the trial design based on ongoing discussions with the FDA, NMPA, TGA, Health Canada, EMA and/or other regulatory authorities. The FDA, NMPA, TGA, Health Canada, EMA and other regulatory authorities could change their position on the acceptability of trial designs or clinical endpoints, which could require us to complete additional clinical trials or impose approval conditions that we do not currently expect. Successful completion of our clinical trials is a prerequisite to submitting an NDA (or analogous filing) to the FDA, NMPA, TGA, Health Canada, EMA and/or other regulatory authorities for each drug candidate and, consequently, the ultimate approval and commercial marketing of our drug candidates. We do not know whether the clinical trials for our drug candidates will be completed on schedule, if at all.

Results of earlier clinical trials may not be predictive of results of later-stage clinical trials.

The results of preclinical studies and early clinical trials of our drug candidates may not be predictive of the results of later-stage clinical trials. Drug candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. Future clinical trial results may not be favorable for these and other reasons.

In some cases, there can be significant variability in the safety and/or efficacy results between different trials of the same drug candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, including genetic differences, patient adherence to the dosing regimen, and the rate of dropout among clinical trial participants. As drug candidates are developed through preclinical to early- to late-stage clinical trials towards approval and commercialization, it is customary that various aspects of the development program, such as manufacturing and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. In the case of any trials we conduct, results may differ from earlier trials due to the larger number of clinical trial sites and additional countries and languages involved in such trials. Any of these changes could make the results of planned clinical trials or other future clinical trials we may initiate less predictable and could cause our drug candidates to perform differently, which could delay completion of clinical trials, delay approval of our drug candidates, and/or jeopardize our ability to commence commercialization of our drug candidates.

Clinical trials of our drug candidates may fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities, or may not otherwise produce positive results, which may cause us to incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our drug candidates.

Before obtaining regulatory approval for the sale of our drug candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of our drug candidates in humans. We may experience numerous unexpected events during, or as a result of, clinical trials that could delay or prevent us from receiving regulatory approval or commercializing our drug candidates, including:

- regulators, IRBs, or HRECs may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- our inability to reach agreements on acceptable terms with prospective CROs, clinical trial vendors, and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- manufacturing issues, including problems with manufacturing, supply quality, compliance with GMP, or obtaining from third parties sufficient quantities of a drug candidate for use in a clinical trial;
- clinical trials of our drug candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon drug development programs;
- the number of patients required for clinical trials of our drug candidates may be larger than we anticipate;
- our third-party contractors, including clinical investigators, may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

- we may not investigate, may not be able to license, or may be unable to properly conduct companion diagnostic tests to identify patients who are likely to benefit from treatment with our drug candidates;
- we might have to suspend or terminate clinical trials of our drug candidates for various reasons, including a finding of a lack of clinical response or other unexpected characteristics or a finding that participants are being exposed to unacceptable health risks;
- regulators, IRBs or HRECs may require that we or our investigators suspend or terminate clinical research or not rely on the results of clinical research for various reasons, including non-compliance with regulatory requirements;
- the cost of clinical trials of our drug candidates may be greater than we anticipate;
- the supply or quality of our drug candidates or other materials necessary to conduct clinical trials of our drug candidates may be insufficient or inadequate; and
- our drug candidates may have undesirable side effects or unexpected characteristics, causing us or our investigators, regulators, IRBs or ethics committees to suspend or terminate the clinical trials, or reports may arise from preclinical studies or clinical trials of other therapies that raise safety or efficacy concerns about our drug candidates.

If we are required to conduct additional clinical trials or other testing of our drug candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our drug candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if they raise safety concerns, we may (i) be delayed in obtaining regulatory approval for our drug candidates; (ii) not obtain regulatory approval at all; (iii) obtain approval for indications that are not as broad as intended; (iv) have the drug removed from the market after obtaining regulatory approval; (v) be subject to additional post-market testing requirements; (vi) be subject to restrictions on how the drug is distributed or used; or (vii) be unable to obtain reimbursement for use of the drug.

Significant clinical trial delays may also increase our development costs and could shorten any periods during which we have the exclusive right to commercialize our drug candidates or allow our competitors to bring drugs to market before we do. This could impair our ability to commercialize our drug candidates and may harm our business and results of operations.

If we encounter difficulties enrolling patients in clinical trials, clinical trials of our drug candidates may be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until our conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons, including:

- the COVID-19 pandemic;
- the size and nature of the patient population;
- the design of the trial, including the patient eligibility criteria defined in the protocol;
- the size of the study population required for analysis of the trial's primary endpoints;
- the proximity of patients to trial sites;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials for similar therapies or other new therapeutics;
- clinicians' and patients' perceptions as to the potential advantages and side effects of the drug candidate being studied in relation to other available therapies, including any new drugs or treatments that may be approved for the indications we are investigating;
- our ability to obtain and maintain patient consents;
- the risk that patients enrolled in clinical trials will not complete a clinical trial; and
- the availability of approved therapies that are similar in mechanism to our drug candidates.

Failure of our timely completion of clinical trials would delay the approval and commercialization of our drug candidates, impair the commercial performance of our drug candidates, and consequently harm our business and results of operations.

If we are not able to obtain, or experiences delays in obtaining, required regulatory approvals, we will not be able to commercialize our drug candidates, and our ability to generate revenue will be materially impaired.

Before obtaining regulatory approvals for the commercial sale of any drug candidate for a target indication, we must demonstrate in preclinical studies and well-controlled clinical trials, and, with respect to approval in the U.S., to the satisfaction of the FDA, that the drug candidate is safe and effective for use for that target indication and that the manufacturing facilities, processes and controls are adequate. In addition to preclinical and clinical data, the NDA must include significant information regarding the CMC for the drug candidate. Obtaining approval of an NDA is a lengthy, expensive and uncertain process, and approval may not be obtained. After we submit an NDA to the FDA, the FDA decides whether to accept or reject the submission for filing. We cannot be certain that any submissions will be accepted for filing and review by the FDA.

We have not yet demonstrated an ability to file for or receive regulatory approval for our drug candidates. For example, we do not have experience in preparing the required materials for regulatory submission or navigating the regulatory approval process. As a result, our ability to successfully submit an NDA and obtain regulatory approval for our drug candidates may involve more inherent risk, take longer, and cost more than it would if we were a company with experience in obtaining regulatory approvals.

Regulatory authorities outside of the U.S., such as the NMPA, TGA, Health Canada and EMA, also have requirements for approval of drugs for commercial sale with which we must comply prior to marketing in those areas. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our drug candidates. Clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and obtaining regulatory approval in one country does not mean that regulatory approval will be obtained in any other country. Approval processes vary among countries and can involve additional product testing and validation, and additional administrative review periods. Seeking non-U.S. regulatory approval could require additional nonclinical studies or clinical trials, which could be costly and time consuming. The non-U.S. regulatory approval process may include all of the risks associated with obtaining FDA approval. For all of these reasons, we may not obtain non-U.S. regulatory approvals on a timely basis, if at all.

The process to develop, obtain regulatory approval for and commercialize drug candidates is long, complex and costly both inside and outside the U.S., and approval is never guaranteed. Even if our drug candidates were to successfully obtain approval from the regulatory authorities, any approval might significantly limit the approved indications for use, or require that precautions, contraindications or warnings be included on the product labeling, or require expensive and time-consuming post-approval clinical trials or surveillance as conditions of approval. Following any approval for commercial sale of our drug candidates, certain changes to the drug, such as changes in manufacturing processes and additional labeling claims, may be subject to additional review and approval by the FDA, NMPA, TGA, Health Canada, EMA and comparable regulatory authorities. Also, regulatory approval for any of our drug candidates may be withdrawn. If we are unable to obtain regulatory approval for our drug candidates in one or more jurisdictions, or any approval contains significant limitations, our target market will be reduced and our ability to realize the full market potential of our drug candidates will be harmed. Furthermore, we may not be able to obtain sufficient funding or generate sufficient revenue and cash flows to continue the development of any other drug candidate in the future.

Favorable designations may not be granted, or if granted, may be withdrawn later, for any of our drug candidates, and may not lead to faster development or regulatory review or approval.

We do not currently have Fast Track Designation or Breakthrough Therapy Designation, but may seek one or more of such designations in the future.

If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical need for that condition, the drug sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion in deciding whether or not to grant this designation. Even if we believe a particular drug candidate is eligible for this designation, we cannot assure that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a development, review or approval process faster than conventional FDA procedures. The FDA may withdraw a Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program. Many drugs that have received Fast Track Designation have failed to obtain approval from the FDA.

A Breakthrough Therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor can help to identify the most efficient path for development.

Designation as a Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe, after completing early clinical trials, that one of our drug candidates meets the criteria for designation as a Breakthrough Therapy, the FDA may disagree and instead decide not to grant that designation. In any event, the receipt of a Breakthrough Therapy Designation for a drug candidate may not result in a faster development, review or approval process compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our drug candidates qualify as Breakthrough Therapies, the FDA may later decide that such drug candidates no longer meet the conditions for qualification.

Although we have obtained FDA orphan drug designation for CNM-Au8® for the treatment of ALS, we may not realize any benefit from such designation and it does not increase the chance of approval.

The FDA granted orphan drug designation to our lead drug candidate, CNM-Au8®, for the treatment of ALS in May 2019. Regulatory authorities in some jurisdictions, including the U.S. and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a disease with a patient population of fewer than 200,000 individuals in the U.S., or that affects more than 200,000 individuals in the U.S. and for which there is no reasonable expectation that costs of research and development of the product for the indication can be recovered by sales of the product in the U.S. Generally, if a drug with an orphan drug designation subsequently receives the first regulatory approval for the indication for which it has such designation, the drug is entitled to a period of marketing exclusivity, which precludes the FDA or EMA, from approving another marketing application for the same drug for the same indication during the period of exclusivity. The applicable period is seven years in the U.S. and ten years in the European Union. The European exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or the EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Although we have obtained orphan drug designation for CNM-Au8® for the treatment of ALS in the U.S., and may obtain the same designation for other drug candidates or indications, that designation may not effectively protect the drug candidate from competition, if approved, because different drugs can be approved for the same condition and the same drugs can be approved for a different condition but used off-label for any orphan indication we may obtain. Even after an orphan drug is approved, the FDA can subsequently approve a drug that is otherwise the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective, or makes a major contribution to patient care.

Any of our drug candidates, if approved, would continue to be subject to ongoing or additional regulatory obligations and regulatory review, which may result in significant additional expense and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our drug candidates.

Any of our drug candidates, if approved, will be subject to ongoing or additional regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-market studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the U.S. and requirements of comparable regulatory authorities in the European Union, China, Australia and other markets.

Manufacturers and manufacturers' facilities are required to comply with extensive FDA, NMPA, TGA, Health Canada, EMA and other comparable regulatory authority requirements ensuring that quality control and manufacturing procedures conform to GMP. As such, we will be subject to continual review and inspections to assess compliance with GMP and adherence to commitments made in any NDA, other marketing applications, and previous responses to any inspection observations if we were to build manufacturing facilities in the future. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, and quality control.

Any approvals that we receive for our drug candidates may be subject to limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, which could adversely affect the drug's commercial potential or contain requirements for potentially costly post-market testing and surveillance to monitor the safety and efficacy of the drug candidate. The FDA, NMPA, TGA, Health Canada, EMA or a comparable regulatory authority may also require a risk evaluation mitigation strategy program as a condition of approval of our drug candidates or following approval. In addition, if the FDA, NMPA, TGA, Health Canada, EMA or a comparable regulatory authority approves our drug candidates, we will have to comply with requirements, including, for example, submissions of safety and other post-market information and reports, registration, as well as continued compliance with GMP and GCP, for any clinical trials that we conduct post-approval.

The FDA and other regulatory authorities strictly regulate the marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for their approved indications and for use in accordance with the provisions of the approved label. The FDA, NMPA, TGA, Health Canada, EMA and other regulatory authorities actively enforce the laws and regulations

prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant penalties and enforcement actions.

Even if we are able to commercialize any approved drug candidates, the drugs may become subject to national or other third-party reimbursement practices or unfavorable pricing regulations, which could harm our business.

The regulations that govern regulatory approvals, pricing and reimbursement for new therapeutic products vary widely from country to country. In Europe, Canada, Australia, China, and some markets outside China, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain regulatory approval for a drug in a particular country, but then be subject to price regulations that delay our commercial launch of the drug and negatively impact our revenues.

Our ability to commercialize any approved drug candidates successfully also will depend in part on the extent to which reimbursement for these drugs and related treatments will be available from government health administration authorities, private health insurers, and other organizations.

A primary trend in the global healthcare industry is cost containment. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications.

In the U.S., no uniform policy of coverage and reimbursement for drugs exists among third-party payors. As a result, obtaining coverage and reimbursement approval of a drug from a government or other third-party payor is a time-consuming and costly process that could require us to provide to each payor supporting scientific, clinical, and cost-effectiveness data for the use of our future approved drugs on a payor-by-payor basis, with no assurance that coverage and adequate reimbursement will be obtained. Even if we obtain coverage for a given drug, the resulting reimbursement rates might not be adequate for us to achieve or sustain profitability or may require co-payments that patients find unacceptably high. Additionally, third-party payors may not cover, or provide adequate reimbursement for, long-term follow-up evaluations required following the use of our future approved drug candidates. Patients are unlikely to use any of our future approved drugs unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of the drug. Because some of our drug candidates may have a higher cost of goods than conventional small molecule therapies, and may require long-term follow-up evaluations, the risk that coverage and reimbursement rates may be inadequate for us to achieve profitability may be greater.

Increasingly, third-party payors are requiring that companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot assure that reimbursement will be available for any approved drug candidate that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Reimbursement may impact the demand for, or the price of, any approved drug candidate that we commercialize. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any drug candidate that we successfully develop.

There may be significant delays in obtaining reimbursement for approved drug candidates, and coverage may be more limited than the purposes for which the drug candidates are approved by the FDA, NMPA, TGA, Health Canada, EMA or other comparable regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Payment rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on payments allowed for lower cost drugs that are already reimbursed, and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future weakening of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the U.S. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any future approved drug candidates and any new drugs that we develop could have a material adverse effect on our business, operating results and overall financial condition.

We intend to seek approval alone or in conjunction with partners to market our drug candidates in the U.S., China, the European Union, Australia, Canada, and other jurisdictions. In China, Australia, Canada, and the European Union, the pricing of drugs is subject to governmental control, and it can take considerable time after obtaining marketing regulatory approval to get the future approved drugs reimbursed. Market acceptance and sales of any of our future approved drug candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for drugs and may be affected by existing and future healthcare reform measures.

Our drug candidates, if approved in the future, may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success and the market opportunity for the drug candidate may be smaller than we estimate.

Our drug candidates, if approved in the future, may fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. For example, current MS treatments are well established in the medical community, and physicians may continue to rely on these treatments to the exclusion of our drug candidates that are in clinical trials for the same or similar indications. In addition, physicians, patients, and third-party payors may prefer other novel products to ours. If our drug candidates do not achieve an adequate level of acceptance, we may not generate significant product sales revenues and we may not become profitable. The degree of market acceptance of our drug candidates, if approved for commercial sale, will depend on a number of factors, including:

- the clinical indications for which our drug candidates are approved;
- whether physicians, hospitals, treatment centers and patients consider our drug candidates as a safe and effective treatment;
- the potential and perceived advantages of our drug candidates over alternative treatments;
- the prevalence and severity of any side effects;
- product labeling or product insert requirements of regulatory authorities;
- limitations or warnings contained in the labeling approved by regulatory authorities;
- the timing of market introduction of our drug candidates as well as competitive drugs;
- the cost of treatment in relation to alternative treatments;
- the availability of adequate coverage, reimbursement and pricing by third-party payors and government authorities;
- the willingness of patients to pay out-of-pocket in the absence of coverage and reimbursement by third-party payors and government authorities; and
- the effectiveness of our sales and marketing efforts.

If any approved drug candidates that we commercialize fail to achieve market acceptance among physicians, patients, hospitals, treatment centers or others in the medical community, we will not be able to generate significant revenue. Even if any future approved drug candidates achieve market acceptance, we may not be able to maintain that market acceptance over time if new products or technologies are introduced that are more favorably received than our drug candidates, are more cost-effective or render our drug candidates obsolete.

If our drug candidates cause, or are perceived to cause, undesirable side effects, it can result in delays or failure to receive regulatory approval or limitations on the commercial profile of an approved label.

Undesirable side effects caused by our drug candidates could cause either us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, NMPA, TGA, Health Canada, EMA or other regulatory authorities. If the results of the ongoing clinical trials of our drug candidates reveal a high and unacceptable severity and prevalence of undesirable side effects, the clinical trials of our drug candidates could be suspended or terminated and the FDA, NMPA, TGA, Health Canada, EMA or comparable regulatory authorities could order us to cease further development of or deny approval of our drug candidates for any or all targeted indications. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the clinical trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Clinical trials assess a sample of the potential patient population. With a limited number of patients and a limited duration of exposure, rare and severe side effects of our drug candidates may only be uncovered with a significantly larger number of patients exposed to the drug candidates. If our drug candidates receive regulatory approval and we or others discover undesirable side effects caused by such drugs (or any other similar drugs) or that such drug candidates are less effective than previously believed, a number of potentially significant negative consequences could result, including:

- the FDA, NMPA, TGA, Health Canada, EMA or other comparable regulatory authorities may withdraw or limit their approval of such drug candidates;
- the FDA, NMPA, TGA, Health Canada, EMA or other comparable regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contra-indication;

- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way such drug candidates are distributed or administered, conduct additional clinical trials or change the labeling of our drug candidates;
- the FDA, NMPA, TGA, Health Canada, EMA or other comparable regulatory authorities may require the development of risk evaluation and mitigation strategies and plans to mitigate risks, which could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools;
- we may be subject to regulatory investigations and government enforcement actions;
- we may decide to, or be required to, remove such drug candidates from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our drugs; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected drug candidates and could substantially increase the costs of commercializing our drugs, if approved, and significantly impact our ability to successfully commercialize our drugs and generate revenue.

Adverse drug reactions and negative results from off-label use of our products could materially harm our business reputation, product brand name, commercial operations, financial condition, including the value of our Common Stock, and expose us to liability.

Products distributed or sold in the pharmaceutical market may be subject to off-label drug use. Off-label drug use is prescribing a product for an indication, patient population, dosage strength or frequency, or other condition of use that is not in accordance with regulatory approved usage and labeling. Even though the FDA, NMPA, TGA, Health Canada, EMA and other comparable regulatory authorities actively enforce the laws and regulations prohibiting the promotion of off-label use, there remains the risk that our products are subject to off-label drug use and are prescribed in a patient population or dosage that has not been approved by competent authorities. Off-label use of our products may be less effective or entirely ineffective and may cause adverse drug reactions. Any of these occurrences can create negative publicity and significantly harm our business reputation, product brand name, commercial operations, and financial condition, including the value of our Common Stock. In addition, this may negatively impact our ability to commercialize our products because it could influence third party payers reimbursement and formulary placement decisions about our products. These occurrences may also expose us to liability and cause, or lead to, a delay in the progress of our clinical trials and may also ultimately result in failure to obtain regulatory approval for our drug candidates.

Off-label use of our products could expose us to government investigation or prosecution.

Regulatory bodies that enforce laws and regulations to prohibit off-label use may investigate whether our products are being used off-label. Even though we take steps to prevent off-label promotion of our products, this would not necessarily prevent regulatory or prosecuting agencies from investigating and taking action against us as if we were engaged in off-label promotion.

As a company, we have no experience in launching and marketing drugs. If we are unable to develop sales, marketing and distribution capabilities or enter into sales, marketing and distribution agreements or arrangements with third parties, we may not be successful in commercializing any drugs, if approved, or generating drug candidate sales revenue.

We have not yet demonstrated an ability to launch and commercialize any of our drug candidates, if approved. As a result, our ability to successfully commercialize any approved drugs may involve more inherent risk, take longer, and cost more than it would if we were a company with prior experience launching and marketing drugs.

We will have to compete with other pharmaceutical and biopharmaceutical companies to recruit, hire, train and retain marketing and sales personnel. We must either develop internal sales, marketing, and commercial distribution capabilities for any or all of our approved drugs or pursue collaborative arrangements regarding the sales and marketing of our approved drugs. However, there can be no assurance that we will be able to develop such distribution capabilities or establish or maintain such collaborative arrangements, or if we are able to do so, that they will have effective sales forces. Any revenue we receive will depend upon the efforts of such third parties. We would have little or no control over the marketing and sales efforts of such third parties, and our revenue from product sales, if approved, may be lower than if we had commercialized any approved drugs by ourselves or we may fail to generate any product sales revenue in the future at all.

We face substantial competition from other pharmaceutical and biotechnology companies, and our operating results may suffer if we fail to compete effectively.

The development and commercialization of new drugs is highly competitive. We face competition from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell drugs or are pursuing the development of drugs for the treatment of neurological diseases and other disorders for which we are commercializing our drugs or developing our drug candidates. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing, and commercialization.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any drugs that we may commercialize or may develop. Our competitors may also obtain approval from the FDA, NMPA, TGA, Health Canada, EMA or other comparable regulatory authorities for their drugs more rapidly than we may obtain approval for our drugs, which could result in our competitors establishing a strong market position before we are able to enter the market and/or could slow our regulatory approval.

Many of our current or future competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved drugs than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We may be subject, directly or indirectly, to applicable anti-kickback, false claims laws, physician payment transparency laws, privacy and security laws, fraud and abuse laws or similar healthcare and security laws and regulations in the U.S. and other jurisdictions, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and others play a primary role in the recommendation and prescription of any products for which we obtain regulatory approval. If we obtain FDA approval for any of our drug candidates and begin commercializing those drugs in the U.S., our operations may be subject to various federal and state fraud and abuse laws, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and physician payment sunshine laws and regulations. These laws may impact, among other things, our proposed sales, marketing, and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act;
- the federal false claims and civil monetary penalties laws, including the civil False Claims Act and the Civil Monetary Penalties Law, which can be enforced by private citizens through civil whistleblower or qui tam actions, prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- HIPAA prohibits, among other things, executing or attempting to execute a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by HITECH, and their implementing regulations, also imposes obligations, including mandatory contractual terms, certain covered healthcare providers, health plans, and healthcare clearinghouses and their respective business associates and covered subcontractors that perform services for them that involve the use, or disclosure of,

individually identifiable health information with respect to safeguarding the privacy, security and transmission of individually identifiable health information; and

- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to annually report to the CMS information regarding payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members. Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified nurse anesthetists and certified nurse-midwives. The information reported is publicly available on a searchable website, with disclosure required annually.

Additionally, we are subject to state and non-U.S. equivalents of each of the healthcare laws described above, among others, some of which may be broader in scope and may apply to healthcare services reimbursed by any source, not just governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or other voluntary industry codes of conduct. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements, and if we fail to comply with applicable state law requirements, we could be subject to penalties.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines and/or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government.

Neither the U.S. government nor the U.S. courts have provided definitive guidance on limitations to potential liability under the fraud and abuse laws as they may apply to our business. Law enforcement authorities are increasingly focused on enforcing these laws, often using new and creative legal theories, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. Regardless of the compliance efforts, it is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. In addition, private individuals have the ability to bring actions on behalf of the U.S. government under the federal False Claims Act as well as under the false claims laws of several states. If any such actions are instituted against us, defending against such actions, even if successful, would distract us and our key personnel from our core mission and impose potentially significant costs. If we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid, and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our approved drugs outside the U.S. will also likely subject us to non-U.S. equivalents of the healthcare laws mentioned above, among other non-U.S. laws, as well as the U.S. Foreign Corrupt Practices Act.

If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business.

We may face difficulties from changes to current regulations and future legislation.

In the U.S. and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of drug candidates, restrict or regulate post-approval activities, and affect the ability to profitably sell drug candidates for which marketing approval is obtained. Among policy makers and payors in the U.S. and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the U.S., the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

For example, the Affordable Care Act has substantially changed healthcare financing and delivery by both governmental and private insurers. Among the Affordable Care Act provisions of importance to the pharmaceutical and biotechnology industries are the following: among other things, subjected biological products to potential competition by lower-cost biosimilars, created a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are

inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D.

Some of the provisions of the Affordable Care Act have yet to be implemented, and there have been legal and political challenges to certain aspects of the Affordable Care Act. For example, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Affordable Care Act is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the Affordable Care Act will remain in effect in its current form. Further, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the Affordable Care Act marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Affordable Care Act. It is possible that the Affordable Care Act will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the Affordable Care Act and our business.

Further legislation or regulation could be passed that could harm our business, financial condition and results of operations. Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. For example, in August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect beginning on April 1, 2013. However, COVID-19 relief legislation suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2021. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024.

Additionally, there has been increasing legislative and enforcement interest in the U.S. with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed federal legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Additionally, based on a recent executive order, the Biden administration expressed its intent to pursue certain policy initiatives to reduce drug prices. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. In addition, Congress is considering drug pricing as part of the budget reconciliation process. Individual states in the U.S. have also become increasingly active in passing legislation and implementing regulations designed to control biopharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We anticipate that the Affordable Care Act, if substantially maintained in its current form, will continue to result in additional downward pressure on coverage and the price that we receive for any approved product, and could seriously harm our business. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. Further, the implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Such reforms could have an adverse effect on anticipated revenue from drug candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop drug candidates.

Any failure to perform proper quality control and quality assurance would have a material adverse effect on our business and financial results.

The manufacturing of our drug candidates and any drugs, if approved, is subject to applicable laws, regulations, and GMP. These regulations govern manufacturing processes and procedures, including record keeping and the implementation and operation of quality

management systems to control and assure the quality of investigational products and products approved for sale. We apply stringent quality controls at each stage of our production process to comply with these requirements. We perform extensive tests throughout the manufacturing processes to ensure the safety and effectiveness of our drug candidates. We may, however, detect instances in which an unreleased product was produced without adherence to our manufacturing procedures or the raw material used in our production process was not collected to store in accordance with the GMP or other regulations, resulting in a determination that the implicated products should be destroyed.

In addition, if we fail to comply with relevant quality control requirements under laws, regulations, and GMP, we could experience a disruption in the supply of our products, which could delay or prevent further sales of such products, which could have a material adverse effect on our business and financial results.

In addition, quality issues may arise during scale-up activities. If we are unable to successfully ensure consistent and high quality of our products during large-volume production, the sales of our products may not be able to be promoted, which could have a material adverse effect on our business and financial results.

We may explore the licensing of commercialization rights or other forms of collaboration worldwide, which will expose us to additional risks.

Non-U.S. markets are an important component of our growth strategy. We initially intend to focus on opportunities in the U.S., the European Union, Canada, Australia, Japan, Korea and China, in particular. If we fail to obtain licenses or enter into collaboration arrangements with third parties in these or other markets, or if these arrangements are not successful, our revenue-generating growth potential will be adversely affected. Moreover, international business relationships subject us to additional risks that may materially adversely affect our ability to attain or sustain profitable operations, including:

- efforts to enter into collaboration or licensing arrangements with third parties in connection with our international sales, marketing, and distribution efforts may increase our expenses or divert our management's attention from the development of our drug candidates;
- difficulty of effective enforcement of contractual provisions in foreign jurisdictions;
- differing regulatory requirements for drug approvals and marketing internationally, including differing product reimbursement regimes;
- changes in a specific market's political and cultural climate or economic condition;
- potential third-party patent rights or potentially reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers, and regulatory requirements;
- economic weakness, including inflation;
- compliance with tax, employment, immigration, and labor laws for employees traveling abroad;
- the effects of applicable non-U.S. tax structures and potentially adverse tax consequences;
- currency fluctuations, which could result in increased operating expenses and reduced revenue;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad;
- workforce uncertainty and labor unrest;
- failure of our employees and contracted third parties to comply with Office of Foreign Assets Control rules and regulations and the Foreign Corrupt Practices Act; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters, including earthquakes, volcanoes, typhoons, floods, hurricanes, and fires.

These and other risks may materially and adversely affect our ability to attain or sustain revenue from international markets and could have a material adverse effect on our business, financial condition, results of operations and prospects.

Illegal and/or parallel imports and counterfeit pharmaceutical products may reduce demand for our future approved drug candidates and could have a negative impact on our reputation and business.

The imports, whether authorized by governmental policy or illegal, of competing products from countries where government price controls or other market dynamics result in lower prices may adversely affect the demand for any of our future drugs, if approved, and,

in turn, may adversely affect our sales and profitability if we commercialize our products. Unapproved foreign imports of prescription drugs are illegal under the current laws of the U.S., China, the European Union, Australia and other jurisdictions. However, illegal imports may continue to occur or even increase as the ability of patients to obtain these lower priced imports continues to grow. Furthermore, cross-border imports from lower-priced markets (parallel imports) into higher-priced markets could harm sales of our future drugs, if approved, and exert commercial pressure on pricing within one or more markets. In addition, competent government authorities may expand consumers' ability to import lower-priced versions of our future drugs, if approved, or competing products from outside the countries where we operate. Any future legislation or regulations that increase consumer access to lower-priced medicines from outside the countries where we operate could have a material adverse effect on our business.

Certain products distributed or sold in the pharmaceutical market may be manufactured without proper licenses or approvals, or may be fraudulently mislabeled with respect to their content or manufacturers. These products are generally referred to as counterfeit pharmaceutical products. The counterfeit pharmaceutical product control and enforcement system, particularly in developing markets such as China, may be inadequate to discourage or eliminate the manufacturing and sale of counterfeit pharmaceutical products imitating our products. Since counterfeit pharmaceutical products in many cases have very similar appearances to the authentic pharmaceutical products but are generally sold at lower prices, counterfeits of our products can quickly erode the demand for our future drugs, if approved. Our reputation and business could suffer harm as a result of counterfeit pharmaceutical products sold under our or our collaborators' brand names. In addition, theft of inventory at warehouses, plants or while in-transit, which are not properly stored and which are sold through unauthorized channels, could adversely impact patient safety, as well as our reputation and business.

We rely on third parties to conduct our preclinical studies and clinical trials and we must work effectively with collaborators to develop our drug candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize our drug candidates and our business could be substantially harmed.

We rely on and plan to continue to rely on third-party CROs and third-party vendors to monitor, collect samples, analyze samples, report data, and manage data for our ongoing preclinical and clinical programs. We rely on these third parties for execution of our preclinical studies and clinical trials. While we control only certain aspects of their activities, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal and regulatory requirements, and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities. We, our CROs, third-party vendors supporting our clinical programs, and our clinical investigators, are required to comply with GCPs, which are regulations and guidelines enforced by the FDA, NMPA, TGA, Health Canada, EMA, and other comparable regulatory authorities for all of our drugs in clinical development. If we, any of our CROs, third-party vendors, or clinical investigators fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, NMPA, TGA, Health Canada, EMA or comparable regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. In addition, our pivotal clinical trials must be conducted with products produced under GMP. Our failure, or the failure of any third party, to comply with these regulations may results in our having to repeat clinical trials, which would delay the regulatory approval process.

If any of our relationships with these third parties terminates, we may not be able to enter into arrangements with alternative CROs, vendors or clinical investigators, or to do so on commercially reasonable terms. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical and other programs. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they or our clinical investigators obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements, or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our drug candidates. As a result, our results of operations and any commercial prospects for our drugs would be harmed, our costs would increase and our ability to generate revenues would be delayed.

Switching or adding additional CROs or clinical investigators involves additional cost and delays, which can materially affect our ability to meet our desired clinical development timelines. There can be no assurance that we will not encounter these delays in the future or that these delays or challenges will not have a material adverse effect on our business, financial condition, results of operations and prospects.

Our ability to generate future revenues is dependent on our ability to work effectively with collaborators to develop our drug candidates, including to obtain regulatory approval. Our arrangements with collaborators will be critical to successfully bringing products to market and commercializing them, if approved. We rely on collaborators in various respects, including to undertake research and development programs, to conduct clinical trials, to manage or assist with the regulatory filings and approval process, and to assist with our commercialization efforts. We do not control our collaborators and we cannot ensure that these third parties will adequately and timely perform all of their obligations to us. If they fail to complete the remaining studies successfully, or at all, it would delay, adversely affect or prevent regulatory approval. We cannot guarantee the satisfactory performance of any of our collaborators'

obligations and if any of our collaborators breach or terminate their agreements with us, we may not be able to successfully commercialize the drug candidates which could materially and adversely affect our business, financial condition, results of operations and prospects.

Our CROs, clinical investigators and third-party vendors may also be impacted by the COVID-19 outbreak. See "—Our financial condition and results of operations may be adversely affected by the COVID-19 pandemic."

We have entered into research collaborations and may form or seek collaborations, joint ventures or strategic alliances or enter into licensing arrangements in the future, and we may not realize the benefits of such collaborations, alliances, or licensing arrangements.

We may form or seek strategic alliances, create joint ventures or collaborations, or enter into licensing arrangements with third parties that we believe will complement or augment our development and commercialization efforts with respect to our drug candidates and any future drug candidates that we may develop. Any of these relationships may require us to incur non-recurring and other costs, increase our near and long-term expenditures, disrupt our management and business, or issue securities that dilute our existing stockholders.

While we have entered into collaborative research arrangements with some of the world's leading academic institutions and research centers and are working with key scientists in the field of central nervous system disorders, we face significant competition in seeking appropriate strategic partners and the negotiation process is time-consuming and complex. Moreover, we may not be successful in our efforts to establish a strategic partnership or other alternative arrangements for our drug candidates because they may be deemed to be at too early of a stage of development for collaborative effort and third parties may not view our drug candidates as having the requisite potential to demonstrate safety and efficacy or commercial viability. If and when we collaborate with a third party for development and commercialization of a drug candidate, if approved, we can expect to relinquish some or all of the control over the future success of that drug candidate to the third party. For any drug candidates that we may seek to in-license from third parties, we may face significant competition from other pharmaceutical or biotechnology companies with greater resources or capabilities than we have, and any agreement that we do enter into may not result in the anticipated benefits.

Further, collaborations involving our drug candidates are subject to numerous risks, which may include the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to a collaboration;
- collaborators may not pursue development and commercialization of our drug candidates, if approved, or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in their strategic focus due to the acquisition of competitive drugs, availability of funding, or other external factors outside of our control, such as a business combination that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial, stop a clinical trial, abandon a drug candidate, repeat or conduct new clinical trials, or require a new formulation of a drug candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, drugs that compete directly or indirectly with our drugs;
- collaborators with marketing and distribution rights to one or more drugs may not commit sufficient resources to their marketing and distribution;
- collaborators may not properly develop, maintain, or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liability;
- disputes may arise between us and a collaborator that cause the delay or termination of the research, development, or commercialization of our drug candidates, if approved, or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of our drug candidates, if approved; and
- collaborators may own or co-own intellectual property covering our drugs that results from our collaborating with them, and in such cases, we would not have the exclusive right to commercialize such intellectual property.

As a result, we may not be able to realize the benefit of any current or future research collaborations, strategic partnerships, or the potential licensing of third-party drugs if we are unable to successfully integrate such products with our existing operations and company culture, which could delay our timelines or otherwise adversely affect our business. We also cannot be certain that, following a strategic

transaction or license, we will achieve the revenue or net income that justifies such transaction. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of one of more of our drug candidates, reduce or delay our development program or one or more of our future development programs, delay our potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our drug candidates or, if approved, bring them to market and generate product sales revenue, which would harm our business, financial condition, results of operations and prospects.

Our business depends on the use of raw materials, and a decrease in the supply or an increase in the cost of these raw materials or any quality issues in such raw materials could materially and adversely affect our business, financial condition, results of operations and prospects.

In order to manufacture our products, we must obtain sufficient quantities of high-quality raw materials at commercially acceptable prices and in a timely manner. Certain critical raw materials, such as wires made of high-purity gold and other transition elements, are available from a limited number of suppliers in the market. As a result, any disruption in production or inability of our suppliers to produce adequate quantities to meet our needs could impair our ability to operate our business on a day-to-day basis and to continue our research and development of future drug candidates. Moreover, we expect our demand for such materials to increase as we expand our business scale and commercialize our products, if approved, and we cannot guarantee that current suppliers have the capacity to meet our demand. We are also exposed to the risk of increased material costs, which we may not be able to pass on to customers and as a result, we could have lower profitability. In addition, although we have implemented quality inspection procedures on such materials before they are used in our manufacturing processes and also require our suppliers to maintain high quality standards, we cannot guarantee that we will be able to secure sufficient quantities of raw materials at high quality standards, nor detect all quality issues in the supplies we use. For example, should the highly purified water that we utilize be compromised in any way, it could render entire batches unusable or, depending on the nature of the impurity, could be dangerous to patients. Further, we cannot assure you that third parties will be able to maintain and renew all licenses, permits, and approvals necessary for their operations or comply with all applicable laws and regulations. Failure to do so by them may lead to interruption in their business operations, which in turn may result in shortages of the raw materials utilized by us. If we are unable to obtain adequate raw materials and the quality of our products suffers as a result, we may have to delay clinical trials and regulatory filings, recall our products, be subject to product liability claims, fail to comply with continuing regulatory requirements, and incur significant costs to rectify such issues, which may have a material and adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to obtain and maintain sufficient patent protection for our drug candidates through intellectual property rights, or if the scope of such intellectual property rights obtained is not sufficiently broad, third parties could develop and commercialize products similar or identical to our products, and our ability to commercialize our approved drugs successfully may be adversely affected.

Our success depends in large part on our ability to protect our proprietary technology, drug candidates in clinical trials, and approved drugs on market (if approved) from competition by obtaining, maintaining and enforcing our intellectual property rights, including patent rights. We seek to protect the drug candidates and technology that we consider commercially important by filing patent applications in most important commercial markets, including the U.S., China, Europe, Canada, Japan, Korea, and other countries, relying on trade secrets or pharmaceutical regulatory protection or employing a combination of these methods. However, the patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. As a result, we may not be able to prevent competitors from developing and commercializing competitive drugs in all such fields and territories.

Patents may be invalidated and patent applications may not be granted for a number of reasons, including known or unknown prior art, deficiencies in the patent application or the lack of novelty of the underlying invention or technology. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and any other third parties, any of these parties may breach such agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the U.S. and other jurisdictions are typically not published until 18 months after filing, or in some cases, not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications or that we were the first to file for patent protection of such inventions. Furthermore, China, EPO, and the U.S. have adopted the “first-to-file” system under which whoever first files a patent application will

be awarded the patent if all other patentability requirements are met. Under the first-to-file system, third parties may be granted a patent relating to a technology which we invented.

The coverage sought by the claims in a patent application can be significantly reduced before the patent is issued, and the scope of the claims can be reinterpreted after issuance. Even if patent applications we license or own currently or in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. In addition, the patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain.

The issuance of a patent is not conclusive as to our inventorship, scope, validity, or enforceability, and our patents may be challenged in the courts or patent offices in any country. We may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office ("USPTO"), or become involved in opposition, derivation, revocation, re-examination, post-grant and *inter partes* review, or interference proceedings or similar proceedings in foreign jurisdictions challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or approved drugs and compete directly with us without payment, or result in our inability to manufacture or commercialize drug candidates and approved drugs without infringing, misappropriating or otherwise violating third-party patent rights. Moreover, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge the priority of our invention or other features of patentability of our patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity, or in patent claims being narrowed, invalidated, or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and drug candidates. Such proceedings also may result in substantial costs and require significant time from our scientists and management, even if the eventual outcome is favorable to us. Consequently, we do not know whether any of our technology or drug candidates will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

Furthermore, although various extensions may be available, the life of a patent and the protection it affords, are limited. For example, approved therapies may face competition from generic medications after the related patents have expired, or if they are challenged and invalidated even before their expiry. Manufacturers of generic drugs may challenge the scope, validity or enforceability of our patents in court, and we may not be successful in enforcing or defending those intellectual property rights and, as a result, may not be able to develop or market the relevant product exclusively, which would have a material adverse effect on any potential sales of that product. The issued patents and pending patent applications, if issued, for our drug candidates are expected to expire on various dates as described in "Business—Intellectual Property" of this Annual Report. Upon the expiration of our issued patents or patents that may issue from our pending patent applications, we will not be able to assert such patent rights against potential competitors and our business and results of operations may be adversely affected.

Given the amount of time required for the development, testing and regulatory review of new drug candidates, patents protecting such drug candidates might expire before or shortly after such drugs are commercialized. As a result, our patents and patent applications may not provide us with sufficient rights to exclude others from commercializing products similar or identical to our products. Moreover, some of our patents and patent applications may in the future be co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

We may not be able to protect our intellectual property rights throughout the world or prevent unfair competition by third parties.

Filing, prosecuting, maintaining, and defending patents on drug candidates in all countries throughout the world could be prohibitively expensive for us, and our intellectual property rights in some non-U.S. countries can have a different scope and strength than do those in the U.S. In addition, the laws of certain non-U.S. countries do not protect intellectual property rights to the same extent as the laws of the U.S. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the U.S., or from selling or importing drugs made using our inventions in and into the U.S. or non-U.S. jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own drugs and further, may export otherwise infringing drugs to non-U.S. jurisdictions where we have patent protection, but where enforcement rights are not as strong as

those in the U.S. These drugs may compete with our future approved drugs and our patent rights or other intellectual property rights may not be effective or adequate to prevent them from competing.

We may become involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful. Our patent rights relating to our drugs could be found invalid or unenforceable if challenged in court or before the U.S. Patent and Trademark Office or comparable non-U.S. authority.

Competitors may infringe our patent rights or misappropriate or otherwise violate our intellectual property rights. To counter infringement or unauthorized use, litigation may be necessary in the future to enforce or defend our intellectual property rights, protect our trade secrets or determine the validity and scope of our own intellectual property rights or the proprietary rights of others. Enforcement or defense of intellectual property rights can be expensive and time consuming. Any claims that we assert against perceived infringers could also provoke these parties to assert counterclaims against us alleging that we infringe their intellectual property rights. Many of our current and potential competitors have the ability to dedicate substantially greater resources to enforce and/or defend their intellectual property rights than we can. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating our intellectual property. An adverse result in any litigation proceeding could put our patents, as well as any patents that may issue in the future from our pending patent applications, at risk of being invalidated, held unenforceable or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

In patent litigation in the U.S., defendant counterclaims in district courts or in the Patent Trademark and Appeal Board alleging invalidity or unenforceability are commonplace, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Third parties may also raise similar claims before administrative bodies in the U.S. or abroad, even outside the context of litigation. Such mechanisms include *ex parte* re-examination, *inter partes* review, post-grant review, derivation and equivalent proceedings in non-U.S. jurisdictions, such as opposition proceedings. Such proceedings could result in revocation or amendment to our patents in such a way that they no longer cover and protect our drug candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity of our patents, for example, we cannot be certain that there is no invalidating prior art of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our drug candidates. Such a loss of patent protection could have a material adverse impact on our business.

We may not be able to prevent misappropriation of our trade secrets or confidential information, particularly in countries where the laws may not protect those rights as fully as in the U.S. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

If we are sued for infringing the intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our drug candidates.

Our commercial success depends in part on our avoiding infringement of the patents and other intellectual property rights of third parties. We are aware of other issued patents belonging to third parties that exist in fields in which we are developing our drug candidates. There may also be third-party patents or patent applications of which we are currently unaware, and given the dynamic area in which we operate, additional patents are likely to be issued that relate to some aspects of our business. There is a substantial amount of litigation and other claims and proceedings involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries generally. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our drug candidates may give rise to claims of infringement of the patent rights of others.

Third parties may assert that we are using technology in violation of their patent or other proprietary rights. Defense of these claims, regardless of their merit, could involve substantial litigation expense and divert our technical personnel, management personnel, or both from their normal responsibilities. If third parties bring successful claims against us for infringement of their intellectual property rights, we may be subject to injunctive or other equitable relief, which could prevent us from developing and commercializing one or more of our drug candidates. We may also have to pay substantial damages, including treble damages and attorneys' fees in the case of willful infringement, or redesign our infringing drug candidates, which may be impossible or require substantial time and cost. In the event of an adverse result in any such litigation, or even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our drug candidates. Any such license might not be available on reasonable terms or at all. In the event that we are unable to obtain such a license, we would be unable to further develop and commercialize one or more of our drug candidates, which could harm our business significantly. We may also elect to enter into license agreements in order to settle patent infringement claims or to resolve disputes prior to litigation, and any such license agreements may require us to pay royalties and other fees that could significantly harm our business.

Intellectual property litigation may lead to unfavorable publicity that harms our reputation and increases our operating losses, causing the market price of our Common Stock to decline.

During the course of any intellectual property litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the market price of our Common Stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for noncompliance with these requirements.

Periodic maintenance fees on any issued patent are due to be paid to the USPTO and most foreign jurisdictions either annually or in several stages over the lifetime of the patent. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent application process. Although an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Noncompliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees, and failure to properly legalize and submit formal documents. In any such event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

If we do not obtain patent term extension and data exclusivity for any drug candidates we may develop, our business may be materially harmed.

Depending upon the timing, duration, and specifics of any FDA marketing approval of any drug candidates we may develop, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Action of 1984, or Hatch Waxman Amendments. The Hatch Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during clinical trials and the FDA regulatory review process. A comparable extension right may exist in other foreign jurisdictions as well. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of drug approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. In addition, no patent term extension system has been established in China beyond the new pilot program, and implementation of the pilot program may not occur quickly. As a result, the patents we have in China are not yet eligible to be extended for patent term lost during clinical trials and the regulatory review process. If we are unable to obtain patent term extension or if the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations, and prospects could be materially harmed.

Changes in patent law could diminish the value of patents in general, thereby impairing our ability to protect our drug candidates.

The U.S. has recently enacted and is currently implementing wide-ranging patent reform legislation. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained, if any. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. There could be similar changes in the laws of foreign jurisdictions that may impact the value of our patent rights or other intellectual property rights.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to our issued patents and pending patent applications, we rely on trade secrets, including unpatented know-how, technology, and other proprietary information, to maintain our competitive position and to protect our drug candidates. We seek to

protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties that have access to them, such as our employees, corporate collaborators, outside scientific collaborators, sponsored researchers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. However, any of these parties may breach such agreements and disclose our proprietary information, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret can be difficult, expensive, time-consuming, and the outcome is unpredictable. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent the competitor from using that technology or information to compete with us and our competitive position would be harmed.

We may be subject to claims that our employees have wrongfully used or disclosed the alleged trade secrets of their former employers.

Many of our employees, including our senior management, were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment. Although we try to ensure that our employees do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's former employer. We are not aware of any threatened or pending claims related to these matters or concerning the agreements with our senior management, but in the future litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

Intellectual property rights do not necessarily protect us from all potential threats to our competitive advantages.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business, or permit us to maintain our competitive advantage. The following examples are illustrative:

- others may be able to make compounds that are similar to our drug candidates but that are not covered by the claims of the patents that we own or may in the future exclusively license;
- we might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own or may in the future exclusively license, which could result in the patent applications not issuing or being invalidated after issuing;
- we might not have been the first to file patent applications covering certain of our inventions, which could prevent the issuance of the patent applications or cause them to be invalidated after issuance;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own or have exclusively licensed may not provide us with any competitive advantages, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;
- we may obtain patents for certain drug candidates many years before we receive NDA approval for these drugs, and because patents have a limited life, which may begin to run prior to the commercial sale of the related drugs, limiting the commercial value of our patents;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive drugs for commercialization in our major markets;
- we may fail to develop additional proprietary technologies that are patentable;
- we may fail to apply for or obtain adequate intellectual property protection in all the jurisdictions in which we operate;
- the patents of others may have an adverse effect on our business, for example by preventing us from commercializing one or more of our drug candidates for one or more indications; and
- any of the aforementioned threats to our competitive advantage could have a material adverse effect on our business.

Risks Related to the Reverse Recapitalization and Integration of Businesses

We have incurred significant increased expenses and administrative burdens as a public company, which could have an adverse effect on our business, financial condition and results of operations.

As a newly public company, and particularly after we are no longer an emerging growth company or smaller reporting company, we have faced and will continue to face increased legal, accounting, administrative and other costs and expenses as a public company that we did not incur as a private company. The Sarbanes-Oxley Act, including the requirements of Section 404, as well as rules and regulations subsequently implemented by the U.S. Securities and Exchange Commission ("SEC"), the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010 and the rules and regulations promulgated and to be promulgated thereunder, the Public Company Accounting Oversight Board and the securities exchanges, impose additional reporting and other obligations on public companies. Compliance with public company requirements has increased costs and made certain activities more time-consuming. A number of those requirements has required us to carry out activities we have not done previously. Our management and other personnel also have devoted and will continue to devote a substantial amount of time to these compliance initiatives. In addition, additional expenses associated with SEC reporting requirements have been incurred. Furthermore, if any issues in complying with those requirements are identified (for example, if the auditors identify a material weakness or significant deficiency in the internal control over financial reporting), we could incur additional costs rectifying those issues, and the existence of those issues could adversely affect our reputation or investor perceptions of it. It is also more expensive to obtain director and officer liability insurance. Risks associated with our status as a public company may make it more difficult to attract and retain qualified persons to serve on the board of directors or as executive officers. The additional reporting and other obligations imposed by these rules and regulations has increased legal and financial compliance costs and the costs of related legal, accounting and administrative activities. These increased costs require us to divert a significant amount of money that could otherwise be used to expand our business and achieve strategic objectives. Advocacy efforts by stockholders and third parties may also prompt additional changes in governance and reporting requirements, which could further increase costs.

We qualify as an emerging growth company and smaller reporting company within the meaning of the Securities Act, and if we take advantage of certain exemptions from disclosure requirements available to emerging growth companies, it could make our Common Stock less attractive to investors and may make it more difficult to compare our performance to the performance of other public companies.

We qualify as an "emerging growth company" as defined in Section 2(a)(19) of the Securities Act, as modified by the JOBS Act. As such, we are eligible for and may take advantage of certain exemptions from various reporting requirements applicable to other public companies that are not emerging growth companies for as long as we continue to be an emerging growth company, including (i) the exemption from the auditor attestation requirements with respect to internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act, (ii) the exemptions from say-on-pay, say-on-frequency and say-on-golden parachute voting requirements and (iii) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We will remain an emerging growth company until the earlier of: (i) the last day of the fiscal year (a) following the fifth anniversary of the closing of the initial public offering of Tottenham, (b) in which we have total annual gross revenue of at least $1.07 billion, or (c) in which we are deemed to be a "large accelerated filer" under the Exchange Act, which would occur if the market value of the shares of our Common Stock held by non-affiliates exceeds $700.0 million as of the last business day of our most recently completed second fiscal quarter; or (ii) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this extended transition period and, as a result, we may adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-public companies instead of the dates required for other public companies. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

In addition, we are also a "smaller reporting company" because the market value of our stock held by non-affiliates is less than $700 million as of June 30, 2021 and our annual revenue was less than $100 million during the fiscal year ended December 31, 2021. We may continue to be a smaller reporting company in any given year if either (i) the market value of our stock held by non-affiliates is less than $250 million as of June 30 in the most recently completed fiscal year or (ii) our annual revenue is less than $100 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700 million as of June 30 in the most recently completed fiscal year. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

We cannot predict if investors will find our Common Stock less attractive because we rely on these exemptions. If some investors find our Common Stock less attractive as a result, there may be a less active trading market for our Common Stock and our stock price may be more volatile.

Risks Related to Our Common Stock

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws could make a merger, tender offer or proxy contest difficult, thereby depressing the trading price of our Common Stock.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage, delay or prevent a merger, acquisition or other change in control that stockholders may consider favorable, including transactions in which stockholders might otherwise receive a premium for their shares of our Common Stock. These provisions could also limit the price that investors might be willing to pay in the future for shares of our Common Stock, thereby depressing the market price of our Common Stock. Such provisions include the following:

- a classified board of directors with three-year staggered terms, which could delay the ability of stockholders to change the membership of a majority of our board of directors (the "Board");
- the ability of our Board to approve the issuance shares of preferred stock and to determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquiror and/or existing stockholders;
- the requirement for the affirmative vote of holders of at least 66⅔% of the voting power of all of the then-outstanding shares of the Common Stock, voting together as a single class, to amend certain provisions of our amended and restated certificate of incorporation or our amended and restated bylaws, which may inhibit the ability of an acquiror to effect such amendments to facilitate an unsolicited takeover attempt;
- the exclusive right of our Board to elect a director to fill a vacancy created by the expansion of our Board or the resignation, retirement death, disqualification or removal of a director, which prevents stockholders from being able to fill vacancies on our Board for a period of time; and
- the requirement that a special meeting of stockholders may be called only by our Board, the chairman of our Board or our Chief Executive Officer, which could delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors.

These and other provisions in our amended and restated certificate of incorporation and amended and restated bylaws could make it more difficult for stockholders or potential acquirors to obtain control of our Board or initiate actions that are opposed by our then-current Board, including the ability to delay or impede a merger, tender offer or proxy contest. The existence of these provisions could negatively affect the price of our Common Stock and limit opportunities for stockholders to realize value in a corporate transaction.

Future offerings of debt or equity securities by us may adversely affect the market price of our Common Stock.

In the future, we may attempt to obtain financing or to further increase our capital resources by issuing additional shares of our Common Stock or offering debt or other equity securities, including commercial paper, medium-term notes, senior or subordinated notes, debt securities convertible into equity or shares of preferred stock. Future clinical trials, commercialization efforts, and acquisitions could require substantial additional capital in excess of cash from operations. We would expect to obtain the capital required for acquisitions through a combination of additional issuances of equity, corporate indebtedness and/or cash from operations.

Issuing additional shares of our Common Stock or other equity securities or securities convertible into equity may dilute the economic and voting rights of our existing stockholders or reduce the market price of our Common Stock or both. Upon liquidation, holders of such debt securities and preferred shares, if issued, and lenders with respect to other borrowings would receive a distribution of our available assets prior to the holders of our Common Stock. Debt securities convertible into equity could be subject to adjustments in the conversion ratio pursuant to which certain events may increase the number of equity securities issuable upon conversion. Preferred shares, if issued, could have a preference with respect to liquidating distributions or a preference with respect to dividend payments that could limit our ability to pay dividends to the holders of our Common Stock. Our decision to issue securities in any future offering will depend on market conditions and other factors beyond our control, which may adversely affect the amount, timing and nature of our future offerings.

General Risk Factors

There can be no assurance that we will be able to comply with the continued listing standards of Nasdaq.

If Nasdaq delists our shares of Common Stock or warrants from trading on its exchange for failure to meet Nasdaq's listing standards, we and our stockholders could face significant material adverse consequences including:

- a limited availability of market quotations for our securities;
- reduced liquidity for our securities;
- a determination that our Common Stock is a "penny stock" which will require brokers trading in our Common Stock to adhere to more stringent rules and possibly result in a reduced level of trading activity in the secondary trading market for our securities;
- a limited amount of news and analyst coverage; and
- a decreased ability to issue additional securities or obtain additional financing in the future.

The price of our Common Stock may be volatile.

The stock markets in general and the markets for biotechnology stocks have experienced extreme volatility. The market for the common stock of smaller companies such as ours is characterized by significant price volatility when compared to the shares of larger, more established companies that trade on a national securities exchange and have large public floats, and the share price of our Common Stock is more volatile than the price of the shares of such larger, more established companies and will continue to be for the indefinite future.

The price of our Common Stock may fluctuate due to a variety of factors, including:

- changes in the industries in which we operate;
- variations in our operating performance and the performance of our competitors in general;
- material and adverse impact of the COVID-19 pandemic on the markets and the broader global economy;
- actual or anticipated fluctuations in our quarterly or annual operating results;
- publication of research reports by securities analysts about us or our competitors or our industry;
- the public's reaction to our press releases, our other public announcements and our filings with the SEC;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- additions and departures of key personnel;
- changes in laws and regulations affecting our business;
- commencement of, or involvement in, litigation involving us;
- changes in our capital structure, such as future issuances of securities or the incurrence of additional debt;
- the volume of shares of our Common Stock available for public sale; and
- general economic and political conditions such as recessions, interest rates, fuel prices, foreign currency fluctuations, international tariffs, social, political and economic risks, pandemics and acts of war or terrorism.

These market and industry factors may materially reduce the market price of our Common Stock regardless of our operating performance.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

To date, we do not have any owned properties. We have leased a number of properties from independent third parties in the U.S. Our leased Salt Lake City headquarters is utilized for finance, clinical development, clinical operations, translational medicine, and business operations. Our leased North East, Maryland facility is utilized for manufacturing and research and development activities. Our newly-leased Elkton, Maryland facility will be utilized to increase our manufacturing capability. We believe that our facilities are suitable and adequate for present purposes and that our productive capacity is substantially being utilized.

The following summary sets forth the details of our leased properties:

- *EOS at Millrock Park, LLC (Salt Lake City, Utah)*—approximately 5,028 square feet, expiring April 2027 with an option to extend thereafter.
- *Upper Chesapeake Flex One, LLC (North East, Maryland)*—approximately 32,603 square feet, expiring January 2029 with an option to extend thereafter.
- *100 Chesapeake Blvd LLC (Elkton, Maryland)*—approximately 74,210 square feet, expiring August 2031 with an option to extend thereafter and a purchase option at the expiration of the seventh year.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings. From time to time, we may, however, be involved in legal proceedings in the ordinary course of business. We cannot predict the outcome of any such legal proceedings, and despite the potential outcomes, the existence thereof may have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. As of the date of this Annual Report, we are not aware of any pending or threatened litigation or administrative proceedings against us, our officers or our directors which may have a material and adverse impact on our business, financial condition or results of operations.

Item 4. Mine Safety Disclosures

Not Applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our Common Stock and publicly-traded warrants are traded on Nasdaq under the symbols "CLNN" and "CLNNW," respectively.

Holders

As of March 8, 2022, there were 63,138,351 issued and outstanding shares of our Common Stock held by 80 stockholders of record. The number of stockholders of record was determined from the records of our transfer agent and does not include beneficial owners whose shares are held in the names of various security brokers, dealers, and registered clearing agencies.

Dividends

We intend to retain all available funds and any future earnings to finance the growth and development of our business. We have never declared or paid cash dividends on our Common Stock, and we do not intend to pay cash dividends in the foreseeable future. Our ability to declare dividends is limited by the terms of financing or other agreements that we have entered into. Future debt or other financing arrangements also may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our Common Stock. Investors should not purchase our Common Stock with the expectation of receiving cash dividends.

Any future determination to declare dividends will be made at the discretion of our Board and will depend on our financial condition, results of operations, capital requirements, general business conditions, and other factors that our Board may deem relevant.

Recent Sales of Unregistered Securities

On February 1, 2021, prior to the effectiveness of a registration statement for our 2020 Stock Plan, we granted to our employees, consultants, and other service providers options to purchase an aggregate of 130,000 shares of our Common Stock under our 2020 Stock Plan at an exercise price of $6.55 per share. This issuance was made in reliance upon the exemption to the registration requirements of the Securities Act provided by Section 4(a)(2).

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. [Reserved]

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements reflecting our current expectations, hopes, beliefs, intentions, strategies, estimates, and assumptions concerning events and financial trends that may affect our future financial condition or results of operations. Actual results and the timing of events may differ materially from those contained in these forward-looking statements due to a number of factors, including those discussed in the sections titled "Cautionary Note Regarding Forward-Looking Statements" and "Risk Factors" appearing elsewhere in this Annual Report on Form 10-K. Unless the context otherwise requires, for purposes of this section, the terms "we," "us," the "Company" or "our" are intended to mean the business and operations of Clene Inc. and its consolidated subsidiaries.

Business Overview

We are a clinical-stage pharmaceutical company pioneering the discovery, development, and commercialization of novel clean-surfaced nanotechnology ("CSN®") therapeutics. CSN® therapeutics are comprised of atoms of transition elements that, when assembled in nanocrystal form, possess unusually high, unique catalytic activities not present in those same elements in bulk form. These catalytic activities drive, support, and maintain beneficial metabolic and energetic cellular reactions within diseased, stressed, and damaged cells.

Our patent-protected, proprietary position affords us the potential to develop a broad and deep pipeline of novel CSN® therapeutics to address a range of diseases with high impact on human health. We began in 2013 by innovating an electro-crystal-chemistry drug development platform that draws from advances in nanotechnology, plasma and quantum physics, material science, and biochemistry. Our platform process results in nanocrystals with faceted structures and surfaces that are free of the chemical surface modifications that accompany other production methods. Many traditional methods of nanoparticle synthesis involve the unavoidable deposition of potentially toxic organic residues and stabilizing surfactants on the particle surfaces. Synthesizing stable nanocrystals that are both nontoxic and highly catalytic has overcome this significant hurdle in harnessing transition metal catalytic activity for human therapeutic use.

Our clean-surfaced nanocrystals exhibit catalytic activities many-fold higher than multiple other commercially available nanoparticles, produced using various techniques, that we have comparatively evaluated. We now have multiple drug assets currently in development and/or clinical trials for applications in neurology, infectious disease, and oncology. Our development and clinical efforts are currently focused on addressing the high unmet medical needs in two areas: first, those related to central nervous system disorders including Amyotrophic Lateral Sclerosis ("ALS"), Multiple Sclerosis ("MS"), and Parkinson's Disease ("PD"); and second, those related to COVID-19, a highly infectious viral respiratory disease with serious and sometimes fatal co-morbidities.

We currently have no drugs approved for commercial sale and have not generated any revenue from drug sales. We have never been profitable and have incurred operating losses in each year since inception. We generate revenue from sales of dietary supplements through our wholly owned subsidiary, dOrbital, Inc., or through an exclusive license with 4Life Research LLC ("4Life"), a stockholders and related party. We anticipate these revenues to be small compared to our operating expenses and to the revenue we expect to generate from potential future sales of our drug candidates, for which we are currently conducting clinical trials. Our total loss from operations was $50.0 million and $20.2 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021 and 2020, we had an accumulated deficit of $163.3 million and $153.6 million, respectively.

We expect to continue investing in product development and sales and marketing, and we expect to incur additional losses in the future to fund our operations and conduct product research and development. We also recognize the need to raise additional capital to fully implement our business plan. The long-term continuation of our business plan is dependent upon the generation of sufficient revenues from our products to offset expenses and capital expenditures. In the event that we do not generate sufficient revenues and are unable to obtain funding, we will be forced to delay, reduce, or eliminate some or all of our research and development programs, product portfolio expansion, commercialization efforts, or capital expenditures, which could adversely affect our business prospects, ability to meet long-term liquidity needs, or we may be unable to continue operations.

Recent Developments of Our Clinical Programs

We have one Phase 2/3 registration clinical trial, the Healey ALS Platform Trial, which is currently ongoing to establish the safety and efficacy of CNM-Au8® in patients with ALS. Results for CNM-Au8® are anticipated in the second half of 2022. We completed the first dosing cohort of REPAIR-MS and REPAIR-PD, two open-label, investigator-blinded Phase 2 clinical trials which demonstrated target engagement of CNM-Au8® on the brain's energy metabolites. REPAIR-MS will continue with the initiation of a second dosing cohort in 2022. In addition, we have an ongoing Phase 2 clinical trial, VISIONARY-MS, for the treatment of visual pathway deficits in chronic optic neuropathy to assess the efficacy, safety, tolerability, and pharmacokinetics of CNM-Au8® for remyelination in stable relapsing MS. The VISIONARY-MS trial will conclude early due to COVID pandemic-related challenges. The full unblinded results

from the study are anticipated in the second half of 2022. We anticipate launching RESCUE-PD, a Phase 2 clinical trial for the treatment of patients with PD, in mid-2022. Finally, we have one Phase 2 clinical trial presently underway to establish the efficacy and safety of ZnAg liquid solution for the treatment of COVID-19.

We also support two Expanded Access Programs ("EAPs") for patients with ALS. The initial EAP was launched in partnership with the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital in September 2019, which is closed to new enrollment, but remains ongoing for current participants. A second EAP was recently implemented in conjunction with the Healey ALS Platform Trial at three participating clinical sites.

Impact of the COVID-19 Pandemic

The COVID-19 pandemic, which began in December 2019 and has spread worldwide, has caused many governments to implement measures to slow the spread of the COVID-19 outbreak. The COVID-19 pandemic and government measures taken in response have had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred, supply chains have been disrupted, and facilities and production have been suspended. The future progression of the COVID-19 pandemic and its effects on our business and operations remain uncertain. The COVID-19 pandemic may affect our ability to initiate and complete preclinical studies, delay the initiation of future clinical trials, disrupt regulatory activities, or have other adverse effects on our business and operations. In particular, we and our third-party contract research organizations ("CROs") have faced disruptions that may affect our ability to initiate and complete preclinical studies, cause manufacturing disruptions, or create delays at clinical trial sites. The COVID-19 pandemic has already caused significant disruptions in the financial markets, and may continue to cause such disruptions, which could impact our ability to raise additional funds to support our operations. Moreover, the COVID-19 pandemic has significantly impacted economies worldwide and could result in adverse effects on our business and operations.

We are monitoring the potential impact of the COVID-19 pandemic on our business and financial statements. While the COVID-19 pandemic has led to various research restrictions and paused certain of our clinical trials, these impacts have been temporary and to date we have not experienced material business disruptions or incurred impairment losses in the carrying values of our assets as a result of the COVID-19 pandemic. We are not aware of any specific related event or circumstance that would require us to revise the estimates reflected in our financial statements. The extent to which the COVID-19 pandemic will directly or indirectly impact our business, results of operations, and financial condition, including planned and future clinical trials and research and development costs, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19, the actions taken to contain or treat it, and the duration and intensity of the related effects.

Reverse Recapitalization with Tottenham and Clene Nanomedicine

On December 30, 2020 (the "Closing Date"), we completed the previously announced business combination (the "Reverse Recapitalization") with Tottenham Acquisition I Limited ("Tottenham"). At the closing of the Reverse Recapitalization, Clene Inc. acquired 100% of the issued and outstanding Clene Nanomedicine, Inc. ("Clene Nanomedicine") common stock, in exchange for 54,339,012 shares of Clene Inc. Common Stock, par value $0.0001 ("Common Stock") issued to the Clene Nanomedicine common stockholders, of which 2,716,958 shares were to be issued and held in escrow to satisfy any indemnification obligations. The escrowed shares were released without restrictions following the six-month anniversary of the completion of the Reverse Recapitalization.

At the closing of the Reverse Recapitalization, each stock option of Clene Nanomedicine common stock was cancelled and the holders thereof in exchange received 0.1320 newly-issued stock options of our Common Stock, which is 95% of the Reverse Recapitalization exchange ratio. Additionally, we issued (i) rights to 370,101 restricted stock awards under the 2020 Plan to the option holders which complements the 5% closing payment shares held in escrow for Clene Nanomedicine common stockholders discussed above, and (ii) rights to 1,136,961 restricted stock awards to option holders to complement the earn-out payments that would contingently be issued to certain current Clene Nanomedicine stockholders upon the achievement of milestones. See "Earn-out Shares" for the milestones detail.

Immediately after giving effect to the Reverse Recapitalization and the 2020 PIPE offering (discussed below), there were 59,526,171 shares of Common Stock issued and outstanding.

Earn-out Shares

In connection with the Reverse Recapitalization, certain of Clene Nanomedicine's common stockholders are entitled to receive earn-out payments (the "Clene Nanomedicine Contingent Earn-out"), and Tottenham's former officers and directors and Norwich Investment Limited (collectively, the "Initial Stockholders") are entitled to receive earn-out payments (the "Initial Stockholders Contingent Earn-out," and both collectively the "Contingent Earn-outs") based on achieving milestones discussed below. The Contingent Earn-outs have been classified as liabilities in the consolidated balance sheets and were initially measured at fair value on

the date of the Reverse Recapitalization and are subsequently remeasured to fair value at each reporting date. The change in fair value of the Contingent Earn-outs has been recorded in the consolidated statements of operations and comprehensive loss for the years ended December 31, 2021 and 2020.

The PIPE Offerings

Prior to the Closing Date, we entered into subscription agreements on December 28, 2020, with various investors (the "2020 PIPE"). Pursuant to the subscription agreements, we issued 2,239,500 shares of Common Stock at a price of $10.00 per share with net proceeds of $22.2 million. The purpose of the 2020 PIPE was to fund general corporate expenses. In addition, investors in the 2020 PIPE offering also received warrants to purchase a number of shares equal to one-half (1/2) of the number of 2020 PIPE shares, for an aggregate total of 1,119,750 shares of Common Stock, at an exercise price of $0.01 per share (the "PIPE Warrants"), subject to a 180-day holding period.

On May 24, 2021, we entered into subscription agreements with various investors for the 2021 PIPE. Pursuant to the subscription agreements, we issued 960,540 shares of Common Stock at a price of $9.63 per share with net proceeds of approximately $9.3 million. The closing of the 2021 PIPE occurred substantially concurrently with, and was conditioned upon, the closing of a loan agreement with Avenue Venture Opportunities Fund, L.P. ("Avenue"). The purpose of the 2021 PIPE was to fund the expansion of manufacturing capabilities in the state of Maryland and to fund general corporate expenses.

Between July 1, 2021 and December 20, 2021, various investors exercised PIPE Warrants for 1,119,750 shares of Common Stock at an exercise price of $0.01 per share. The PIPE Warrants were issued prior to the Closing Date and were subject to a 180-day holding period which expired on June 28, 2021. We received cash proceeds of $11,198.

Financial Overview

Our results of operations, financial condition, and the period-to-period comparability of our financial results are principally affected by the following factors:

Research and Development Expense

The discovery and development of novel drug candidates require a significant investment of resources over a prolonged period of time, and a core part of our strategy is to continue making sustained investments in this area. As a result of this commitment, our pipeline of drug candidates has been advancing and expanding, with two clinical-stage drug candidates currently being investigated.

Historically, substantially all of our research and development expenses relate to CNM-Au8®, our lead asset. Our research and development expenses are affected by the timing and advancement of our existing product pipeline as well as the timing and quantity of new drug programs commenced. Drug candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to per patient clinical trial site fees for larger clinical trials, the costs of opening and monitoring clinical sites, CRO activity, and manufacturing expenses. We anticipate that our research and development expenses will increase significantly due to the increase in clinical trial expenses incurred to develop our drug candidates.

Research and development costs are charged to operations as incurred. Research and development costs include payroll and personnel expenses, including salaries and related benefits and stock-based compensation expense for employees engaged in research and development functions; clinical trial supplies and materials to support our clinical trials; payments to CROs, principal investigators, and clinical trial sites; costs associated with preclinical activities; consulting costs; and allocated overhead, including rent, equipment, utilities, depreciation, insurance, and facilities maintenance costs. We account for nonrefundable advance payments for goods and services that will be used in future research and development activities initially as an asset and then as expenses when the goods have been received or when the service has been performed rather than when the payment is made.

Our clinical trial accrual process seeks to account for expenses resulting from obligations under contracts with CROs, consultants, and under clinical site agreements in connection with conducting clinical trials. The financial terms of these contracts are subject to negotiations, which vary from contract to contract and may result in payment flows that do not match the periods over which materials or services are provided to us under such contracts. We reflect the appropriate trial expenses in the consolidated financial statements by matching the appropriate expenses with the period in which services and efforts are expended. In the event advance payments are made to a CRO, the payments will be recorded as a prepaid asset, which will be expensed over the period of time the contracted services are performed.

General and Administrative Expense

General and administrative expenses consist primarily of payroll and personnel expenses, including salaries and related benefits and stock-based compensation expense; professional fees for legal, accounting, tax, and information technology services; fees for directors and officers' insurance; expenses for business development activities; utilities and facility expenses; travel expenses; rental fees; consulting fees; and other administrative expenses.

We anticipate that our general and administrative expenses will increase in future periods to support increases in our drug development activities and as we build out our commercial capabilities in advance of receiving regulatory approval for the rapidly advancing clinical trials of our drug candidates. These increases will likely include increased headcount, increased stock compensation expenses, expanded infrastructure including certain sales and marketing activities performed ahead of regulatory approval, and increased insurance expenses. We also anticipate increasing legal, compliance, accounting, and investor and public relations expenses associated with being a public company.

Other Income (Expense), Net

Other income (expense), net, consists primarily of (i) changes in the fair value of our (a) preferred stock warrant liability, (b) common stock warrant liability, and (c) Contingent Earn-outs; (ii) interest expense resulting from changes in fair value of our notes payable; (iii) gains and losses on extinguishment of convertible notes payable and notes payable; (iv) gain on termination of a lease; and (v) the Australia research and development credit, discussed below.

We also received grants issued by non-government entities which require us to comply with conditions attached to the grants. Income from grants is recognized in the period during which the related qualifying expenses are incurred, provided that the conditions under which the grants were provided have been met. We receive tax incentives from the Australian government in the form of cash subsidies for research and development activities related to clinical trial activities conducted by our Australian subsidiary, which are recognized as other income upon compliance with certain conditions.

Components of Results of Operations

Comparison of the Years Ended December 31, 2021 and 2020

Our results of operations for the years ended December 31, 2021 and 2020 was as follows:

	Year Ended December 31,		Change	
(in thousands)	**2021**	**2020**	**Dollars**	**%**
Product revenue	$ 570	$ 176	$ 394	224 %
Royalty revenue	153	30	123	410 %
Total revenue	723	206	517	251 %
Operating expenses:				
Cost of revenue	289	65	224	345 %
Research and development	28,416	15,204	13,212	87 %
General and administrative	21,996	5,151	16,845	327 %
Total operating expenses	50,701	20,420	30,281	148 %
Loss from operations	(49,978)	(20,214)	(29,764)	147 %
Total other income (expense), net	39,810	1,343	38,467	2,864 %
Net loss before income taxes	(10,168)	(18,871)	8,703	(46)%
Income tax expense	428	(406)	834	(205)%
Net loss	$ (9,740)	$ (19,277)	$ 9,537	(49)%

Revenue

We generated product revenue totaling $0.6 million and $0.2 million for the years ended December 31, 2021 and 2020, respectively, in our Supplements segment under a supply agreement with 4Life for KHC46 and Zinc Factor™, two dietary (mineral) supplements that we began supplying during those periods. We generated royalty revenue totaling $0.2 million and $30,000 for the years ended December 31, 2021 and 2020, respectively, under an exclusive and royalty-bearing license agreement with 4Life relating to the sale of KHC46. For more details on the supply and license agreements, see Note 20 to our consolidated financial statements.

We also generated minimal product revenue from sales of rMetx™ ZnAg Immune Boost during those periods.

Cost of Revenue

Cost of revenue totaled $0.3 million and $0.1 million for the years ended December 31, 2021 and 2020, respectively, relating to production and distribution costs for the sales of KHC46, Zinc Factor™, and rMetx™ dietary supplements.

Research and Development Expense

Research and development expense for the years ended December 31, 2021 and 2020 was as follows:

	Year Ended December 31,		Change	
(in thousands)	2021	2020	Dollars	%
CNM-Au8	$ 11,659	$ 5,921	$ 5,738	97 %
CNM-ZnAg	970	1,176	(206)	(18)%
Unallocated	3,542	2,471	1,071	43 %
Personnel	7,414	5,156	2,258	44 %
Stock-based compensation	4,831	480	4,351	906 %
Total research and development	$ 28,416	$ 15,204	$ 13,212	87 %

The majority of our research and development expenses were related to the development of our lead drug candidate, CNM-Au8®, including ongoing clinical trials. The increase in research and development expense related to CNM-Au8® was primarily due to the progression of the clinical development process, including increased enrollment in the REPAIR-PD, REPAIR-MS, VISIONARY-MS, and RESCUE-ALS clinical trials and calendar payments for our participation in the Healey ALS Platform Trial. The increase in unallocated research and development expense was primarily due to increased rent expense related to our newly-leased facility in Elkton, Maryland and a decrease in milestone funding from certain grant awards; partially offset by decreased manufacturing and materials expenses. The increase in personnel and stock-based compensation expense was due to our increased headcount.

General and Administrative Expenses

General and administrative expense for the years ended December 31, 2021 and 2020 was as follows:

	Year Ended December 31,		Change	
(in thousands)	2021	2020	Dollars	%
Directors and officers' insurance	$ 3,719	$ 160	$ 3,559	2,224 %
Legal	1,518	275	1,243	452 %
Finance and accounting	3,183	1,889	1,294	69 %
Public and investor relations	887	—	887	100 %
Personnel	3,530	1,466	2,064	141 %
Stock-based compensation	7,553	281	7,272	2,588 %
Other	1,606	1,080	526	49 %
Total general and administrative	$ 21,996	$ 5,151	$ 16,845	327 %

The increase in general and administrative expense of $16.8 million or 327.0% was primarily due to (i) increased directors and officers insurance as a public company, (ii) increased legal fees as a public company, (iii) increased finance and accounting fees resulting from our SEC compliance function, filing fees for two registration statements on Form S-1, costs to improve our processes and internal controls, and fees for various financial vendors, institutions, investment bankers, and advisors, (iv) increased fees related to our public and investor relations efforts, (v) increased fees for information technology services, (vi) increased fees for pre-commercial activities in advance of receiving regulatory approval for the rapidly advancing clinical trials of our drug candidates, and (vii) increased personnel costs and stock-based compensation expense due to our increased headcount.

Other Income (Expense), Net

Other income (expense), net, for the years ended December 31, 2021 and 2020 included the following:

(i) interest expense of $0.9 million and $1.0 million, respectively, due to a decrease in the fair value of certain notes payable, resulting from a decrease in the closing price of our Common Stock on the Nasdaq Stock Market LLC ("Nasdaq") from September 30, 2021 to December 31, 2021; and interest expense on notes payable of $1.4 million;

(ii) gain on extinguishment of notes payable of $0.6 million and $0, respectively, due to the forgiveness of a Paycheck Protection Program loan (the "PPP Loan") by the U.S. Small Business Administration;

(iii) loss on extinguishment of convertible notes payable of $0 and $0.5 million, respectively;

(iv) gain on termination of lease of $0 and $0.1 million, respectively, due to the termination of an operating lease for office space;

(v) expense of $0 and $14.6 million, respectively, relating to the change in fair value of the preferred stock warrant liability. Upon the consummation of the Reverse Recapitalization, the preferred stock warrant liability qualified for classification as permanent equity and was reclassified to additional paid-in capital;

(vi) income of $1.0 million and $0, respectively, relating to the change in fair value of the common stock warrant liability. The change in fair value was primarily a result of the decrease of the closing price of our Common Stock on Nasdaq from $9.01 per share on May 21, 2021, when we initially measured the common stock warrant liability, to $4.10 per share on December 31, 2021, when we remeasured the common stock warrant liability; partially offset by the decrease of the expected term from 5.00 years on May 21, 2021 to 3.89 for the Tranche 1 warrants (defined below) and 4.39 years for the Tranche 2 warrants (defined below) on December 31, 2021;

(vii) recognized income of $34.0 million and $12.7 million, respectively, relating to the change in fair value of the Clene Nanomedicine Contingent Earn-out liability; and recognized income of $3.6 million and $1.5 million, respectively, relating to the change in fair value of the Initial Stockholders Contingent Earn-out liability. The change in fair value was primarily a result of the decrease of the closing price of our Common Stock on Nasdaq from $9.01 per share on December 31, 2020 to $4.10 per share on December 31, 2021 when we remeasured the Contingent Earn-out liabilities; and

(viii) recognized income of $1.5 million and $3.2 million, respectively, relating to the Australia research and development credit. We recognized Australia research and development credit in an amount equal to the qualifying expenses incurred in each period multiplied by the applicable reimbursement percentage. The decrease in research and development credit is the result of decreased research and development activities in Australia during the year ended December 31, 2021.

Taxation

United States

We are incorporated in Delaware in the U.S. and subject to statutory U.S. federal corporate income tax at a rate of 21% for the years ended December 31, 2021 and 2020. We are also subject to state income tax in Utah and Maryland, at a rate of 4.95% and 8.25%, respectively, for the years ended December 31, 2021 and 2020. As of December 31, 2021 and 2020, we recorded a full valuation allowance against our net deferred tax assets due to the uncertainty as to whether such assets will be realized resulting from our three-year cumulative loss position and the uncertainty surrounding our ability to generate pre-tax income in the foreseeable future.

Australia

Our wholly-owned subsidiary, Clene Australia Pty Ltd (“Clene Australia”), was established in Australia on March 5, 2018 and is subject to corporate income tax at a rate of 25% and 27.5% for the years ended December 31, 2021 and 2020, respectively. Clene Australia income tax expense totaled $0.4 million and $0.4 million for the years ended December 31, 2021 and 2020, respectively. We recorded $1.5 million and $3.2 million as other income during the years ended December 31, 2021 and 2020, respectively, for a refund of research and development credits pertaining to Clene Australia for the 2021 and 2020 tax years, respectively.

Netherlands

Our wholly-owned subsidiary, Clene Netherlands B.V. (“Clene Netherlands”), was established in the Netherlands on April 21, 2021 and will be subject to corporate income tax at a rate of 15% up to €245,000 of taxable income and 25% for taxable income in excess of €245,000. During the year ended December 31, 2021, Clene Netherlands had no taxable income and no provision for income taxes.

Liquidity and Capital Resources

Sources of Capital

We have incurred significant losses and negative cash flows from operations since our inception. We expect to incur additional losses in the future to fund our operations and conduct product research and development. We recognize the need to raise additional capital to fully implement our business plan. The long-term continuation of our business plan is dependent upon the generation of sufficient revenues from our products to offset expenses and capital expenditures. In the event that we do not generate sufficient revenues and are unable to obtain funding, we will be forced to delay, reduce, or eliminate some or all of our research and development programs, product portfolio expansion, commercialization efforts, or capital expenditures, which could adversely affect our business prospects, ability to meet long-term liquidity needs, or we may be unable to continue operations.

Since our inception, we have dedicated substantially all of our resources to the development of our drug candidates. We have financed our operations principally through the following sources:

- gross proceeds of $87.2 million from sales of our preferred stock and other equity financing;
- gross proceeds of $28.1 million from borrowings under convertible promissory notes;
- gross proceeds of $0.6 million through government lending;
- gross proceeds of $2.3 million from grants from various organizations;
- gross cash proceeds of $31.8 million from the Reverse Recapitalization and the 2020 PIPE;
- gross cash proceeds of $0.6 million from a Program Paycheck Protection loan obtained through the U.S. Small Business Administration, which was forgiven in January 2021;
- gross cash proceeds of approximately $9.3 million from the 2021 PIPE; and
- gross cash proceeds of $20.0 million borrowings under notes payable.

We also receive indirect financial support for the Healey ALS Platform Trial, administered by Massachusetts General Hospital, which is conducting a platform trial of CNM-Au8® alongside other drugs at significantly lower costs than we would otherwise incur if we were to conduct a comparably designed clinical trial at reasonable market rates.

Liquidity

We incurred a loss from operations of $50.0 million and $20.2 million for the years ended December 31, 2021 and 2020, respectively, and a net loss of $9.7 million and $19.3 million for the years ended December 31, 2021 and 2020, respectively. Our accumulated deficit was $163.3 million as of December 31, 2021. Our cash and restricted cash totaled $50.3 million and $59.3 million as of December 31, 2021 and 2020, respectively, and we used net cash in operating activities of $34.6 million and $18.9 million during the years ended December 31, 2021 and 2020, respectively.

We have incurred significant losses and negative cash flows from operations since our inception. We have not generated significant revenues to date, and we do not anticipate generating significant revenues unless we successfully complete development and obtain regulatory approval for our drug candidates. We expect our expenses to increase significantly and to incur additional losses in the future to fund our operations, particularly as we advance the development of our clinical-stage drug candidates, continue research and development of our preclinical drug candidates, and initiate additional clinical trials of, and seek regulatory approval for, these and other future drug candidates. We expect our expenses relating to regulatory compliance and sales and marketing personnel to increase significantly as we prepare to commence commercialization if we obtain regulatory approval for our drug candidates.

The accompanying consolidated financial statements have been prepared presuming we will continue as a going concern, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business. Our long-term operations require obtaining additional capital to fund our operations. As part of our ongoing business plans, we will continue seeking to raise additional capital through equity financing and may seek debt financing or other capital sources, and we may attempt to collaborate with a third party for development and commercialization of our drug candidates. We may not be able to obtain capital on acceptable terms, or at all. The terms of any financing may adversely affect the holdings or rights of our stockholders. Depending on the results of our current business plans, we may need to implement cost-saving initiatives, including potentially delaying or reducing research and development programs and commercialization efforts beginning as early as the third quarter of 2022. Currently, without additional capital, we believe we have sufficient resources to fund our continuing operations into the second quarter of 2023.

Short-Term Material Cash Requirements

For at least the next twelve months, our primary capital requirements are to fund our operations, including research and development, personnel, regulatory, and other clinical trial costs related to development of our lead drug candidate, CNM-Au8®; and general and administrative costs to support our drug development and pre-commercial activities in advance of receiving regulatory approval for our drug candidates.

Firm commitments for funds include approximately $0.1 million and $0.9 million of payments under finance and operating lease obligations, respectively; payment of interest on notes payable totaling $2.0 million; and commitments under various agreements for capital expenditures totaling $0.6 million related to the construction of our manufacturing facilities. We expect to meet our short-term liquidity requirements primarily through cash on hand. Additional sources of funds, should we need them, include equity financing, debt financing, or other capital sources.

We enter into agreements in the normal course of business with CROs for clinical trials and with vendors for preclinical studies and other services and products for operating purposes, which are cancelable at any time by us, subject to payment of our remaining obligations under binding purchase orders and, in certain cases, nominal early termination fees. These commitments are not deemed significant.

Long-Term Material Cash Requirements

Beyond the next twelve months, our primary capital requirements are to fund our operations, including research and development, personnel, regulatory, and other clinical trial costs related to development of our lead drug candidate, CNM-Au8®; and general and administrative costs to support our drug development and pre-commercial activities in advance of receiving regulatory approval for our drug candidates. Additional funds may be spent to initiate new clinical trials, at our discretion. Known obligations beyond the next twelve months include $0.1 million and $6.9 million of payments under finance and operating lease obligations, respectively; and interest and principal repayment of notes payable of $24.0 million.

Use of Funds

Our cash flows for the years ended December 31, 2021 and 2020 were as follows:

	Year Ended December 31,	
(in thousands)	**2021**	**2020**
Net cash used in operating activities	$ (34,624)	$ (18,929)
Net cash used in investing activities	(1,332)	(387)
Net cash provided by financing activities	27,112	69,534
Effect of foreign exchange rate changes on cash	(85)	269
Net increase (decrease) in cash	$ (8,929)	$ 50,487

Our primary use of cash in all periods presented was to fund our research and development, regulatory and other clinical trial costs, and general corporate expenditures.

Operating Activities

Net cash used in operating activities represents cash receipts and disbursements related to all of our activities other than investing and financing activities. Operating cash flow is derived by adjusting our net loss for non-cash items and the net change in our operating assets and liabilities. Net cash used in operating activities was $34.6 million during the year ended December 31, 2021, which resulted from a net loss of $9.7 million adjusted for non-cash items totaling ($25.9) million and a net change in operating assets and liabilities of $1.0 million. Significant non-cash items included the change in the fair value of our (i) common stock warrant liability related to the Avenue Warrant of ($1.0) million, and (ii) Clene Nanomedicine and Initial Stockholders Contingent Earn-outs from the Reverse Recapitalization of ($34.0) million and ($3.6) million, respectively. The changes in fair value of these instruments were primarily driven by the decrease in our stock price as discussed under “Other Income (Expenses)” above. Additional significant non-cash items included (a) stock-based compensation expense of $12.4 million, driven by our increased headcount; (b) depreciation expense of $1.0 million relating to laboratory and office equipment and leasehold improvements; and (c) gain on extinguishment of notes payable of ($0.6) million, relating to the forgiveness of the PPP Loan. The net change in our operating assets and liabilities was primarily attributable to the following: (A) increases in accounts payable and accrued liabilities of $1.3 million and $0.9 million, respectively, which in both cases was due to the timing of vendor invoicing and payments, and (B) an increase in prepaid expenses and other current assets of $0.7 million due to the timing of vendor invoicing and payments and timing of receipt of metals to be used in research and development, partially offset by a decrease in Australia research and development credit receivable.

Net cash used in operating activities was $18.9 million during the year ended December 31, 2020, which resulted from a net loss of $19.3 million, adjusted for non-cash items totaling $3.7 million and a net change in operating assets and liabilities of ($3.3) million. Non-cash items primarily consisted of the following: (i) depreciation expense of $1.0 million, (ii) stock-based compensation expense of $0.8 million, (iii) change in fair value of preferred stock warrant liability of $14.6 million, (iv) change in fair value of Clene Nanomedicine Contingent Earn-out of ($12.7) million, (v) change in fair value of Initial Stockholders Contingent Earn-out of ($1.5) million, (vi) loss on extinguishment of convertible notes payable of $0.5 million, and (vii) increase in interest accrued on notes payable and accretion of debt discount of $0.7 million and $0.2 million, respectively. The net change in our operating assets and liabilities was primarily attributable to the following: (a) increase in inventory of $0.2 million, (b) increase in prepaid expenses and other current assets of $2.8 million due to an increase in prepayments to CROs and other vendors and an increase in Australia research and development credit receivable, (c) decrease in accounts payable of $0.3 million, (d) increase in income tax payable of $0.2 million related to Clene Australia, (e) decrease in accrued liabilities of $0.3 million due to the timing of vendor invoicing and payments, (f) decrease in payable

to related parties of $0.1 million, (g) increase in deferred income tax of $0.3 million, (h) increase in deferred revenue from related parties of $0.1 million, and (i) decrease in operating lease obligations of $0.1 million.

Investing Activities

Net cash used in investing activities was $1.3 million and $0.4 million during the years ended December 31, 2021 and 2020, respectively, which in each instance consisted of purchases of property and equipment.

Financing Activities

Net cash provided by financing activities was $27.1 million during the year ended December 31, 2021, which primarily consisted of the following: (i) proceeds from issuance of notes payable of $20.0 million offset by payments of notes payable offering costs of $0.5 million, (ii) proceeds from the 2021 PIPE of $9.3 million, (iii) payments of deferred offering costs of $1.9 million related to the Reverse Recapitalization, (iv) proceeds from exercise of stock options of $0.4 million, and (ii) payments of finance lease obligations of $0.2 million.

Net cash provided by financing activities was $69.5 million during the year ended December 31, 2020, which primarily consisted of the following: (i) proceeds from the issuance of Series D preferred stock of $35.1 million,, (ii) proceeds from the Reverse Recapitalization and 2020 PIPE of $31.8 million, offset by payments of related deferred offering costs of $4.0 million, (iii) proceeds from the issuance of convertible notes payable of $6.1 million, (iv) proceeds from issuance of notes payable of $0.7 million, (v) proceeds from exercise of stock options of $0.1 million, and (vi) payments of finance lease obligations of $0.2 million.

Maryland Loan

In February 2019, we entered into a loan agreement (the “2019 MD Loan”) with the Department of Housing and Community Development, a principal department of the State of Maryland. The agreement provides for a term loan of $0.5 million. Amounts outstanding under the 2019 MD Loan bear simple interest at an annual rate of 8.0%. Under the 2019 MD Loan, we agreed to affirmative and negative covenants to which we will remain subject until maturity. These covenants include providing information about our Company and operations; limitations on our ability to retire, repurchase, or redeem our common or preferred stock, options, and warrants other than per the terms of the securities; and limitations on our ability to pay dividends of cash or property. There are no financial covenants associated with the 2019 MD Loan. Events of default under the 2019 MD Loan include failure to make payments when due, insolvency events, and failure to comply with covenants. We are not in violation of any affirmative covenants. Repayment of the full balance outstanding is due on February 22, 2034. The 2019 MD Loan establishes “Phantom Shares,” based on 119,907 shares of Common Stock (based on 863,110 Series C Preferred Shares prior to the Reverse Recapitalization), determined at issuance. The 2019 MD Loan states the repayment amount is to be the greater of the balance of principal and accrued interest or the Phantom Shares value. We determined that the note should be accounted for at fair value. We record the fair value of the debt at the end of each reporting period. In order to value the note, we consider the amount of the simple interest expense that would be due and the value of Phantom Shares. The fair value of the 2019 MD Loan is determined based on the closing price of CLNN shares listed on Nasdaq.

Income of $0.5 million and expense of $0.5 million was recognized during the years ended December 31, 2021 and 2020, respectively. The fair value of $0.6 million and $1.1 million of principal and accrued interest is included in long-term notes payable as of December 31, 2021 and 2020, respectively.

Cecil County Loan

In April 2019, we entered into a loan agreement (the “2019 Cecil Loan”) with Advance Cecil Inc., a non-stock corporation formed under the laws of the State of Maryland with application for 501(c)(3) status pending before the Internal Revenue Service at the time of execution of the 2019 Cecil Loan. The agreement provides for a term loan of $0.1 million. Amounts outstanding under the 2019 Cecil Loan bear simple interest at an annual rate of 8.0%. Under the 2019 Cecil Loan, we agreed to affirmative covenants to which we will remain subject until maturity. These covenants include providing information about our Company and operations. There are no financial covenants associated with the 2019 Cecil Loan. Events of default under the 2019 Cecil Loan include failure to make payments when due, insolvency events, and failure to comply with covenants. We are not in violation of any affirmative covenants. Repayment of the full balance outstanding is due on April 30, 2034. The 2019 Cecil Loan establishes “Phantom Shares,” based on 23,981 shares of Common Stock (based on 172,622 Series C Preferred Shares prior to the Reverse Recapitalization), determined at issuance. The 2019 Cecil Loan states the repayment amount is to be the greater of the balance of principal and accrued interest or the Phantom Share value. We determined that the note should be accounted for at fair value. We record the fair value of the debt at the end of each reporting period. In order to value the note, we consider the amount of the simple interest expense that would be due and the value of Phantom Shares. The fair value of the 2019 Cecil Loan is determined based on the closing price of CLNN shares listed on Nasdaq.

Income of $0.1 million and expense of $0.1 million was recognized during the years ended December 31, 2021 and 2020, respectively. The fair value of $0.1 million and $0.2 million of principal and accrued interest is included in long-term notes payable as of December 31, 2021 and 2020, respectively.

Avenue Loan

In May 2021, we entered into a loan agreement (the "2021 Avenue Loan") with Avenue. The agreement provides for a 42-month term loan of up to $30.0 million. The first tranche is $20.0 million, of which $15.0 million was funded at close and $5.0 million was funded in September 2021 ("Tranche 1"). We incurred issuance costs of $0.6 million of which $46,951 was expensed immediately. The remaining unfunded tranche of $10.0 million ("Tranche 2") is available at our request until December 31, 2022. Funding of Tranche 2 is subject to (a) our receipt of $5.0 million financing through Maryland's State Incentive Programs and/or other Maryland State programs; (b) our achievement of a statistically significant result on the primary endpoint, or if the totality of the results for any study warrant advancement into a subsequent clinical efficacy study, with respect to at least two of the following clinical trials: (i) RESCUE-ALS or the Healey ALS Platform Trial; (ii) REPAIR-PD; or (iii) REPAIR-MS ("Performance Milestone 1"); (c) our receipt of net proceeds of at least $30.0 million from the sale and issuance of our equity securities (including private placements or follow-on offerings) between May 2, 2021 and December 31, 2022; and (d) mutual agreement of us and Avenue.

The loans bear interest at a variable rate per annum equal to the sum of (i) the greater of (a) the prime rate, as published by the Wall Street Journal from time to time or (b) 3.25%, plus (ii) 6.60%. Payments are interest-only for the first 12 months and can be extended up to (i) 12 months (the "First Interest-only Period Extension") if we achieve Performance Milestone 1 and (ii) 36 months if (a) we achieve the First Interest-only Period Extension and (b) have drawn from Tranche 2. On August 16, 2021, we mutually confirmed with Avenue that Performance Milestone 1 and the First Interest-only Period Extension had been achieved. The loan will amortize in equal payments of principal from the end of the interest period to the expiration of the 42-month term on December 1, 2024. On the maturity date, an additional payment equal to 4.25% of the funded loans, or $0.9 million, is due in addition to the remaining unpaid principal and accrued interest. The final payment was recorded as a debt premium and is being amortized over the contractual term using the effective interest method. The final payment provision is related to the loan host and is not bifurcated pursuant to ASC 815.

Pursuant to the agreement, we granted to Avenue a warrant for the purchase of 115,851 shares of Common Stock (the "Avenue Warrant") at an exercise price equal to the lower of (i) $8.63 (which is equal to the five-day volume-weighted average price ("VWAP") per share, determined as of the end of trading on the last trading day prior to execution of the loan agreement), or (ii) the lowest price per share paid by cash investors for our Common Stock issued in the next bona fide round of equity financing prior to March 31, 2022 (the "Next Round Price"). Upon the funding of Tranche 2, the Avenue Warrant shall be automatically adjusted to include an additional estimated 145,740 shares of Common Stock, which is equal to 5% of the principal amount of Tranche 2, divided by the lower of (i) the five (5)-day VWAP per share; determined as of the end of trading on the last trading day before the date of issuance of Tranche 2; or (ii) the Next Round Price. We accounted for the Tranche 2 warrants at inception of the 2021 Avenue Loan in accordance with ASC 815 and the fair value and issuable shares will be remeasured at each reporting period. Avenue also has the right, in its discretion, but not the obligation, at any time from time to time from the first- through the third-year anniversary of the agreement, while the loan is outstanding, to convert an amount of up to $5.0 million of the principal amount of the outstanding loan into Common Stock (the "Conversion Feature") at a price per share equal to 120% of the stock purchase price set forth in the warrant. The Conversion Feature is subject to (i) the closing price of our Common Stock for each of the seven consecutive trading days immediately preceding the conversion being greater than or equal to the conversion price and (ii) the Common Stock issued in connection with any such conversion not exceeding 20% of the total trading volume of our Common Stock for the twenty-two consecutive trading days immediately prior to and including the effective date of such conversion.

Under the 2021 Avenue Loan, we agreed to affirmative and negative covenants to which we will remain subject upon maturity in the absence of prepayments. These covenants include providing information about our Company and operations; limitation on our ability to retire, repurchase, or redeem our Common Stock, options, and warrants other than per the terms of the securities; and limitations on our ability to pay dividends of cash or property. The financial covenant associated with the loan agreement includes maintaining minimum unrestricted cash and cash equivalents of at least $5.0 million; provided that upon our (i) achievement of Performance Milestone 1, and (ii) receiving of net proceeds of at least $30.0 million from the sale and issuance of our equity securities (including any PIPE or follow-on offering), we shall no longer be subject to financial covenants. We are not in violation of the covenants. The agreement provides for events of default customary for loans of this type, including but not limited to non-payment, breaches, the occurrence of a material adverse change, or defaults in the performance of covenants, insolvency, and bankruptcy. The 2021 Avenue Loan is collateralized by substantially all of our assets other than intellectual property, including our capital stock and the capital stock of our subsidiaries, in which Avenue is granted continuing security interest. The net proceeds from the issuance of the loan were initially allocated to the warrant at an amount equal to their fair value of $1.5 million and the remainder to the loan. The allocation of incurred financing costs of $0.5 million, which together with the fair value of the warrant and the final payment, are recorded as a debt discount and debt premium, respectively, and are being amortized over the contractual term using the effective interest method. During the year ended December 31, 2021, we recorded interest expense of $1.4 million.

Critical Accounting Policies and Estimates

Our discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. Generally Accepted Accounting Principles. The preparation of these financial statements requires us to make estimates, assumptions, and judgments that affect the reported amounts of assets, liabilities, revenues, costs, and expenses. We evaluate our estimates and judgments on an ongoing basis, and our actual results may differ from these estimates. We base our estimates on historical experience, known trends and events, contractual milestones, and other various factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources.

We consider the following estimates to be critical as they involve a significant level of estimation uncertainty and have had or are reasonably likely to have a material impact on our financial condition and results of operations. See Note 2 to our consolidated financial statements for a description of other significant accounting policies.

Contingent Earn-Out Liabilities

In connection with the Reverse Recapitalization, certain stockholders are entitled to the Contingent Earn-outs payments based on achievement of certain milestones. In accordance with ASC 815, *Derivatives and Hedging* ("ASC 815"), we classified the Contingent Earn-outs as liabilities in the consolidated balance sheets that were initially measured at fair value on the date of the Reverse Recapitalization. We remeasure the liabilities at each reporting date and record the change in fair value as a component of other income (expense), net, in the consolidated statements of operations and comprehensive loss. We estimate the fair value of the Contingent Earn-outs using a Monte Carlo valuation model. The unobservable inputs include the expected stock price volatility, the risk-free interest rate, and the expected term. Additionally, for one milestone, we estimated of the probability of completing a clinical trial for treatment of COVID-19 which results in a statistically significant finding of clinical efficacy within twelve months after the closing of the Reverse Recapitalization ("Milestone 3"), which requires significant judgment.

As of December 31, 2021 and 2020, the expected stock price volatility was 105.00% and 85.00%, respectively; the risk-free interest rate was 1.10% and 0.40%, respectively; the expected term was 4.00 years and 5.00 years, respectively. Milestone 3 was not achieved and was not an input in the valuation model as of as of December 31, 2021, and the probability of achieving Milestone 3 ranged between 5.80% and 11.70% as of December 31, 2020.

During the years ended December 31, 2021 and 2020, we recorded a change in the fair value of the Clene Nanomedicine Contingent Earn-out of $34.0 million and $12.7 million, respectively; and in the Initial Shareholders Contingent Earn-out of $3.6 million and $1.5 million, respectively.

Convertible Notes

Pursuant to the 2021 Avenue Loan, $5.0 million of the outstanding principal is subject to the Conversion Feature. In accordance with ASU 2020-06, Debt—*Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*, we classified this portion as convertible notes payable in the consolidated balance sheets and did not bifurcate the Conversion Feature from the host contract. Consequently, we account for the convertible note as a single liability measured at its amortized cost. As of December 31, 2021, the convertible note was carried at $4.6 million.

Common Stock Warrant Liability

Pursuant to Tranche 1 of the 2021 Avenue Loan, we granted to Avenue the Avenue Warrant. In accordance with ASC 815, we also recognized the Tranche 2 warrants issuable pursuant to the potential draw of Tranche 2. We classified the warrants as a liability in the consolidated balances sheets that were initially measured at fair value at the inception of the 2021 Avenue Loan. We remeasure the liability at each reporting date and record the change in fair value as a component of other income (expense), net, in the consolidated statements of operations and comprehensive loss. We estimate the fair value of the Avenue Warrant using a Black-Scholes option-pricing model, with a probability weight related to the potential draw of Tranche 2, which requires significant judgment. The unobservable inputs include the expected stock price volatility, risk-free interest rate, expected term, and the probability of drawing Tranche 2.

As of December 31, 2021 and May 21, 2021, when the Avenue Warrant was issued, the expected stock price volatility was 105.00% and 90.00%, respectively; and the risk-free interest rate was 1.20% and 0.80%, respectively; and the probability of drawing Tranche 2 of the 2021 Avenue Loan was 50.00% and 50.00%, respectively. The expected term ranged between 3.89 and 4.39 years as of December 31, 2021, and was 5.00 years as of May 21, 2021.

During the year ended December 31, 2021, we recorded a change in the fair value of the common stock warrant liability of $1.0 million.

Income Taxes

We account for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. Additionally, we assess the likelihood that our deferred tax assets will be recovered from future taxable income and, to the extent we believe, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies. The estimation of these factors requires significant judgment. Based on our evaluation of these factors, we have not recorded income tax benefits for the net operating losses or for research and development tax credits or other deferred tax assets due to uncertainty of realizing benefits from these items.

Stock-Based Compensation

We account for stock-based compensation arrangements using a fair value-based method for costs related to all share-based payments including stock options and stock awards. The fair value is recognized over the period during which a grantee was required to provide services in exchange for the option award and service-based stock awards, known as the requisite service period (usually the vesting period), on a straight-line basis. For stock awards with market conditions, the fair value is recognized over the period based on the expected milestone achievement dates as the derived service period (usually the vesting period), on a straight-line basis. For stock awards with performance conditions, the grant-date fair value of these awards is the market price on the applicable grant date, and compensation expense will be recognized when the conditions become probable of being satisfied. We will recognize a cumulative true-up adjustment once the conditions become probable of being satisfied as the related service period had been completed in a prior period. We elect to account for forfeitures as they occur, rather than estimating expected forfeitures.

We estimate the fair value of stock options using a Black-Scholes option-pricing model. The unobservable inputs include the expected price volatility, risk-free interest rate, expected dividend yield, and expected term. The expected stock price volatility ranged between 87.40% and 91.51% during the year ended December 31, 2021, and between 75.00% and 119.30% during the year ended December 31, 2020. The risk-free interest rate ranged between 0.72% and 1.34% during the year ended December 31, 2021, and between 0.39% and 0.53% during the year ended December 31, 2020. The expected term was 6.00 years during the years ended December 31, 2021 and 2020.

We estimate the fair value of restricted stock awards using a Monte Carlo valuation model to simulate the achievement of certain stock price milestones. The unobservable inputs include the expected stock price volatility, risk-free interest rate, and expected term. As of December 31, 2020, the expected stock price volatility was 85.00%, the risk-free interest rate was 0.40%, and the expected term was 5.00 years. There were no restricted stock awards granted during the year ended December 31, 2021.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

As a smaller reporting company, we are not required to provide information required by this Item.

Item 8. Financial Statements and Supplementary Data

Index to Consolidated Financial Statements

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the shareholders and the Board of Directors of Clene Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheet of Clene Inc. and subsidiaries (the "Company") as of December 31, 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for the year ended December 31, 2021, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021, and the results of its operations and its cash flows for the year ended December 31, 2021, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audit provides a reasonable basis for our opinion.

/s/ Deloitte & Touche LLP

Salt Lake City, Utah
March 11, 2022

We have served as the Company's auditor since 2021.

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Clene Inc.

Opinion on the Financial Statements

We have audited the consolidated balance sheet of Clene Inc. and its subsidiaries (the "Company") as of December 31, 2020, and the related consolidated statement of operations and comprehensive loss, of redeemable convertible preferred stock and stockholders' equity (deficit) and of cash flows for the year ended December 31, 2020, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020, and the results of its operations and its cash flows for the year ended December 31, 2020 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audit included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audit provides a reasonable basis for our opinion.

Emphasis of Matter

As discussed in Note 1 to the consolidated financial statements, the Company will require additional financing or a collaboration agreement to fund future operations. Management's evaluation of the events and conditions and management's plans to mitigate this matter are also described in Note 1.

/s/ PricewaterhouseCoopers LLP

Salt Lake City, Utah
March 26, 2021

We served as the Company's auditor from 2019 to 2021.

CLENE INC.
CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share amounts)

	December 31, 2021	December 31, 2020
ASSETS		
Current assets:		
Cash	$ 50,288	$ 59,275
Accounts receivable	49	21
Inventory	41	191
Prepaid expenses and other current assets	4,205	3,502
Total current assets	54,583	62,989
Restricted cash	58	—
Right-of-use assets	3,250	1,029
Property and equipment, net	5,172	4,225
TOTAL ASSETS	$ 63,063	$ 68,243
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 1,923	$ 1,124
Accrued liabilities	3,610	3,960
Income tax payable	—	164
Deferred revenue from related parties	—	112
Operating lease obligations, current portion	347	194
Finance lease obligations, current portion	146	190
Clene Nanomedicine contingent earn-out, current portion	—	5,924
Total current liabilities	6,026	11,668
Operating lease obligations, net of current portion	4,370	1,785
Finance lease obligations, net of current portion	97	205
Notes payable	14,484	1,949
Convertible notes payable	4,598	—
Deferred income tax	—	260
Common stock warrant liability	474	—
Clene Nanomedicine contingent earn-out, net of current portion	18,100	46,129
Initial Stockholders contingent earn-out	2,317	5,906
TOTAL LIABILITIES	50,466	67,902
Commitments and contingencies (Note 13)		
Stockholders' equity:		
Common stock, $0.0001 par value: 150,000,000 and 100,000,000 shares authorized at December 31, 2021 and December 31, 2020, respectively; 62,312,097 and 59,526,171 shares issued and outstanding at December 31, 2021 and December 31, 2020, respectively	6	6
Additional paid-in capital	175,659	153,571
Accumulated deficit	(163,301)	(153,561)
Accumulated other comprehensive income	233	325
TOTAL STOCKHOLDERS' EQUITY	12,597	341
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	$ 63,063	$ 68,243

See accompanying notes to the consolidated financial statements.

CLENE INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except share and per share amounts)

	Year Ended December 31,	
	2021	2020
Revenue:		
Product revenue	$ 570	$ 176
Royalty revenue	153	30
Total revenue	723	206
Operating expenses:		
Cost of revenue	289	65
Research and development	28,416	15,204
General and administrative	21,996	5,151
Total operating expenses	50,701	20,420
Loss from operations	(49,978)	(20,214)
Other income (expense), net:		
Interest expense	(870)	(950)
Gain on extinguishment of notes payable	648	—
Loss on extinguishment of convertibles notes payable	—	(540)
Gain on termination of lease	—	51
Change in fair value of preferred stock warrant liability	—	(14,615)
Change in fair value of common stock warrant liability	983	—
Change in fair value of derivative liability	—	29
Change in fair value of Clene Nanomedicine contingent earn-out	33,953	12,659
Change in fair value of Initial Stockholders contingent earn-out	3,589	1,465
Australia research and development credit	1,519	3,210
Other income (expense), net	(12)	34
Total other income (expense), net	39,810	1,343
Net loss before income taxes	(10,168)	(18,871)
Income tax benefit (expense)	428	(406)
Net loss	(9,740)	(19,277)
Other comprehensive income (loss):		
Foreign currency translation adjustments	(92)	284
Total other comprehensive income (loss)	(92)	284
Comprehensive loss	$ (9,832)	$ (18,993)
Net loss per share-- basic and diluted (Note 19)	$ (0.16)	$ (1.10)
Weighted average common shares used to compute basic and diluted net loss per share	61,558,455	17,503,992

See accompanying notes to the consolidated financial statements.

CLENE INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share amounts)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Income	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balances at December 31, 2019[1]	27,499,837	$ 72,661	17,357,505	$ 2	$ 1,754	$ (69,571)	$ 41	$ (67,774)
Issuance of Series D preferred stock, net of issuance costs[1]	7,896,922	35,051	—	—	—	—	—	—
Issuance of Series D preferred stock upon extinguishment of convertible promissory notes[1]	1,497,135	6,891	—	—	—	—	—	—
Exercise of stock options[1]	—	—	87,613	—	78	—	—	78
Conversion of redeemable convertible preferred stock upon the Reverse Recapitalization[1]	(36,893,894)	(114,603)	36,893,894	4	114,599	—	—	114,603
Extinguishment of preferred stock warrant liability upon conversion of redeemable convertible preferred stock	—	—	—	—	17,828	—	—	17,828
Issuance of common stock upon the Reverse Recapitalization and private offering	—	—	4,542,995	—	31,833	—	—	31,833
Reverse Recapitalization offering costs	—	—	—	—	(5,911)	—	—	(5,911)
Issuance of common stock as payment of offering costs	—	—	644,164	—	—	—	—	—
Clene Nanomedicine contingent earn-out recognized upon the Reverse Recapitalization	—	—	—	—	—	(64,713)	—	(64,713)
Initial Stockholders contingent earn-out recognized upon the Reverse Recapitalization	—	—	—	—	(7,371)	—	—	(7,371)
Stock-based compensation expense	—	—	—	—	761	—	—	761
Foreign currency translation adjustment	—	—	—	—	—	—	284	284
Net loss	—	—	—	—	—	(19,277)	—	(19,277)
Balances at December 31, 2020	—	—	59,526,171	6	153,571	(153,561)	325	341
Issuance of common stock upon the private placement	—	—	960,540	—	9,250	—	—	9,250
Exercise of stock options	—	—	427,444	—	443	—	—	443
Exercise of warrants	—	—	1,119,750	—	11	—	—	11
Exercise of underwriter's option	—	—	54,083	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	12,384	—	—	12,384
Issuance of common stock upon vesting of restricted stock awards	—	—	224,109	—	—	—	—	—
Foreign currency translation adjustment	—	—	—	—	—	—	(92)	(92)
Net loss	—	—	—	—	—	(9,740)	—	(9,740)
Balances at December 31, 2021	—	$ —	62,312,097	$ 6	$ 175,659	$ (163,301)	$ 233	$ 12,597

(1) Retroactively restated for the Reverse Recapitalization as described in Note 3.

See accompanying notes to the consolidated financial statements.

CLENE INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,	
	2021	2020
Cash flows from operating activities:		
Net loss	$ (9,740)	$ (19,277)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	955	963
Non-cash lease expense	171	108
Change in fair value of preferred stock warrant liability	—	14,615
Change in fair value of common stock warrant liability	(983)	—
Change in fair value of Clene Nanomedicine contingent earn-out	(33,953)	(12,659)
Change in fair value of Initial Stockholders contingent earn-out	(3,589)	(1,465)
Stock-based compensation expense	12,384	761
Change in fair value of derivative	—	(29)
Gain on extinguishment of notes payable	(648)	—
Loss on extinguishment of convertible notes payable	—	540
Gain on termination of lease	—	(51)
Accretion of debt discount	336	179
Change in fair value of notes payable	(560)	732
Changes in operating assets and liabilities:		
Accounts receivable	(28)	(21)
Inventory	150	(163)
Prepaid expenses and other current assets	(702)	(2,841)
Accounts payable	1,267	(312)
Accrued liabilities	894	(272)
Income tax payable	(164)	164
Payable to related parties	—	(131)
Deferred revenue from related parties	—	112
Deferred income tax	(260)	260
Operating lease obligations	(154)	(142)
Net cash used in operating activities	(34,624)	(18,929)
Cash flows from investing activities:		
Purchases of property and equipment	(1,332)	(387)
Net cash used in investing activities	(1,332)	(387)
Cash flows from financing activities:		
Proceeds from exercise of stock options	443	78
Proceeds from warrants exercised	11	—
Payments of finance lease obligations	(152)	(194)
Proceeds from the issuance of notes payable	20,000	652
Payments of debt issuance costs	(534)	—
Payments of notes payable	(5)	—
Proceeds from the private placement	9,250	—
Payment of deferred offering costs	(1,901)	(4,011)
Proceeds from the Reverse Recapitalization and from the private placement	—	31,833
Proceeds from issuance of Series D Preferred Stock, net of issuance costs	—	35,051
Proceeds from the issuance of convertible notes payable	—	6,125
Net cash provided by financing activities	27,112	69,534
Effect of foreign exchange rate changes on cash and restricted cash	(85)	269
Net increase (decrease) in cash and restricted cash	(8,929)	50,487
Cash and restricted cash – beginning of year	59,275	8,788
Cash and restricted cash – end of year	$ 50,346	$ 59,275
Reconciliation of cash and restricted cash to the consolidated balance sheets		
Cash	50,288	59,275
Restricted cash	58	—
Cash and restricted cash	$ 50,346	$ 59,275

See accompanying notes to the consolidated financial statements.

CLENE INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS (Continued)
(In thousands)

	Year Ended December 31,	
	2021	2020
Supplemental disclosure of non-cash investing and financing activities:		
Lease liability arising from obtaining right-of-use assets, leasehold improvements, and lease incentives	$ 2,892	$ 820
Common stock warrant liability recorded at issuance of notes payable	$ 1,457	$ —
Lease liability settled through termination of lease	$ —	$ 348
Issuance of derivative instrument related to convertible notes	$ —	$ 705
Issuance of Series D Preferred Stock upon extinguishment of convertible promissory notes	$ —	$ 5,675
Extinguishment of derivative liability in connection with extinguishment of convertible promissory notes	$ —	$ 676
Deferred transaction costs in accounts payable	$ —	$ 546
Deferred transaction costs in accrued liabilities	$ —	$ 1,354
Conversion of redeemable convertible preferred stock into common stock	$ —	$ 114,603
Extinguishment of preferred stock warrant liability in connection with the conversion of redeemable convertible preferred stock	$ —	$ 17,828
Issuance of common stock as payment of related offering costs	$ —	$ 6,442
Clene Nanomedicine contingent earn-out recognized in connection with the Reverse Recapitalization	$ —	$ 64,713
Initial Stockholders contingent earn-out recognized in connection with the Reverse Recapitalization	$ —	$ 7,371
Supplemental disclosures:		
Cash paid for interest expense	$ 1,095	$ 39

See accompanying notes to the consolidated financial statements.

CLENE INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Nature of the Business

Clene Inc. (formerly Chelsea Worldwide Inc.) (the "Company," "we," "us," or similar such references) is a clinical-stage pharmaceutical company pioneering the discovery, development, and commercialization of novel clean-surfaced nanotechnology therapeutics. We have developed an electro-crystal-chemistry drug development platform which enables production of concentrated, stable, highly active, clean-surfaced nanocrystal suspensions. We have multiple drug assets currently in development for applications in neurology, infectious disease, and oncology. Our efforts are currently focused on addressing the high unmet medical needs in two areas: first, those related to central nervous system disorders including Amyotrophic Lateral Sclerosis ("ALS"), Multiple Sclerosis ("MS"), and Parkinson's Disease ("PD"); and second, those related to COVID-19, a highly infectious viral respiratory disease with serious and sometimes fatal co-morbidities. Our patented electro-crystal-chemistry manufacturing platform further enables us to develop very low concentration dietary supplements to advance the health and well-being of broad populations. These dietary supplements can vary greatly and include nanocrystals of varying composition, shapes and sizes as well as ionic solutions with diverse metallic constituents. Dietary supplements are marketed and distributed through our wholly owned subsidiary, dOrbital, Inc. ("dOrbital"), or through an exclusive license with 4Life Research LLC ("4Life"), a related party (see Note 20).

The accompanying consolidated financial statements include the accounts of Clene Inc. and our wholly-owned subsidiaries, Clene Nanomedicine, Inc. ("Clene Nanomedicine"), a subsidiary incorporated in Delaware, Clene Australia Pty Ltd ("Clene Australia"), a subsidiary incorporated in Australia, and dOrbital, a subsidiary incorporated in Delaware, after elimination of all intercompany accounts and transactions. The wholly-owned subsidiary, Clene Netherlands B.V. was established on April 21, 2021 and has no financial positions or operations to date.

Liquidity

We incurred a loss from operations of $50.0 million and $20.2 million for the years ended December 31, 2021 and 2020, respectively, and a net loss of $9.7 million and $19.3 million for the years ended December 31, 2021 and 2020, respectively. Our accumulated deficit was $163.3 million as of December 31, 2021. Our cash and restricted cash totaled $50.3 million and $59.3 million as of December 31, 2021 and 2020, respectively, and we used net cash in operating activities of $34.6 million and $18.9 million for the years ended December 31, 2021 and 2020, respectively.

We have incurred significant losses and negative cash flows from operations since our inception. We have not generated significant revenues to date, and we do not anticipate generating significant revenues unless we successfully complete development and obtain regulatory approval for our drug candidates. We expect our expenses to increase significantly and to incur additional losses in the future to fund our operations, particularly as we advance the development of our clinical-stage drug candidates, continue research and development of our preclinical drug candidates, and initiate additional clinical trials of, and seek regulatory approval for, these and other future drug candidates. We expect our expenses relating to regulatory compliance and sales and marketing personnel to increase significantly as we prepare to commence commercialization if we obtain regulatory approval for our drug candidates.

The accompanying consolidated financial statements have been prepared presuming we will continue as a going concern, which contemplates the realization of assets and satisfaction of liabilities in the normal course of business. Our long-term operations require obtaining additional capital to fund our operations. As part of our ongoing business plans, we will continue seeking to raise additional capital through equity financing and may seek debt financing or other capital sources, and we may attempt to collaborate with a third party for development and commercialization of our drug candidates. We may not be able to obtain capital on acceptable terms, or at all. The terms of any financing may adversely affect the holdings or rights of our stockholders. Depending on the results of our current business plans, we may need to implement cost-saving initiatives, including potentially delaying or reducing research and development programs and commercialization efforts beginning as early as the third quarter of 2022. Currently, without additional capital, we believe we have sufficient resources to fund our continuing operations into the second quarter of 2023.

Impact of the COVID-19 Pandemic

The COVID-19 pandemic, which began in December 2019 and has spread worldwide, has caused many governments to implement measures to slow the spread of the outbreak. The outbreak and government measures taken in response have had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred, supply chains have been disrupted, and facilities and production have been suspended. The future progression of the pandemic and its effects on our business and operations remains uncertain. The COVID-19 pandemic may affect our ability to initiate and complete preclinical studies and clinical trials, delay the initiation of future clinical trials, disrupt regulatory activities, or have other adverse effects on our business and operations. In particular, we and our contract research organizations ("CROs") have faced disruptions that have affected our ability to initiate and

complete preclinical studies, caused manufacturing disruptions, and created delays at clinical trial site initiation and clinical trial enrollment, leading to the early conclusion of an ongoing clinical trial. The pandemic has already caused significant disruptions in the financial markets, and may continue to cause such disruptions, which could impact our ability to raise additional funds to support our operations. Moreover, the pandemic has significantly impacted economies worldwide and could result in adverse effects on our business and operations.

We are monitoring the potential impact of the COVID-19 pandemic on our business and financial statements. While the COVID-19 pandemic has led to various research restrictions and led to pauses and early conclusion of certain of our clinical trials, these impacts have been temporary and to date we have not experienced material business disruptions or incurred impairment losses in the carrying values of our assets as a result of the pandemic and we are not aware of any specific related event or circumstance that would require us to revise the estimates reflected in these consolidated financial statements. The extent to which the COVID-19 pandemic will directly or indirectly impact our business, results of operations, cash flows, and financial condition, including planned and future clinical trials and research and development costs, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19, the actions taken to contain or treat it, and the duration and intensity of the related effects.

Registration Statements

On February 16, 2021, we filed a registration statement on Form S-1 (file number 333-253173) to register 4,541,481 shares of Clene Inc. common stock, par value $0.0001 (“Common Stock”) underlying outstanding warrants that we have previously issued, among which 2,517,500 and 904,231 were originally issued by Tottenham Acquisition I Limited (“Tottenham”) and Clene Nanomedicine, respectively, prior to the closing of the business combination (the “Reverse Recapitalization”), and 1,119,750 (the “PIPE Warrants”) were issued as part of a private placement (the “2020 PIPE”) in connection with the closing of the Reverse Recapitalization. We will receive aggregate proceeds of $30.7 million if all of the warrants are exercised. On April 19, 2021, the registration statement was declared effective by the U.S. Securities and Exchange Commission (the “SEC”). In connection with the registration statement on Form S-1, we incurred an immaterial amount of offering costs, recognized as general and administrative expenses in the consolidated statement of operations and comprehensive loss during the year ended December 31, 2021. During the year ended December 31, 2021, we received aggregate proceeds of $11,198 from the exercise of all of the PIPE Warrants, at an exercise price of $0.01 per share.

On July 22, 2021, we filed a registration statement on Form S-1 (file number 333-258098) to register 1,140,731 shares of Common Stock underlying outstanding warrants that we have previously issued, among which 1,024,880 were originally issued by Clene Nanomedicine prior to the Reverse Recapitalization in April 2013 and 115,851 were issued pursuant to a loan agreement (the “2021 Avenue Loan”) with Avenue Venture Opportunities Fund, L.P. (“Avenue”). We will receive aggregate proceeds of $3.0 million if all of these warrants are exercised. In addition, we registered 960,540 shares of Common Stock issued in a private placement in May 2021 (the “2021 PIPE”). We will not receive any proceeds from the possible sale of these shares by the selling shareholders named in the Registration Statement. On August 2, 2021, the registration statement was declared effective by the SEC. In connection with the registration statement on Form S-1, we incurred an immaterial amount of offering costs, recognized as general and administrative expenses in the consolidated statements of operations and comprehensive loss during the year ended December 31, 2021.

2. Summary of Significant Accounting Policies

Basis of Presentation

We have prepared the accompanying consolidated financial statements in accordance with U.S. Generally Accepted Accounting Principles (“GAAP”). In the opinion of management, the consolidated financial statements reflect all adjustments, which are normal and recurring in nature, necessary for fair financial statement presentation. Prior period balances for accounts receivable have been reclassified to conform to the current year presentation.

Use of Estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities, and disclosure of contingent assets and liabilities, and the reported amounts of expenses. We base our estimates on historical experience and various other assumptions that we believe to be reasonable. Actual results may differ from those estimates or assumptions. Estimates are periodically reviewed in light of changes in circumstances, facts, and experience, and any changes in estimates will be recorded in future periods as they develop.

Risks and Uncertainties

The product candidates we develop require approvals from regulatory agencies prior to commercial sales. There can be no assurance that our current and future product candidates will receive the necessary approvals or be commercially successful. If we are denied approval or approval is delayed, it will have a material adverse impact on our business and our consolidated financial statements.

We are subject to certain risks and uncertainties and believe that changes in any of the following areas could have a material adverse effect on future financial condition or results of operations: ability to obtain additional financing; regulatory approval and market acceptance of, and reimbursement for, product candidates; performance of third-party CROs and manufacturers upon which we rely; protection of our intellectual property; litigation or claims against us based on intellectual property, patent, product, regulatory, or other factors; and our ability to attract and retain employees necessary to support our growth.

Concentrations of Credit Risk

Financial instruments which potentially subject us to significant concentrations of credit risk consist primarily of cash. Our cash is mainly held in financial institutions. Amounts on deposit may at times exceed federally insured limits. We have not experienced any losses on our deposits of cash and do not believe that we are subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

Cash and Cash Equivalents

We consider all short-term investments with an original maturity of three months or less when purchased to be cash equivalents. As of December 31, 2021 and 2020, we had no cash equivalents.

Restricted Cash

We classify cash as restricted when it is unavailable for withdrawal or use in our general operating activities. Restricted cash and investments are classified as current and noncurrent on the consolidated balance sheets based on the nature of the restriction. Our restricted cash balance includes contractually restricted deposits related to our corporate credit card. As of December 31, 2021 and 2020, we had restricted cash of $0.1 million and $0, respectively.

Accounts Receivable

Accounts receivable are stated at invoice value less estimated allowances for sales returns and doubtful accounts. We estimate the allowance for sales returns based on historical percentage of returns over a 12-month trailing average of sales. We continually monitor customer payments and maintain a reserve for estimated losses resulting from our customers' inability to make required payments. We consider factors when estimating the allowance for doubtful accounts such as historical experience, age of the accounts receivable balances, geographic related risks, and economic conditions that may affect a customer's ability to pay. In cases where there are circumstances that may impair a specific customer's ability to meet its financial obligations, a specific allowance is recorded against amounts due, thereby reducing the net recognized receivable to the amount reasonably believed to be collectible. Accounts receivable are written off when deemed uncollectible. Recoveries of accounts receivable previously written off are recorded when received. Historically, there have been no sales returns, no written-off accounts receivable, and no allowance for doubtful accounts reducing the balance of the accounts receivable.

Inventory

Inventory is stated at historic cost on a first-in first-out basis. Our inventory consisted of $26,308 in raw materials and $14,391 in finished goods as of December 31, 2021, and $71,290 in raw material and $119,275 in finished goods as of December 31, 2020. Inventory primarily relates to our Supplements segment.

Debt

When debt is issued and a derivative is required to be bifurcated (e.g., bifurcated conversion option) or another separate freestanding financial instrument (e.g., warrant) is issued, costs and fees incurred are allocated to the instruments issued (or bifurcated) in proportion to the allocation of proceeds. When some portions of the costs and fees relate to a bifurcated derivative or freestanding financial instrument that is being subsequently measured at fair value, those allocated costs are expensed immediately. Debt discounts, debt premiums, and debt issuance costs related to debt are recorded as deductions that net against the principal value of the debt and are amortized to interest expense over the contractual term of the debt using the effective interest method.

Deferred Offering Costs

We capitalize certain legal, professional accounting. and other third-party fees that are directly associated with in-process equity financings, including the Reverse Recapitalization and the 2020 PIPE, as deferred offering costs until such financings are consummated. After consummation of the equity financing, these costs are recorded in stockholders' equity (deficit) as a reduction of proceeds generated as a result of the offering. Should any in-process equity financing be abandoned, the deferred offering costs will be expensed immediately as a charge to operating expenses in the consolidated statements of operations and comprehensive loss.

During the year ended December 31, 2021, we did not incur any deferred offering costs. During the year ended December 31, 2020, we incurred $5.9 million of deferred offering costs in connection with the Reverse Recapitalization which were reclassified to additional paid-in capital as of December 31, 2020.

Leases

At inception of a contract, we determine if a contract meets the definition of a lease. We determine if the contract conveys the right to control the use of an identified asset for a period of time. We assess throughout the period of use whether we have both of the following: (i) the right to obtain substantially all of the economic benefits from use of the identified asset, and (ii) the right to direct the use of the identified asset. This determination is reassessed if the terms of the contract are changed. Leases are classified as operating or finance leases based on the terms of the lease agreement and certain characteristics of the identified asset. Right-of-use assets and lease liabilities are recognized at the lease commencement date based on the present value of the future lease payments less any lease incentives received. At the lease commencement date, the discount rate implicit in the lease is used to discount the lease liability if readily determinable. If not readily determinable or leases do not contain an implicit rate, our incremental borrowing rate is used as the discount rate.

Our policy is to not record leases with an original term of twelve months or less within the consolidated balance sheets. We recognize lease expense for these short-term leases on a straight-line basis over the lease term in the consolidated statements of operations and comprehensive loss.

Certain lease agreements may require us to pay additional amounts for taxes, insurance, maintenance, and other expenses, which are generally referred to as non-lease components. Such variable non-lease components are treated as variable lease payments and recognized in the period in which the obligation for these payments is incurred. Variable lease components and variable non-lease components are not measured as part of the right-of-use asset and liability. Only when lease components and their associated non-lease components are fixed are they accounted for as a single lease component and are recognized as part of a right-of-use asset and liability. Total contract consideration is allocated to the combined fixed lease and non-lease component. This policy election applies consistently to all asset classes under lease agreements.

Leases may contain clauses for renewal at our option. Payments to be made in option periods are recognized as part of the right-of-use lease assets and lease liabilities when it is reasonably certain that the option to extend the lease will be exercised, or is not at our option. We determine whether the reasonably certain threshold is met by considering contract-, asset-, market-, and entity-based factors. In the consolidated statements of operations and comprehensive loss, operating lease expense, which is recognized on a straight-line basis over the lease term, and the amortization of finance lease right-of-use assets, which are included in property and equipment and depreciated, are included in research and development or general and administrative expenses consistent with the leased assets' primary use. Accretion on the liabilities for finance leases is included in interest expense.

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation. Property and equipment consist of laboratory and office equipment and leasehold improvements. Depreciation is calculated using the straight-line method over the estimated economic useful lives of the assets, which are 3-5 years for laboratory equipment and 3-7 years for furniture and fixtures. Leasehold improvements are amortized over the lesser of the estimated lease term or the estimated useful life of the assets. Costs for capital assets not yet placed into service are capitalized as construction in progress and depreciated or amortized in accordance with the above useful lives once placed into service. Upon retirement or sale, the related cost and accumulated depreciation and amortization are removed from the accounts and any resulting gain or loss is included in the consolidated statements of operations and comprehensive loss. Maintenance and repairs that do not improve or extend the lives of the respective assets are expensed to operations as incurred.

We capitalize costs to obtain or develop computer software for internal use, including development costs incurred during the software development stage and costs to obtain software for access and conversion of old data. We also capitalize costs to modify, upgrade, or enhance existing internal-use software that result in additional functionality. Amortization is calculated using the

straight-line method over the estimated economic useful life of the asset. We expense costs related to internal-use software, including costs incurred during the preliminary project stage, training costs, data conversion costs, and maintenance costs.

Impairment of Long-Lived Assets

Long-lived assets are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors we consider in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in the use of assets. If an impairment review is performed to evaluate an asset group for recoverability, we compare the forecasted undiscounted cash flows expected to result from the use and eventual disposition of the asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use and eventual disposition of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, determined based on discounted cash flows using market participant assumptions. We did not record any impairment losses on long-lived assets during the years ended December 31, 2021 and 2020.

Convertible Notes

In accordance with ASU 2020-06, Debt—*Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity*, when we issue notes with conversion features, we evaluate if the conversion feature is freestanding or embedded. If the conversion feature is embedded, we do not separate the conversion feature from the host contract for convertible notes that are not required to be accounted for as derivatives, or that do not result in substantial premiums accounted for as paid-in-capital. Consequently, we account for a convertible note as a single liability measured at its amortized cost, and we account for a convertible preferred stock as a single equity instrument measured at its historical cost, as long as no other features require bifurcation and recognition as derivatives.

If the conversion feature is freestanding, or is embedded and meets the requirements to be bifurcated, we account for the conversion feature as a derivative under ASC 815, *Derivatives and Hedging* ("ASC 815"). We record the derivative instrument at fair value at inception, and subsequently re-measure to fair value at each reporting period and immediately prior to the extinguishment of the derivative instrument, with any changes recorded in the consolidated statements of operations and comprehensive loss.

Debt With Warrants

In accordance with ASC 470-20, *Debt with Conversion and Other Options*, when we issue debt with warrants, we treat the warrants as a debt discount, recorded as a contra-liability against the debt, and amortize the balance over the life of the underlying debt as interest expense in the consolidated statements of operations and comprehensive loss. The offset to the contra-liability is recorded as additional paid-in capital in the consolidated balance sheets if the warrants are not treated as a derivative or liability under ASC 480, *Distinguishing Liabilities from Equity* ("ASC 480"). Otherwise, the offset to the contra-liability is recorded as a warrant liability in the consolidated balance sheets and is subject to re-measurement to fair value at each balance sheet date, with any changes in fair value recognized in the consolidated statements of operations and comprehensive loss. If the debt is retired early, the associated debt discount is then recognized immediately as interest expense in the consolidated statements of operations and comprehensive loss.

Contingent Earn-Out Liabilities

In connection with the Reverse Recapitalization, certain stockholders are entitled to receive additional shares of Common Stock (the "Contingent Earn-outs") upon us achieving certain milestones (see Notes 3 and 12). In accordance with ASC 815, the Contingent Earn-outs are not indexed to our own stock and therefore are accounted for as a liability at the Reverse Recapitalization date and subsequently remeasured at each reporting date with changes in fair value recorded as a component of other income (expense), net, in the consolidated statements of operations and comprehensive loss.

Common Stock Warrants

We account for common stock warrants as either equity-classified instruments or liability-classified instruments based on an assessment of the warrant terms and applicable authoritative guidance. The assessment considers whether the warrants are freestanding financial instruments pursuant to ASC 480, meet the definition of a liability pursuant to ASC 480, and whether the warrants meet all of the requirements for equity classification under ASC 815, including whether the warrants are indexed to our Common Stock, among other conditions for equity classification. This assessment, which requires the use of professional judgment, is conducted at the time of warrant issuance and, for liability-classified warrants, as of each subsequent quarterly period end date while the warrants are outstanding.

Revenue Recognition

Under ASC 606, *Revenue from Contracts with Customers* ("ASC 606"), an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration to which we are entitled in exchange for the goods or services we transfer to the customer.

Once a contract is determined to be within the scope of ASC 606 at contract inception, we review the contract to determine which performance obligations we must deliver, and which performance obligations are distinct. We recognize as revenue the amount of the transaction price that is allocated to each performance obligation when that performance obligation is satisfied or as it is satisfied. We typically satisfy our performance obligations via delivery of dietary supplements to the customer. Payments are due upon receipt for commercial transactions, or a prepayment is collected for online retail sales. Our revenue during the years ended December 31, 2021 and 2020 was comprised of sales of dietary supplements and royalties.

We recorded deferred revenue of $0 and $0.1 million as of December 31, 2021 and 2020, respectively, from a dietary supply agreement with a related party (see Note 20).

Grant Funding

We may submit applications to receive grant funding from governmental and non-governmental entities. Grant funding received that involves no conditions or continuing performance obligations is recognized upon receipt. Grant funding with conditions or obligations is recognized as the conditions or obligations are fulfilled. We have made an accounting policy election to record such unconditional grants, such as the Australian Research and Development Credit, as other income in the consolidated statements of operations and comprehensive loss. Income from grants with conditions or obligations is recognized in the period during which the related qualifying expenses are incurred, provided that the conditions under which the grants were provided have been met. We recognize the Australian Research and Development Credit in an amount equal to the qualifying expenses incurred in each period multiplied by the applicable reimbursement percentage. During the years ended December 31, 2021 and 2020, we recognized $1.5 million and $3.2 million, respectively, of Australian Research and Development Credit within other income (expense), net, in the consolidated statements of operations and comprehensive loss. As of December 31, 2021 and 2020, we recorded $1.6 million and $2.1 million, respectively, of Australian Research and Development Credit receivable in prepaid expenses and other current assets on the consolidated balance sheets.

Any amount received in advance of fulfilling such conditions or obligations is recorded in accrued liabilities on the consolidated balance sheets if the conditions or obligations are expected to be met within the next twelve months. As of December 31, 2021 and 2020, we recorded $0.5 million and $0.3 million, respectively, of deferred grant funds received in advance in accrued liabilities.

Grant funding recognized on conditional grants is included as a reduction in research and development expenses in the consolidated statements of operations and comprehensive loss as the conditions are tied to our research and development efforts, and as the arrangement between us and the organizations are not part of our ongoing, major, or central operations. During the years ended December 31, 2021 and 2020, we recorded a grant of $0.2 million and $0.8 million, respectively, as a reduction of research and development expenses in the consolidated statements of operations and comprehensive loss.

Fair Value of Financial Instruments

Certain assets and liabilities are carried at fair value under GAAP. Fair value is defined as the price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy:

Level 1—Inputs based upon quoted market prices for identical assets or liabilities in active markets at the measurement date.

Level 2—Observable inputs other than quoted market prices included in Level 1, such as quoted prices for similar assets and liabilities in active markets; quoted prices for identical or similar assets and liabilities in markets that are not active; or other inputs that are observable or can be corroborated by observable market data.

Level 3—Inputs that are management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. The inputs are unobservable in the market and significant to the instrument's valuation.

We review the fair value hierarchy classification of our applicable assets and liabilities on a quarterly basis. Changes in the observability of valuation inputs may result in a reclassification for certain financial assets or liabilities. Reclassifications impacting all levels of the fair value hierarchy are reported as transfers in or out of the Level 1, 2, or 3 categories as of the beginning of the quarter during which the reclassifications occur.

Foreign Currency Translation and Transactions

Our functional currency is the U.S. dollar. Clene Australia determined its functional currency to be the Australian dollar and our Netherlands subsidiary determined its functional currency to be the Euro. We use the U.S. dollar as our reporting currency for the consolidated financial statements. The results of our non-U.S. dollar based functional currency operations are translated to U.S. dollars at the average exchange rates during the period. Our assets and liabilities are translated using the current exchange rate as of the balance sheet date and stockholders' equity is translated using historical rates.

Adjustments resulting from the translation of the consolidated financial statements of our foreign functional currency subsidiaries into U.S. dollars are excluded from the determination of net loss and are accumulated in a separate component of stockholders' equity. These foreign currency translation gains and losses are currently the only component of other comprehensive loss.

We also incur foreign exchange transaction gains and losses for purchases denominated in foreign currencies. Foreign exchange transaction gains and losses are included in other income (expense) in the consolidated statements of operations and comprehensive loss as incurred.

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity (deficit) that result from transactions and economic events other than those with stockholders. The only element of other comprehensive income (loss) in any period presented was translation of Australian dollar denominated balances of Clene Australia to U.S. dollars for consolidation.

Net Loss Per Share Attributable to Common Stockholders

Basic net loss per share attributable to common stockholders is calculated using our weighted-average outstanding common shares. Diluted net income (loss) per share attributable to common stockholders is calculated using our weighted-average outstanding common shares including the dilutive effect of securities as determined under the treasury stock method, except for the dilutive effect of convertible notes payable, which is calculated under the if-converted method, even if the embedded conversion option is out-of-the-money. In periods in which we report a net loss attributable to common stockholders, diluted net loss per share attributable to common stockholders is the same as basic net loss per share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is anti-dilutive.

Segment Information

We have determined that our chief executive officer is the chief operating decision maker ("CODM"). Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the CODM in making decisions regarding resource allocation and assessing performance. We view our operations and manage our business in two operating segments, which are our reportable segments: (1) the development and commercialization of novel clean-surfaced nanotechnology therapeutics ("Drugs"), and (2) the development and commercialization of dietary supplements ("Supplements").

Income Taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in our tax returns. Deferred tax assets and liabilities are determined based on the differences between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. We assess the likelihood that our deferred tax assets will be recovered from future taxable income and, to the extent we believe, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

We account for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, which are considered appropriate as well as the related net interest and penalties.

Stock-Based Compensation

We account for stock-based compensation arrangements using a fair value-based method for costs related to all share-based payments including stock options and stock awards. Stock-based compensation expense is recorded in research and development and general and administrative expenses based on the classification of the work performed by the grantees.

The fair value is recognized over the period during which a grantee was required to provide services in exchange for the option award and service-based stock awards, known as the requisite service period (usually the vesting period), on a straight-line basis. For stock awards with market conditions, the fair value is recognized over the period based on the expected milestone achievement dates as the derived service period (usually the vesting period), on a straight-line basis. For stock awards with performance conditions, the grant-date fair value of these awards is the market price on the applicable grant date, and compensation expense will be recognized when the conditions become probable of being satisfied. We will recognize a cumulative true-up adjustment once the conditions become probable of being satisfied as the related service period had been completed in a prior period.

Stock-based compensation expense is recognized at fair value. We elect to account for forfeitures as they occur, rather than estimating expected forfeitures.

After the closing of the Reverse Recapitalization, we determine the fair value of each share of Common Stock underlying stock-based awards based on the closing price of our Common Stock as reported by the Nasdaq Stock Market LLC (“Nasdaq”) on the date of grant. The fair value of stock awards with market conditions are determined using a Monte Carlo valuation model.

Research and Development

Research and development costs are charged to expense as incurred. We account for nonrefundable advance payments for goods and services that will be used in future research and development activities as expenses when the goods have been received or when the service has been performed. Research and development expenses consist of costs incurred for the discovery and development of our product candidates. Research and development costs include, but are not limited to, payroll and personnel expenses including stock-based compensation, clinical trial supplies, fees for clinical trial services, consulting costs, and allocated overhead, including rent, equipment, and utilities.

Clinical Trial Accrual

Our clinical trial accrual process accounts for expenses resulting from obligations under contracts with CROs, consultants, and under clinical site agreements in connection with conducting clinical trials. Clinical trial costs are charged to research and development expense as incurred. The financial terms of these contracts are subject to negotiations, which vary from contract to contract and may result in payment flows that do not match the periods over which materials or services are provided to us under such contracts. We reflect the appropriate clinical trial expense in the consolidated financial statements by matching the appropriate expenses with the period in which services and efforts are expended. In the event advance payments are made to a CRO, the payments will be recorded as a prepaid asset which will be amortized to research and development expense over the period the contracted services are performed. In addition to pass-through costs, we generally incur costs in clinical trials in four distinct groups as follows:

CRO Start-Up—These costs include the initial set-up of the clinical trial and usually occur within a few months after the contract has been executed and includes costs which are expensed ratably over the start-up period when such period is identifiable and expensed as incurred when no such period exists. Start-up phase activities include study initiation, site recruitment, regulatory applications, investigator meetings, screening, preparation, pre-study visits, and training.

CRO Site and Study Management—These costs include medical and safety monitoring, patient administration and data management. These costs are usually calculated on a per-patient basis and expensed ratably over the treatment period beginning on the date that the patient enrolls.

CRO Close-Down and Reporting—These costs include analyzing the data obtained and reporting results, which occurs after patients have ceased treatment and the database of information collected is locked. These costs are expensed as incurred over the course of any close-down and reporting period.

Third-Party Contracts—These costs include fees charged by third parties for various support services which are not provided by CROs and include such items as laboratory fees, data quality review costs, and fees incurred for investigational product monitoring and inventory control. These items are expensed ratably over any identifiable service period with the engaged third-party vendors.

The CRO contracts generally include pass-through fees including, but not limited to, regulatory expenses, investigator fees, travel costs, and other miscellaneous costs, including shipping and printing fees. We determine accrual estimates through reports from and discussion with applicable personnel and outside service providers as to the progress or state of completion of trials or the services completed. We estimate accrued expenses as of each reporting date in the consolidated financial statements based on the facts and circumstances known to us at that time.

Recently Adopted Accounting Pronouncements

In August 2020, the FASB issued ASU 2020-06, *Debt—Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging—Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity* to simplify accounting for certain financial instruments by removing certain separation models for convertible instruments. Under the amendments in ASU 2020-06, the embedded conversion features no longer are separated from the host contract for convertible instruments with conversion features that are not required to be accounted for as derivatives, or that do not result in substantial premiums accounted for as paid-in-capital. Consequently, a convertible debt instrument will be accounted as a single liability measured at its amortized cost, and a convertible preferred stock will be accounted for as a single equity instrument measured at its historical cost, as long as no other features require bifurcation and recognition as derivatives. The new standard also introduces additional disclosures for convertible debt and freestanding instruments that are indexed to and settled in an entity's own equity. ASU 2020-06 amends the diluted earnings per share guidance, including the requirements to use the if-converted method for all convertible instruments. For smaller reporting companies, the new guidance is effective for fiscal years beginning after December 15, 2023, and should be applied on a full or modified retrospective basis, with early adoption permitted, but no earlier than fiscal years beginning after December 15, 2020, including interim periods with those fiscal years. We early adopted ASU 2020-06 on January 1, 2021. The adoption of this guidance did not have a material impact on our consolidated financial statements.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes (Topic 740)*, which amends the existing guidance relating to the accounting for income taxes. This ASU is intended to simplify the accounting for income taxes by removing certain exceptions to the general principles of accounting for income taxes and to improve the consistent application of GAAP for other areas of accounting for income taxes by clarifying and amending existing guidance. The new guidance was effective for our fiscal year, and interim periods within our fiscal year, beginning after December 15, 2020. The adoption of this guidance did not have a material impact on our consolidated financial statements.

In August 2018, the FASB issued ASU 2018-15, *Intangibles—Goodwill and Other—Internal-Use Software (Subtopic 350-40): Customer's Accounting for Implementation Costs Incurred in a Cloud Computing Arrangement That is a Service Contract*. The new guidance provides for the deferral of implementation costs for cloud computing arrangements and expensing those costs over the term of the cloud services arrangement. The new guidance was effective for our fiscal year beginning after December 15, 2020. The adoption of this guidance did not have a material impact on our consolidated financial statements.

Recent Accounting Pronouncements Not Yet Adopted

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments—Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments*. The amendments in this ASU, among other things, require the measurement of all expected credit losses for financial assets held at the reporting date based on historical experience, current conditions, and reasonable and supportable forecasts. Financial institutions and other organizations will now use forward-looking information to better inform their credit loss estimates. As a smaller reporting company, the guidance is effective for our fiscal years beginning after December 15, 2022. We are currently evaluating the expected impact of the new guidance as a result of this extended deadline of implementation for smaller reporting companies.

3. Reverse Recapitalization with Tottenham and Clene Nanomedicine

On December 30, 2020 (the "Closing Date"), Chelsea Worldwide Inc., our predecessor, consummated the previously announced business combination (referred to as the "Reverse Recapitalization") pursuant to a merger agreement, dated as of September 1, 2020 (the "Merger Agreement"), by and among Clene Nanomedicine, Tottenham, Chelsea Worldwide Inc. ("PubCo"), a Delaware corporation

and wholly-owned subsidiary of Tottenham, Creative Worldwide Inc. ("Merger Sub"), a Delaware corporation and wholly-owned subsidiary of PubCo, and Fortis Advisors LLC, a Delaware limited liability company as the representative of our stockholders. Prior to the Reincorporation Merger discussed below, Tottenham was incorporated in the British Virgin Islands as a blank check company for the purpose of entering into a merger, share exchange, asset acquisition, stock purchase, recapitalization, reorganization, or other similar business combination with one or more businesses or entities. Prior to the Reverse Recapitalization, there was not a public market for the shares of Clene Nanomedicine common stock.

The Reverse Recapitalization was effected in two steps: (i) Tottenham was reincorporated to the state of Delaware by merging with and into PubCo (the "Reincorporation Merger"); and (ii) promptly following the Reincorporation Merger, Merger Sub was merged with and into Clene Nanomedicine, resulting in Clene Nanomedicine becoming a wholly-owned subsidiary of PubCo (the "Acquisition Merger"). On the Closing Date, PubCo changed its name from Chelsea Worldwide Inc. to Clene Inc. and listed its shares of Common Stock, par value $0.0001 per share on Nasdaq under the symbol "CLNN."

Upon the consummation of the Reverse Recapitalization, each Tottenham ordinary share issued and outstanding immediately prior to the effective time of the Reincorporation Merger, which totaled 2,303,495 shares held by Tottenham's former officers and directors and Norwich Investment Limited and Tottenham's public stockholders (the "Initial Stockholders") (excluding certain shares that were canceled pursuant to the Merger Agreement, any redeemed shares, and any dissenting shares), was automatically cancelled and ceased to exist and (i) for each Tottenham ordinary share, we issued to each stockholder one validly-issued share of our Common Stock; (ii) each warrant to purchase one-half (1/2) of one Tottenham Ordinary Share converted into a warrant to purchase one-half (1/2) of one share of our Common Stock; (iii) each right exchangeable into one-tenth (1/10) of one Tottenham ordinary share converted into a right exchangeable for one-tenth (1/10) of one share of our Common Stock; provided, however, that no fractional shares were issued and all fractional shares were rounded down to the nearest whole share.

On the Closing Date, each share of Clene Nanomedicine common stock then issued and outstanding was cancelled and the holders thereof in exchange received 54,339,012 shares of Common Stock, which is equal to 0.1389 newly-issued shares of Common Stock for each single share of Clene Nanomedicine common stock (the "Exchange Ratio"). Pursuant to the Merger Agreement, 5% of the aggregate amount of the closing payment shares, or 2,716,958 shares were held in escrow to satisfy any indemnification obligation incurred and were released six months after the closing of the Reverse Recapitalization. In addition, each share of Clene Nanomedicine's preferred stock outstanding immediately prior to the closing of the Reverse Recapitalization was converted into the right to receive our Common Stock based on the same Exchange Ratio. All outstanding warrants exercisable for common stock in Clene Nanomedicine (other than warrants that expired, were exercised or were deemed automatically net exercised immediately prior to the Acquisition Merger) were exchanged for warrants exercisable for our Common Stock with the same terms and conditions except adjusted by the Exchange Ratio.

All outstanding stock options of Clene Nanomedicine common stock, totaling 53,286,115 stock options, was cancelled and the holders thereof in exchange received 0.1320 newly issued stock options of our Common Stock for a total of 7,032,591 stock options, which is 95% of the Exchange Ratio. Pursuant to the Merger Agreement, we agreed to issue rights to 370,101 restricted stock awards to the option holders which complements the 5% closing payment shares held in escrow for Clene Nanomedicine common stockholders. The modification of the stock options did not result in a material incremental compensation expense upon closing of the Reverse Recapitalization. In addition, we issued rights to 1,136,961 restricted stock awards to option holders to complement the earn-out payments (discussed below) that may be contingently issued to certain current Clene Nanomedicine stockholders upon the achievement of certain milestones.

We received gross proceeds of $9.4 million from the Reverse Recapitalization and incurred offering costs of $5.9 million, which excludes the fair value of Common Stock issued as payment of certain offering costs, resulting in net proceeds of $3.5 million. Offering costs related to third-party legal, accounting, and other professional services and were recorded as a reduction of additional paid-in capital upon the close of the Reverse Recapitalization in our consolidated balance sheets.

In connection with Tottenham's initial public offering in August 2018, Tottenham issued to Chardan Capital Markets, LLC ("Chardan"), an option to purchase 220,000 units at $11.50 per unit (the "Chardan Unit Purchase Option"). Each unit consisted of one and one-tenth shares of Tottenham's ordinary shares and one warrant to purchase one-half of one of Tottenham's ordinary shares at an exercise price of $11.50 per share. In connection with the Reverse Recapitalization, the Chardan Unit Purchase Option was converted into a Clene Inc. unit purchase option. The warrants included in the Chardan Unit Purchase Option were exercisable upon the completion of the Reverse Recapitalization and expire five years after the Closing Date (see Note 10).

Also, in connection with the Reverse Recapitalization, Clene Nanomedicine entered into a letter agreement with LifeSci Capital LLC ("LifeSci") in July 2020, to which LifeSci engaged to act as Clene Nanomedicine's financial advisor with respect to identifying and soliciting special purpose acquisition companies for the purpose of entering into a merger or similar transaction with Clene Nanomedicine and its stockholders. Under this agreement, Clene Nanomedicine agreed that if it consummated a merger with Tottenham,

LifeSci would receive consideration of (i) 3% of the amount by which the total transaction consideration exceeded $350 million, plus (ii) 7% of cash and cash-equivalents received by Clene Nanomedicine from the Tottenham's trust account. Clene Nanomedicine could elect to pay LifeSci either in cash, equity interests of the surviving company, or a combination of the two. Upon the consummation of the Reverse Recapitalization, 644,164 shares of Common Stock were issued to LifeSci as consideration for its services as pursuant to the letter agreement (see Note 18).

Immediately after giving effect to the Reverse Recapitalization, there were 59,526,171 shares of Common Stock issued and outstanding and warrants to purchase 5,566,361 shares of Common Stock issued and outstanding (see Note 10). Based on the number of shares of Common Stock outstanding on the Closing Date (in each case, not giving effect to any shares issuable upon exercise of warrants, options, or earn-out shares), Clene Nanomedicine's stockholders owned approximately 91% of our Common Stock, Tottenham stockholders owned approximately 4% of our Common Stock, and investors from the 2020 PIPE owned approximately 4% of our Common Stock.

During Tottenham's IPO, Tottenham incurred deferred underwriters' fees which were payable to Chardan from the amounts held in the trust account upon completion of the Reverse Recapitalization. Upon the closing of the Reverse Recapitalization, we paid $2.1 million to Chardan as settlement of the deferred underwriting fees, which amount was included in the total offering costs of the Reverse Recapitalization.

The transaction was accounted for as a "reverse recapitalization" in accordance with GAAP. Under this method of accounting, Tottenham was treated as the "acquired" company for financial reporting purposes. This determination was primarily based on the fact that subsequent to the Reverse Recapitalization, Clene Nanomedicine's stockholders have a majority of the voting power of the Company, Clene Nanomedicine comprises all of the ongoing operations of the Company, Clene Nanomedicine comprises a majority of the governing body of the Company, and Clene Nanomedicine's senior management comprises all of the senior management of the Company. Accordingly, for accounting purposes, this transaction was treated as the equivalent of Clene Nanomedicine issuing shares for the net assets of Tottenham, accompanied by a recapitalization. The shares and net loss per common share in historical periods prior to the Reverse Recapitalization have been retroactively restated using the Exchange Ratio established in the Reverse Recapitalization. The net assets of Tottenham were recorded at historical costs, with no goodwill or other intangible assets recorded. Operations prior to the Reverse Recapitalization are those of Clene Nanomedicine.

Earn-Out Shares

Certain of Clene Nanomedicine's stockholders are entitled to receive earn-out shares as follows (the "Clene Nanomedicine Contingent Earn-out"): (i) 3,333,333 shares of Common Stock if (A) the volume-weighted average price ("VWAP") of the shares of our Common Stock equals or exceeds $15.00 (or any foreign currency equivalent) (the "Milestone 1 Price") in any twenty trading days within a thirty trading day period within the three years following the closing of the Reverse Recapitalization on any securities exchange or securities market on which the shares of our Common Stock are then traded or (B) the change of control price equals or exceeds the Milestone 1 Price if a change of control transaction occurs within the three years following the closing of the Reverse Recapitalization (the requirements in (A) and (B) being collectively "Milestone 1"); (ii) 2,500,000 shares of Common Stock if (A) the VWAP of our Common Stock equals or exceeds $20.00 (or any foreign currency equivalent) (the "Milestone 2 Price") in any twenty trading days within a thirty trading day period within the five years following the closing of the Reverse Recapitalization on any securities exchange or securities market on which the shares of our Common Stock are then traded or (B) the change of control price equals or exceeds the Milestone 2 Price if a change of control transaction occurs within the five years following the closing of the Reverse Recapitalization (the requirements set forth in clause (A) or (B), "Milestone 2"); and (iii) 2,500,000 shares of Common Stock if Clene Nanomedicine completed a randomized placebo-controlled clinical trial for treatment of COVID-19 which results in a statistically significant finding of clinical efficacy within twelve months after the closing of the Reverse Recapitalization ("Milestone 3"), which was not achieved. If Milestone 1 is not achieved but Milestone 2 is achieved, the Clene Nanomedicine stockholders will receive a catch-up issuance equal to the shares issued upon satisfaction of Milestone 1. Upon the consummation of the Reverse Recapitalization, the Clene Nanomedicine Contingent Earn-out shares increased by 12,852 as a result of the exercise of stock options during November 2020, and the Clene Nanomedicine Contingent Earn-out shares increased to 8,346,185 shares of Common Stock as of the Closing Date.

The Initial Stockholders may be entitled to receive earn-out shares as follows (the "Initial Stockholders Contingent Earn-out"): (i) 375,000 shares of Common Stock upon satisfaction of the requirements of Milestone 1; and (ii) another 375,000 shares of Common Stock upon satisfaction of the requirements of Milestone 2. If Milestone 1 is not achieved but Milestone 2 is achieved, the Initial Stockholders shall receive a catch-up issuance equal to the shares granted upon satisfaction of the requirements of Milestone 1.

The Contingent Earn-outs have been classified as liabilities in the consolidated balance sheets and were initially measured at fair value on the date of the Reverse Recapitalization and are subsequently remeasured to fair value at each reporting date (see Note 16). As of December 30, 2021, we did not achieve Milestone 3 and the 2,503,851 Milestone 3 Contingent Earn-outs were cancelled.

4. Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Australia research and development credit receivable	$ 1,564	$ 2,148
CRO prepayments	194	1,211
Metals to be used in research and development	2,237	31
Directors and officers insurance	41	—
Other	169	112
Total prepaid expenses	$ 4,205	$ 3,502

5. Property and Equipment

Property and equipment, net, as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Lab equipment	$ 3,327	$ 3,077
Furniture and fixtures	147	147
Leasehold improvements	3,943	3,889
Construction in progress	2,052	490
	9,469	7,603
Less accumulated depreciation	(4,297)	(3,378)
Total property and equipment, net	$ 5,172	$ 4,225

Depreciation expense totaled $1.0 million and $1.0 million for the years ended December 31, 2021 and 2020, respectively. Depreciation expense was reported in research and development expense and in general and administrative expense totaling $0.8 million and $0.1 million, respectively, for the year ended December 31, 2021; and in research and development expense and in general and administrative expense totaling $0.9 million and $0.1 million, respectively, for the year ended December 31, 2020, in the consolidated statements of operations and comprehensive loss.

6. Accrued Liabilities

Accrued liabilities as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Accrued professional fees	$ 30	$ 189
Accrued compensation and benefits	2,049	1,225
Accrued CRO fees	718	788
Deferred grant funds	520	301
Accrued expense reimbursements	33	33
Accrued transaction costs	—	1,354
Other	260	70
Total accrued liabilities	$ 3,610	$ 3,960

7. Leases

We lease laboratory and office space and certain laboratory equipment under non-cancellable operating and finance leases. The carrying value of our right-of-use lease assets is substantially concentrated in our real estate leases, while the volume of lease agreements is primarily concentrated in equipment leases.

Operating Leases

In April 2020, we terminated an operating lease for office space and removed the remaining right-of-use asset of $0.3 million and lease liability of $0.3 million, and recognized a gain of $0.1 million. Concurrently, we commenced a new operating lease in April 2020 and recorded a right-of-use asset value of $0.4 million, leasehold improvements of $0.4 million, and lease liability of $0.8 million.

In September 2021, we commenced an operating lease for laboratory space and recorded a right-of-use asset of $2.4 million and lease liability of $2.4 million, net of a lease incentive of $1.0 million which represents an allowance from the lessor for facility alterations.

As the lease incentive is payable based on events within our control and are deemed reasonably certain to occur, we recorded the lease incentive as a reduction of the right-of-use asset and lease liability at the lease commencement. As of December 31, 2021, we incurred $0.5 million of costs related to the lease incentive which we recorded as construction in progress, with a corresponding increase to the lease liability, and the construction in progress will be capitalized as leasehold improvements when the facility is placed into service. The lease has an initial ten-year term and provides us the right and option to extend or renew for two periods of five years each. In accordance with ASC 842, the payments to be made in option periods have not been recognized as part of the right-of-use asset or lease liability because we do not assess the exercise of the option to be reasonably certain.

Right-of-use assets on the consolidated balance sheets pertain to operating leases. As of December 31, 2021, our operating lease obligations had a weighted-average discount rate of 9.6% and had a weighted-average remaining term of 8.1 years. As of December 31, 2020, our operating lease obligations had a weighted-average discount rate of 9.6% and a weighted-average remaining term of 6.3 years.

Finance Leases

Assets recorded under finance lease obligations and included with property and equipment as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Lab equipment	$ 408	$ 920
Furniture and fixtures	—	46
Work in process	228	228
Total	636	1,194
Less accumulated depreciation	(244)	(593)
Net	$ 392	$ 601

As of December 31, 2021, our finance lease obligations had a weighted-average interest rate of 8.8% and had a weighted-average remaining term of 1.9 years. As of December 31, 2020, our finance lease obligations had a weighted-average interest rate of 8.1% and had a weighted-average remaining term of 2.7 years.

Maturity Analysis of Leases

The maturity analysis of our finance and operating leases as of December 31, 2021 were as follows:

(in thousands)	Finance Leases	Operating Leases
2022	$ 139	$ 870
2023	82	960
2024	20	982
2025	—	1,007
2026	—	1,031
Thereafter	—	2,887
Total undiscounted cash flows	241	7,737
Less amount representing interest/discounting	2	(2,520)
Present value of future lease payments	243	5,217
Less future lease incentives	—	(500)
Less lease obligations, current portion	(146)	(347)
Lease obligations, long term portion	$ 97	$ 4,370

We expect that, in the normal course of business, the existing leases will be renewed or replaced by similar leases.

Components of Lease Cost

The components of finance and operating lease costs for the years ended December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Finance lease costs:		
Amortization	$ 82	$ 175
Interest on lease liabilities	27	37
Operating lease costs	429	293
Short-term lease costs	73	249
Variable lease costs	130	92
Total lease costs	$ 741	$ 846

Supplemental Cash Flow Information

(in thousands)	2021	2020
Operating cash flows from operating leases	$ (633)	$ (635)
Operating cash flows from finance leases	$ (27)	$ (37)
Finance cash flows from finance leases	$ (152)	$ (194)

8. Notes Payable

Our long-term debt, net of original issue discount and unamortized debt issuance costs, as of December 31, 2021 and 2020 was as follows:

(in thousands, except interest rate data)	Interest Rate	2021	2020
Notes payable:			
Maryland Department of Housing & Community Development	8.00%	$ 614	$ 1,080
Advance Cecil, Inc.	8.00%	122	216
Paycheck Protection Program	1.00%	—	647
Avenue Venture Opportunities Fund, L.P.	9.85%	20,000	—
Other	0.00%	—	6
		20,736	1,949
Less unamortized debt issuance costs and original issue discounts		(1,654)	—
Less convertible notes payable, net of unamortized debt discount and issuance costs (see Note 11)		(4,598)	—
Total notes payable		$ 14,484	$ 1,949

Maryland Loan

In February 2019, we entered into a loan agreement (the "2019 MD Loan") with the Department of Housing and Community Development, a principal department of the State of Maryland. The agreement provides for a term loan of $0.5 million. Amounts outstanding under the 2019 MD Loan bear simple interest at an annual rate of 8.0%. Under the 2019 MD Loan, we agreed to affirmative and negative covenants to which we will remain subject until maturity. These covenants include providing information about our Company and operations; limitations on our ability to retire, repurchase, or redeem our common or preferred stock, options, and warrants other than per the terms of the securities; and limitations on our ability to pay dividends of cash or property. There are no financial covenants associated with the 2019 MD Loan. Events of default under the 2019 MD Loan include failure to make payments when due, insolvency events, and failure to comply with covenants. We are not in violation of any affirmative covenants. Repayment of the full balance outstanding is due on February 22, 2034. The 2019 MD Loan establishes "Phantom Shares," based on 119,907 shares of Common Stock (based on 863,110 Series C Preferred Shares prior to the Reverse Recapitalization), determined at issuance. The 2019 MD Loan states the repayment amount is to be the greater of the balance of principal and accrued interest or the Phantom Shares value. We determined that the note should be accounted for at fair value. We record the fair value of the debt at the end of each reporting period. In order to value the note, we consider the amount of the simple interest expense that would be due and the value of Phantom Shares. The fair value of the 2019 MD Loan is determined based on the closing price of CLNN shares listed on Nasdaq.

Income of $0.5 million and expense of $0.5 million was recognized during the years ended December 31, 2021 and 2020, respectively. The fair value of $0.6 million and $1.1 million of principal and accrued interest is included in long-term notes payable as of December 31, 2021 and 2020, respectively.

Cecil County Loan

In April 2019, we entered into a loan agreement (the "2019 Cecil Loan") with Advance Cecil Inc., a non-stock corporation formed under the laws of the state of Maryland with application for 501(c)(3) status pending before the Internal Revenue Service at the time of execution of the 2019 Cecil Loan. The agreement provides for a term loan of $0.1 million. Amounts outstanding under the 2019 Cecil Loan bear simple interest at an annual rate of 8.0%. Under the 2019 Cecil Loan, we agreed to affirmative covenants to which we will remain subject until maturity. These covenants include providing information about our Company and operations. There are no financial covenants associated with the 2019 Cecil Loan. Events of default under the 2019 Cecil Loan include failure to make payments when due, insolvency events, and failure to comply with covenants. We are not in violation of any affirmative covenants. Repayment of the full balance outstanding is due on April 30, 2034. The 2019 Cecil Loan establishes "Phantom Shares," based on 23,981 shares of Common Stock (based on 172,622 Series C Preferred Shares prior to the Reverse Recapitalization), determined at issuance. The 2019 Cecil Loan states the repayment amount is to be the greater of the balance of principal and accrued interest or the Phantom Share value. We determined that the note should be accounted for at fair value. We record the fair value of the debt at the end of each reporting period. In order to value the note, we consider the amount of the simple interest expense that would be due and the value of Phantom Shares. The fair value of the 2019 Cecil Loan is determined based on the closing price of CLNN shares listed on Nasdaq.

Income of $0.1 million and expense of $0.1 million was recognized during the years ended December 31, 2021 and 2020, respectively. The fair value of $0.1 million and $0.2 million of principal and accrued interest is included in long-term notes payable as of December 31, 2021 and 2020, respectively.

PPP Loan

In May 2020, we entered into a note payable in the amount of $0.6 million (the "PPP Loan") under the Paycheck Protection Program of the CARES Act. The Paycheck Protection Program permits forgiveness of amounts loaned for payments of payroll and other qualifying expenses within 24 weeks of receipt of loaned funds, given that at least 60% of the total loan is used for payroll. Amounts not forgiven have a repayment period of five years. In January 2021, the full $0.6 million balance of the PPP Loan was forgiven and has been recorded as a gain on extinguishment of debt during the year ended December 31, 2021. There was no gain on extinguishment of debt recorded during the year ended December 31, 2020.

Avenue Loan

In May 2021, we entered into the 2021 Avenue Loan with Avenue. The agreement provides for a 42-month term loan of up to $30.0 million. The first tranche is $20.0 million ("Tranche 1"), of which $15.0 million was funded at close and $5.0 million was funded in September 2021. We incurred issuance costs of $0.6 million of which $46,951 was expensed immediately. The remaining unfunded tranche of $10.0 million ("Tranche 2") is available at our request until December 31, 2022. Funding of Tranche 2 is subject to (a) our receipt of $5.0 million financing through Maryland's State Incentive Programs and/or other Maryland State programs; (b) our achievement of a statistically significant result on the primary endpoint, or if the totality of the results for any study warrant advancement into a subsequent clinical efficacy study, with respect to at least two of the following clinical trials: (i) RESCUE-ALS or the Healey ALS Platform Trial; (ii) REPAIR-PD; or (iii) REPAIR-MS ("Performance Milestone 1"); (c) our receipt of net proceeds of at least $30.0 million from the sale and issuance of our equity securities (including private placements or follow-on offerings) between May 2, 2021 and December 31, 2022; and (d) mutual agreement of us and Avenue.

The loans bear interest at a variable rate per annum equal to the sum of (i) the greater of (a) the prime rate, as published by the Wall Street Journal from time to time or (b) 3.25%, plus (ii) 6.60%. Payments are interest-only for the first 12 months and can be extended up to (i) 12 months (the "First Interest-only Period Extension") if we achieve Performance Milestone 1 and (ii) 36 months if (a) we achieve the First Interest-only Period Extension and (b) have drawn from Tranche 2. In August 2021 we mutually confirmed with Avenue that Performance Milestone 1 and the First Interest-only Period Extension had been achieved. The loan will amortize in equal payments of principal from the end of the interest period to the expiration of the 42-month term on December 1, 2024. On the maturity date, an additional payment equal to 4.25% of the funded loans, or $0.9 million, is due in addition to the remaining unpaid principal and accrued interest. The final payment was recorded as a debt premium and is being amortized over the contractual term using the effective interest method. The final payment provision is related to the loan host and is not bifurcated pursuant to ASC 815.

Pursuant to the agreement, we granted to Avenue the a warrant for the purchase of 115,851 shares of Common Stock (the "Avenue Warrant") at an exercise price equal to the lower of (i) $8.63 (which is equal to the five-day VWAP per share, determined as of the end of trading on the last trading day prior to execution of the loan agreement), or (ii) the lowest price per share paid by cash investors for our Common Stock issued in the next bona fide round of equity financing prior to March 31, 2022 (the "Next Round Price"). Upon the funding of Tranche 2, the Avenue Warrant shall be automatically adjusted to include an additional estimated 145,740 shares of Common Stock, which is equal to 5% of the principal amount of Tranche 2, divided by the lower of (i) the five (5)-day VWAP per share; determined as of the end of trading on the last trading day before the date of issuance of Tranche 2; or (ii) the Next Round Price. We

accounted for the Tranche 2 warrants at inception of the 2021 Avenue Loan in accordance with ASC 815 and the fair value and issuable shares will be remeasured at each reporting period (see Note 10). Avenue also has the right, in its discretion, but not the obligation, at any time from time to time from the first through the third-year anniversary of the agreement, while the loan is outstanding, to convert an amount of up to $5.0 million of the principal amount of the outstanding loan into Common Stock (the "Conversion Feature") at a price per share equal to 120% of the stock purchase price set forth in the warrant. The Conversion Feature is subject to (i) the closing price of our Common Stock for each of the seven consecutive trading days immediately preceding the conversion being greater than or equal to the conversion price and (ii) the Common Stock issued in connection with any such conversion not exceeding 20% of the total trading volume of our Common Stock for the twenty-two consecutive trading days immediately prior to and including the effective date of such conversion.

Under the 2021 Avenue Loan, we agreed to affirmative and negative covenants to which we will remain subject upon maturity in the absence of prepayments. These covenants include providing information about our Company and operations; limitation on our ability to retire, repurchase, or redeem our Common Stock, options, and warrants other than per the terms of the securities; and limitations on our ability to pay dividends of cash or property. The financial covenant associated with the loan agreement includes maintaining minimum unrestricted cash and cash equivalents of at least $5.0 million; provided that upon our (i) achievement of Performance Milestone 1, and (ii) receiving of net proceeds of at least $30.0 million from the sale and issuance of our equity securities (including any PIPE or follow-on offering), we shall no longer be subject to financial covenants. We are not in violation of the covenants. The agreement provides for events of default customary for loans of this type, including but not limited to non-payment, breaches, the occurrence of a material adverse change, or defaults in the performance of covenants, insolvency, and bankruptcy. The 2021 Avenue Loan is collateralized by substantially all of our assets other than intellectual property, including our capital stock and the capital stock of our subsidiaries, in which Avenue is granted a continuing security interest. The net proceeds from the issuance of the loan were initially allocated to the warrant at an amount equal to their fair value of $1.5 million and the remainder to the loan. The allocation of incurred financing costs of $0.5 million, which together with the fair value of the warrant and the final payment, are recorded as a debt discount and debt premium, respectively, and are being amortized over the contractual term using the effective interest method. During the year ended December 31, 2021, we recorded interest expense of $1.4 million.

Below is a schedule of future payments, net of unamortized debt discounts, if Avenue does not convert up to $5.0 million of the loan into Common Stock between May 21, 2022 through May 21, 2024:

(in thousands)	**As of December 31, 2021**
2022	$ —
2023	6,667
2024	13,333
2025	—
2026	—
Thereafter	—
Subtotal of future principal payments	20,000
Less unamortized debt discount associated with issuance date warrant fair value and financing costs	(1,654)
Total	$ 18,346

9. Preferred Stock Warrant Liability

Prior to the Reverse Recapitalization, in 2013, we issued Series A Preferred Stock Warrants, and ten-year warrants to purchase units of our most senior equity equal to 0.25% of our fully diluted equity at the time of exercise. The warrants expire ten years from issuance and are exercisable at a fixed exercise price of $1.97.

Prior to the Reverse Recapitalization, we classified the preferred stock warrants as liabilities on the consolidated balance sheets because the warrants are freestanding financial instruments that may have required us to transfer assets upon exercise. The preferred stock warrant liabilities were initially recorded at fair value and were subsequently remeasured to fair value as a component of other income (expense), net, in the consolidated statements of operations and comprehensive loss (see Note 16). Upon the closing of the Reverse Recapitalization, all outstanding Clene Nanomedicine preferred stock was converted into Common Stock and the preferred stock warrants were converted to warrants to purchase Common Stock (see Note 10, footnote 4). Upon conversion, we assessed the features of the preferred stock warrant liabilities and determined they qualified for classification as permanent equity. Accordingly, we remeasured the preferred stock warrant liabilities to fair value upon the close of the Reverse Recapitalization and reclassified them to additional paid-in capital and recognized a loss of $14.6 million for the year ended December 31, 2020, within other income, (expense), net, on the consolidated statements of operations and comprehensive loss. As of December 31, 2021 and 2020, we do not have any preferred stock warrant liabilities.

10. Common Stock Warrants

As of December 31, 2021, outstanding warrants to purchase shares of Common Stock were as follows:

Date Exercisable	Number of Shares Issuable		Exercise Price	Exercisable for	Classification	Expiration
December 2020	2,407,500	(1)	$ 11.50	Common Stock	Equity	December 2025
December 2020	24,583	(2)	$ 11.50	Common Stock	Equity	December 2025
December 2020	1,929,111	(3)	$ 1.97	Common Stock	Equity	April 2023
May 2021	115,851	(4)(5)	$ 8.63	Common Stock	Liability	May 2026
Total	4,477,045					

As of December 31, 2020, outstanding warrants to purchase shares of Common Stock were as follows:

Date Exercisable	Number of Shares Issuable		Exercise Price	Exercisable for	Classification	Expiration
June 2021	1,119,750	(6)	$ 0.01	Common Stock	Equity	December 2021
December 2020	2,407,500	(1)	$ 11.50	Common Stock	Equity	December 2025
December 2020	110,000	(2)	$ 11.50	Common Stock	Equity	December 2025
December 2020	1,929,111	(3)	$ 1.97	Common Stock	Equity	April 2023
Total	5,566,361					

(1) Consists of 2,407,500 shares of Common Stock underlying warrants to purchase one-half of one share of Common Stock, issued in connection with Tottenham's initial public offering. We may redeem the outstanding warrants, in whole and not in part, at a price of $0.01 per warrant if, and only if, the last sales price of our Common Stock equals or exceeds $16.50 per share for any 20 trading days within a 30-trading day period ending three business days before we send the notice of redemption. As of December 31, 2021 and 2020, none of the warrants had been exercised.

(2) Consisted of 110,000 shares of Common Stock underlying warrants to purchase one-half of one share of Common Stock, issued as part of the Chardan Unit Purchase Option (see Note 3). In July 2021, the Chardan Unit Purchase Option was net exercised, resulting in the issuance of 54,083 shares of Common Stock and warrants to purchase one-half of one share of Common Stock, or 24,583 shares of Common Stock. As of December 31, 2021, none of the warrants had been exercised, and as of December 31, 2020, the Chardan Unit Purchase Option had not been exercised.

(3) Consists of 1,929,111 shares of Common Stock underlying warrants to purchase one share of Common Stock, issued by Clene Nanomedicine as Series A preferred stock and senior equity Warrants (see Note 9). As of December 31, 2021 and 2020, none of the warrants had been exercised.

(4) Consists of 115,851 shares of Common Stock underlying warrants to purchase one share of Common Stock, issued in connection with the 2021 Avenue Loan at an exercise price equal to $8.63. As of December 31, 2021, none of the warrants had been exercised.

(5) An estimated 145,740 shares of Common Stock underlying warrants to purchase one share of Common Stock are issuable pursuant to the potential draw of Tranche 2 of the 2021 Avenue Loan (see Note 8). In accordance with ASC 815, we recognized these warrants at the inception of the 2021 Avenue Loan and classified them as common stock warrant liability and the fair value and issuable shares will be remeasured at each reporting period (see Note 16). As of December 31, 2021, the warrants are not issued or outstanding.

(6) Consisted of 1,119,750 shares of Common Stock underlying warrants to purchase one-half of one share, issued in connection with the 2020 PIPE. As of December 31, 2021, all outstanding warrants had been exercised into 1,119,750 shares of Common Stock. As of December 31, 2020, none of the warrants had been exercised.

11. Convertible Notes

2020 Convertible Notes

In February through July 2020, we issued convertible promissory notes (the "2020 Convertible Notes") in an aggregate principal amount of $6.1 million, bearing interest at an annual rate of 5%. The 2020 Convertible Notes were convertible at the earlier of (i) one year, into Series C preferred stock at the Series C preferred stock price, or (ii) our next equity financing of at least $10.0 million, into shares issued in the next equity financing at 90% of the next equity financing price. The 2020 Convertible Notes contained embedded features that provided the lenders with multiple settlement alternatives (the "Redemption Features"). The Redemption Features met the requirements to be bifurcated and accounted for as a derivative instrument (the "2020 Derivative Instrument"). Accordingly, the 2020

Derivative Instrument of $0.7 million was recorded at fair value at inception as a redeemable convertible preferred stock derivative liability in the consolidated balance sheets (see Note 12).

In August 2020, in connection with our issuance and sale of Series D preferred stock, the outstanding principal and accrued interest under the 2020 Convertible Notes, totaling $6.9 million, was converted into 1,497,135 shares of Series D preferred stock at a price equal to 90% of $4.60 per share, the Series D preferred stock price paid by cash investors.

In December 2020, upon consummation of the Reverse Recapitalization (see Note 3), all outstanding Series D preferred stock was converted to Common Stock. We accounted for the conversion of the 2020 Convertible Notes as a debt extinguishment and recognized a loss of $0.5 million within other income (expense), net, in the consolidated statements of operations and comprehensive loss for the year ended December 31, 2020. The loss on extinguishment was calculated as the difference between (i) the fair value of Series D preferred stock issued to settle the 2020 Convertible Notes of $6.9 million, less (ii) the fair value of the Derivative Instrument as of the date of extinguishment of $0.7 million and (iii) the carrying value of $5.7 million, which included (a) principal of $6.1 million, and (b) accrued and unpaid interest of $0.1 million, less (c) the unamortized debt discount of $0.5 million.

We recognized interest expense of $0.3 million and amortization of debt discount of $0.2 million during the year ended December 31, 2020.

Convertible Notes Payable

In May 2021, in connection with the 2021 Avenue Loan, we issued the Conversion Feature to Avenue (see Note 8). The Conversion Feature is subject certain conversion criteria related to our stock price and trading volume. The Conversion Feature did not meet the requirements for separate accounting and is not accounted for as a derivative instrument. As of December 31, 2021, the number of shares of Common Stock potentially issuable upon conversion was 482,703.

We classified $5.0 million of the 2021 Avenue Loan as convertible notes payable in the consolidated balance sheets as of December 31, 2021, with unamortized debt discount and issuance costs of $0.4 million. During the year ended December 31, 2021, we recognized (i) total interest expense of $0.4 million; (ii) coupon interest expense of $0.3 million; and (iii) amortization of debt discount and issuance costs of $0.1 million. The effective interest rate was 15.46% during the year ended December 31, 2021.

12. Derivative Instruments

Redemption Features of the 2020 Convertible Notes

The Redemption Features of the 2020 Convertible Notes contained embedded features providing the lenders with multiple settlement alternatives, including (i) a right to a fixed number of our shares upon conversion of the notes, or (ii) a right to receive cash or a variable number of shares upon the completion of a capital raising transaction, change of control, or default. The Redemption Features met the requirements to be bifurcated and accounted for as a derivative instrument. The 2020 Derivative Instrument was recorded at fair value of $0.7 million at issuance. In August 2020, the 2020 Convertible Notes were converted into shares of Series D preferred stock and the derivative liability was extinguished (see Note 11). Prior to extinguishment, the 2020 Derivative Instrument was marked to fair value and we recorded the change in fair value of $29,000 in the consolidated statements of operations and comprehensive loss for the year ended December 31, 2020.

Contingent Earn-Out Shares

The Contingent Earn-out shares met the requirements for separate accounting as derivative instruments. Upon the consummation of the Reverse Recapitalization, we recorded (i) the fair value of the Clene Nanomedicine Contingent Earn-out of $64.7 million as a liability and within accumulated deficit on the consolidated balance sheets, as it was considered a deemed distribution; and (ii) the fair value of the Initial Stockholders Contingent Earn-out of $7.4 million as a liability and within additional paid-in capital on the consolidated balance sheets.

As of December 31, 2021 and 2020, the fair value of the Clene Nanomedicine Contingent Earn-out was $18.1 million and $52.1 million, respectively. We recognized gains due to changes in fair value of the Clene Nanomedicine Contingent Earn-out of $34.0 million and $12.7 million during the years ended December 31, 2021 and 2020, respectively.

As of December 31, 2021 and 2020, the fair value of the Initial Stockholders Contingent Earn-out was $2.3 million and $5.9 million, respectively. We recognized gains due to changes in fair value of the Initial Stockholders Contingent Earn-out of $3.6 million and $1.5 million during the years ended December 31, 2021 and 2020, respectively.

As of December 31, 2021, we did not achieve Milestone 3 and the 2,503,851 Milestone 3 Contingent Earn-out shares were cancelled (see Note 3).

Avenue Warrant

The Avenue Warrant issued pursuant to Tranche 1 of the 2021 Avenue Loan and the warrant issuable pursuant to the potential draw of Tranche 2 (see Note 8) met the requirements for separate accounting as derivative instruments. Upon the issuance of the Avenue Warrant, we recognized the common stock warrant liability as a debt discount based on its fair value of $1.5 million. We recognized a change in fair value of the common stock warrant liability of $1.0 million during the year ended December 31, 2021.

13. Commitments and Contingencies

We enter into agreements in the normal course of business with CROs for clinical trials and with vendors for preclinical studies and other services and products for operating purposes, which are cancelable at any time by us, subject to payment of our remaining obligations under binding purchase orders and, in certain cases, nominal early termination fees. These commitments are not deemed significant.

From time to time, we may have certain contingent legal liabilities that arise in the ordinary course of business activities. We accrue a liability for such matters when it is probable that future expenditures will be made, and such expenditures can be reasonably estimated. We are not aware of any current pending legal matters or claims.

As of December 31, 2021, we had commitments under various agreements for capital expenditures totaling $0.6 million related to the construction of our manufacturing facilities.

14. Income Taxes

We have not recorded income tax benefits for the net operating losses incurred during the years ended December 31, 2021 and 2020 or for research and development tax credits or other deferred tax assets due to uncertainty of realizing benefits from these items.

The components of income (loss) before income taxes for the years ended December 31, 2021 and 2020 was as follows:

(in thousands)	2021	2020
United States	$ (6,269)	$ (18,985)
Foreign	(3,899)	114
Loss before provision for income taxes	$ (10,168)	$ (18,871)

Income tax expense (benefit) for the years ended December 31, 2021 and 2020 was as follows:

(in thousands)	2021	2020
Current tax expense (benefit):		
Federal	$ —	$ —
State	—	—
Foreign	(146)	146
Total current tax expense (benefit)	(146)	146
Deferred tax expense (benefit):		
Federal	—	—
State	—	—
Foreign	(282)	260
Total deferred tax expense (benefit)	(282)	260
Total income tax expense (benefit)	$ (428)	$ 406

A reconciliation of income tax computed at the U.S. federal statutory rate of 21% to expense for income taxes for the years ended December 31, 2021 and 2020 was as follows:

(in thousands)	2021	2020
Income tax expense (benefit) at federal statutory rate	$ (2,135)	$ (3,963)
State income taxes (net of federal benefit)	(1,690)	(917)
Change in fair value of common stock warrant liability	(206)	3,069
Change in fair value of contingent earn-outs	(7,884)	(2,966)
Research and development tax credits	(640)	(425)
Stock compensation	(462)	147
Foreign rate differential	(157)	7
Other	625	88
Change in valuation allowance	12,121	5,366
Income tax expense (benefit)	$ (428)	$ 406

Our effective tax rate was 4.21% and (2.15)% during the years ended December 31, 2021 and 2020, respectively. Significant components of deferred tax assets (liabilities) as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Deferred tax assets (liabilities):		
Net operating loss carryforwards	$ 26,898	$ 17,958
Depreciation and amortization	1,478	1,810
Research and development credits	2,594	1,682
Lease liability	1,158	520
Right-of-use asset	(798)	(270)
Accrued interest	—	160
Non-qualified stock options and restricted stock awards	2,815	146
Accrued compensation	74	115
Other	19	(260)
Total deferred tax assets (liabilities)	34,238	21,861
Less: valuation allowance	(34,238)	(22,121)
Net deferred tax assets (liabilities)	$ —	$ (260)

In assessing the realizability of deferred tax assets, we consider whether it is more-likely-than-not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during periods in which those temporary differences become deductible. We consider the scheduled reversal of deferred tax liabilities, projected future taxable income, carry back opportunities and tax planning strategies in making the assessment. We believe it is more likely than not that we will not realize the benefits of these deductible differences and have applied a full valuation allowance against them.

We have federal and state net operating losses (“NOLs”) of approximately $110.1 million and $77.1 million as of December 31, 2021, respectively that, subject to limitation, may be available in future tax years to offset taxable income. Of the available federal NOLs, approximately $76.7 million can be carried forward indefinitely but utilization is limited to 80% of our taxable income in any given tax year based on current federal tax laws. The remaining balance of $33.4 million will begin to expire after 2034. Of the available state NOLs, approximately $64.2 million can be carried forward indefinitely but utilization is limited to 80% of our taxable income in any given tax year based on current tax laws. The remaining balance of $12.9 million will begin to expire after 2032. Additionally, we have approximately $2.6 million of research and development credit carryforwards that will begin to expire after 2034 if not utilized.

Under the provisions of Section 382 of the Internal Revenue Code of 1986, substantial changes in our ownership may result in limitations on the amount of NOL carryforwards and research and development credits that can be utilized in future years. NOL carryforwards and research and development credits are subject to examination in the year they are utilized regardless of whether the tax year in which they are generated has been closed by statute. The amount subject to disallowance is limited to the amount utilized. Accordingly, we may be subject to examination for prior NOLs and credits generated as such tax attributes are utilized.

We have not recorded any amounts for unrecognized tax benefits as of December 31, 2021 and 2020. We recognize interest and penalties related to income tax matters in income tax expense. We have no accrual of interest and penalties on the consolidated balance sheets and have not recognized interest and penalties in the consolidated statements of operations and comprehensive loss for the years ended December 31, 2021 and 2020.

We are subject to taxation in the United States, Australia, Netherlands, and various state jurisdictions. Our tax returns from 2014 to present are subject to examination by the United States and state authorities due to the carry forward of unutilized net operating losses and research and development credits. There are currently no pending examinations.

15. Benefit Plans

401(k) Plan

Our 401(k) plan is a deferred salary arrangement under Section 401(k) of the Internal Revenue Code. Under the 401(k) plan, participating U.S. employees may defer a portion of their pretax earnings, up to the U.S. Internal Revenue Service annual contribution limit. We match 100% of a participating employee's deferral contributions up to 3% of annual compensation, limited to $4,500 of matching contributions. We contributed $0.2 million and $0.1 million to the 401(k) plan during the years ended December 31, 2021 and 2020, respectively.

2020 Stock Plan

In December 2020, in connection with the Reverse Recapitalization, the Board approved the 2020 Stock Plan and reserved 12,000,000 shares of Common Stock for issuance thereunder, all of which may be issued pursuant to incentive stock options or any other type of award under the 2020 Stock Plan. Selected employees, officers, directors, and consultants are eligible to participate in the 2020 Stock Plan. The purpose of the 2020 Stock Plan is to enable us to offer competitive equity compensation packages in order to attract and retain talent, and align the interests of management with those of stockholders.

The 2020 Stock Plan is administered by the Board. The exercise prices, vesting periods, and other restrictions are determined at the discretion of the Board, except that the exercise price per share of stock options may not be less than 100% of the fair market value of the Common Stock on the date of grant. Stock options expire ten years after the grant date, unless the Board sets a shorter term. Stock options granted to employees, officers, directors, and consultants generally vest over a four-year period. If an option or award granted under the 2020 Stock Plan expires, or is terminated, forfeited, repurchased, or cancelled, the unissued shares subject to that option or award shall again be available under the 2020 Stock Plan.

As of December 31, 2021, the Board granted 4,940,546 stock options and rights to restricted stock awards under the 2020 Stock Plan, and 7,059,454 shares remained available for future grant. As of December 31, 2020, the Board granted rights to 1,507,062 restricted stock awards under the 2020 Stock Plan.

2014 Stock Plan

Following the closing of the Reverse Recapitalization, the 2014 Stock Plan is administered by the Board. Stock options granted under the 2014 Stock Plan expire ten years after the grant date. Stock options and restricted stock awards granted to employees, officers, directors, and consultants generally vest over a four-year period.

As a result of the Reverse Recapitalization, 53,286,115 Clene Nanomedicine stock options outstanding under the 2014 Stock Plan were converted into 7,032,591 Clene Inc. stock options based on the Exchange Ratio (see Note 3). This exchange was treated as a modification of the awards. The modification did not result in material incremental stock-based compensation expense to be recognized at the closing of the Reverse Recapitalization. Effective as of the closing of the Reverse Recapitalization, no additional awards may be granted under the 2014 Stock Plan and as a result, if any option or award granted under the 2014 Stock Plan expires, or is terminated, forfeited, repurchased, cancelled, or tendered by a participant to us to exercise an award, the unissued shares subject to that option or award will not be available for future awards.

Stock-Based Compensation Expense

Stock-based compensation expense recorded in research and development expense and general and administrative expense for the years ended December 31, 2021 and 2020 was as follows:

(in thousands)	2021	2020
General and administrative	$ 7,553	$ 281
Research and development	4,831	480
Total stock-based compensation	$ 12,384	$ 761

Stock Options

Outstanding stock options and related activity for the year ended December 31, 2021 was as follows:

(in thousands, except share, per share, and term data)	Number of Options	Weighted Average Exercise Price Per Share	Weighted Average Remaining Term (Years)	Intrinsic Value
Outstanding - December 31, 2020	7,032,591	0.97	5.34	62,462
Granted	3,881,122	7.54	9.52	—
Exercised	(427,444)	1.04	—	1,310
Forfeited	(91,242)	8.45	—	—
Outstanding - December 31, 2021	10,395,027	$ 3.35	6.32	$ 21,082
Vested and exercisable - December 31, 2021	6,238,796	$ 1.09	4.35	$ 20,254
Vested, exercisable and expected to vest - December 31, 2021	10,395,027	$ 3.35	6.32	$ 21,082

Stock-based compensation expense associated with stock options totaled $4.9 million and $0.8 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021 and 2020, we had approximately $18.3 million and $2.4 million, respectively, of unrecognized stock-based compensation costs related to non-vested stock options which is expected to be recognized over a weighted-average period of 3.05 years and 2.04 years, respectively.

Prior to the Reverse Recapitalization, the exercise price of stock options was based on the fair market value of Clene Nanomedicine common stock on the grant date as determined by the board of directors of Clene Nanomedicine, with input from management. The board of directors of Clene Nanomedicine determined the fair value by considering a number of objective and subjective factors, including third-party 409A valuation reports, valuations of comparable companies, sales of redeemable convertible preferred stock, sales of common stock to non-affiliated third parties, operating and financial performance, the lack of liquidity of our common stock, and general and industry-specific economic outlook.

Subsequent to the Reverse Recapitalization, stock options are valued using a Black-Scholes option-pricing model. Due to the limited trading history of our Common Stock, the expected volatility is derived from the average historical stock volatilities of several unrelated comparable public companies within our industry, over a period equivalent to the expected term of the stock option grants. The risk-free interest rate for periods within the contractual life of the stock options is based on the U.S. Treasury yield curve in effect on the grant date. The expected dividend is assumed to be zero as we have never paid a dividend and have no plans to do so. The expected term represents the period the stock options are expected to be outstanding. For stock options that are considered to be in the ordinary course, we determine the expected term using the simplified method, which considers the term to be the average of the time-to-vesting and the contractual life of the stock options. For other stock option grants, we estimate the expected term using historical data on employee exercises and post-vesting employment termination behavior, while also considering the contractual life of the award.

During the year ended December 31, 2021, the assumptions used to calculate the fair value of stock options granted were as follows:

	2021	2020
Expected stock price volatility	87.40% – 91.51%	75.00% – 119.30%
Risk-free interest rate	0.72% – 1.34%	0.39% – 0.53%
Expected dividend yield	0.00%	0.00%
Expected term of options	6.00 years	6.00 years

The weighted-average grant-date fair value of stock options granted during the year ended December 31, 2021 was $5.49.

Restricted Stock Awards

In connection with the Reverse Recapitalization, we granted rights to the following restricted stock awards:

- 370,101 shares to various employees and non-employee directors, which vest on various dates between June 30, 2021 and July 15, 2022, subject to the employee's continuous employment through such vesting date. The award represents 5% of the converted stock options under the 2014 Stock Plan as a result of the Reverse Recapitalization and complements the 5% closing payment shares held in escrow for Clene Nanomedicine common stockholders (see Note 3). The grant-date fair

value of these awards was $4.0 million based on the closing price of CLNN shares listed on Nasdaq of $10.82 per share on December 30, 2020. As of December 31, 2021 and 2020, there were 224,109 and 0 shares, respectively, of Common Stock issued upon the vesting of these awards.

- 454,781 shares to various employees and non-employee directors, which are eligible to vest based on certain market conditions, subject to the employee's continuous employment through such vesting date. The award complements the Milestone 1 earn-out share entitlement of Clene Nanomedicine stockholders and vests based on the same market condition (see Note 3). The grant-date fair value of these awards, using a Monte Carlo valuation model, was $4.3 million. Based on the outcome of the market condition as of the December 31, 2021 and 2020 measurement dates, no shares were vested.
- 341,090 shares to various employees and non-employee directors, which are eligible to vest based on certain market conditions, subject to the employee's continuous employment through such vesting date. The award complements the Milestone 2 earn-out share entitlement of Clene Nanomedicine stockholders and vests based on the same market condition (see Note 3). The grant-date fair value of these awards, using a Monte Carlo valuation model, was $3.5 million. Based on the outcome of the market condition as of the December 31, 2021 and 2020 measurement dates, no shares were vested.
- 341,090 shares to various employees and non-employee directors, which were eligible to vest based on certain performance conditions tied to the completion of our COVID-19 clinical trial. The award complemented the Milestone 3 earn-out share entitlement of Clene Nanomedicine stockholders and vested based on the same performance condition (see Note 3). The grant-date fair value of these awards was $3.7 million, based on the closing price of CLNN shares listed on Nasdaq of $10.82 per share on December 30, 2020. We did not recognize compensation expense because the occurrence of achieving this milestone was not probable, and as of December 31, 2021, the performance condition was not achieved and the award was forfeited.

Outstanding rights to restricted stock awards and related activity for the year ended December 31, 2021 was as follows:

	Number of Restricted Stock Awards	Weighted Average Grant Date Fair Value
Unvested balance as of December 31, 2020	1,507,062	$ 10.30
Converted to shares of Common Stock upon vesting	(224,109)	10.82
Forfeited	(366,350)	10.75
Unvested balance as of December 31, 2021	916,603	$ 10.00

Stock-based compensation expense associated with the rights to restricted stock awards totaled $7.4 million and $0 for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, there was no unrecognized compensation cost related to unvested rights to restricted stock awards, and as of December 31, 2020, total unrecognized stock-based compensation cost related to unvested rights to restricted stock awards was $15.5 million, which was expected to be recognized over a weighted average period of 6 months.

We estimate the fair value of stock awards using a Monte Carlo valuation model to simulate the achievement of certain stock price milestones. The unobservable inputs include the expected stock price volatility, risk-free interest rate, and expected term. As of December 31, 2020, the expected stock price volatility was 85.00%, the risk-free interest rate was 0.40%, and the expected term was 5.00 years. There were no stock awards granted during the year ended December 31, 2021.

16. Fair Value

Cash is carried at fair value. Financial instruments, including accounts receivable, accounts payable, and accrued expenses are carried at cost, which approximates fair value given their short-term nature. The 2019 MD Loan, the 2019 Cecil Loan, the derivative instruments associated with the 2021 Avenue Loan, and the derivative instruments associated with the Contingent Earn-outs are carried at fair value. The 2021 Avenue Loan, related convertible notes payable, and Conversion Feature are carried at amortized cost, which approximate fair value due to our credit risk and market interest rates.

Liabilities with Fair Value Measurements on a Recurring Basis

The fair value hierarchy for liabilities measured at fair value on a recurring basis as of December 31, 2021 is as follows:

	2021			
	Level 1	Level 2	Level 3	Total
Notes payable	$ 736	$ —	$ —	$ 736
Common stock warrant liability	—	—	474	$ 474
Clene Nanomedicine contingent earn-out	—	—	18,100	$ 18,100
Initial Stockholders contingent earn-out	—	—	2,317	$ 2,317

The fair value hierarchy for liabilities measured at fair value on a recurring basis as of December 31, 2020 is as follows:

	2020			
	Level 1	Level 2	Level 3	Total
Notes payable	$ 1,296	$ —	$ —	$ 1,296
Clene Nanomedicine contingent earn-out	—	—	52,053	$ 52,053
Initial Stockholders contingent earn-out	—	—	5,906	$ 5,906

There were no transfers between Level 1, Level 2, or Level 3 during the year ended December 31, 2021. During the year ended December 31, 2020, notes payable was transferred from Level 3 to Level 1, as subsequent to the Reverse Recapitalization, the fair value of notes payable was determined based on the Common Stock price as reported by Nasdaq.

Valuation of Notes Payable and Convertible Notes Payable

The carrying value of notes payable and convertible notes payable includes certain notes carried at amortized cost, and certain notes remeasured at fair value on a recurring basis in the consolidated balance sheets as of December 31, 2021 and 2020. In order to value the notes, we considered the amount of simple interest expense that would be due and the value of our Common Stock.

As of December 31, 2021 and 2020, the fair value of the 2019 MD Loan and the 2019 Cecil Loan was determined based on the closing price of our Common Stock of $4.10 and $9.01, respectively, as reported by Nasdaq.

As of December 31, 2021, the amortized cost of the 2021 Avenue Loan was $18.3 million, which includes the notes payable, carried at $13.7 million; and the convertible notes payable and embedded Conversion Feature, carried at $4.6 million. The valuation of the Conversion Feature is discussed below. The 2021 Avenue Loan was not outstanding as of December 31, 2020.

Valuation of Conversion Feature

The Conversion Feature of the convertible notes payable from the 2021 Avenue Loan is carried at amortized cost and did not meet the requirements for separate accounting and is not accounted for as a derivative instrument. As of December 31, 2021, the estimated fair value of the Conversion Feature was $0.8 million and was determined using a Black-Scholes option-pricing model. The Conversion Feature was not outstanding as of December 31, 2020. The unobservable inputs to the Black Scholes valuation model as of December 31, 2021 were as follows:

	2021
Expected stock price volatility	105.00%
Risk-free interest rate	0.70%
Expected dividend yield	0.00%
Expected term	2.39 years

Valuation of Warrants to Purchase Preferred Stock

Our preferred stock warrant liabilities contained unobservable inputs that reflected our own assumptions. Accordingly, the preferred stock warrant liabilities were measured at fair value on a recurring basis using unobservable inputs. Prior to the extinguishment of the preferred stock warrant liabilities on December 30, 2020, the preferred stock warrant liability was valued using a Black-Scholes option-pricing model.

The board of directors of Clene Nanomedicine determined the fair value of the preferred stock by considering a number of objective and subjective factors, including third-party valuations, valuations of comparable companies, sales of redeemable convertible preferred stock, sales of common stock to unrelated third parties, operating and financial performance, the lack of liquidity of our capital stock, and general and industry-specific economic outlook. We estimated the volatility of our preferred stock based on comparable peer

companies' historical volatility. The risk-free interest rate for periods within the contractual life of the warrants was based on the U.S. Treasury yield curve in effect at the valuation date. We had no plans to declare any future dividends. The determination of the fair value of the preferred stock warrant liability could change in future periods based upon changes in the value of our preferred stock and other assumptions as presented above. We recorded any such change in fair value to the change in fair value of preferred stock warrant liability expense line in the consolidated statements of operations and comprehensive loss.

Upon the closing of the Reverse Recapitalization (see Note 3), all outstanding Clene Nanomedicine preferred stock was converted to Common Stock and the Clene Nanomedicine preferred stock warrants were converted to warrants for the purchase of Common Stock. Accordingly, the preferred stock warrant liabilities were extinguished in connection with the conversion of Clene Nanomedicine preferred stock on December 30, 2020 (see Note 9).

Valuation of the Common Stock Warrant Liability

Pursuant to Tranche 1 of the 2021 Avenue Loan, we issued the Avenue Warrant to purchase 115,851 shares of Common Stock. In accordance with ASC 815, we recognized an additional warrant to purchase an estimated 145,740 shares of Common Stock that will be issued pursuant to the potential draw of Tranche 2 (see Note 10). The warrants were recorded at fair value at the closing of the 2021 Avenue Loan and the fair value and number of issuable shares are remeasured at each reporting period.

The estimated fair value of the common stock warrant liability was determined using a Black-Scholes option-pricing model. The carrying amount of the liability may fluctuate significantly and actual amounts may be materially different from the liabilities' estimated value. The common stock warrant liability was not outstanding as of December 31, 2020. The unobservable inputs to the Black-Scholes option-pricing model as of December 31, 2021 were as follows:

	2021
Expected stock price volatility	105.00%
Risk-free interest rate	1.20%
Expected dividend yield	0.00%
Expected term	3.89 – 4.39 years

Valuation of the Contingent Earn-Outs

Upon the consummation of the Reverse Recapitalization and as of December 31, 2020, Clene Nanomedicine's common stockholders and the Initial Stockholders were entitled to receive up to 9,096,185 shares of Common Stock upon our achievement of certain milestones (see Note 3). As of December 31, 2021, Clene Nanomedicine's common stockholders and the Initial Stockholders were entitled to receive up to 6,592,334 shares of Common Stock. The Contingent Earn-outs were recorded at fair value at the closing of the Reverse Recapitalization and are remeasured at each reporting period.

The estimated fair value of the Contingent Earn-outs is determined using a Monte Carlo valuation model in order to simulate the future path of our stock price over the earn-out periods. The carrying amount of the liabilities may fluctuate significantly and actual amounts paid may be materially different from the liabilities' estimated value. The unobservable inputs to the Monte Carlo valuation model as of December 31, 2021 and 2020, were as follows:

	2021	2020
Expected stock price volatility	105.00%	85.00%
Risk-free interest rate	1.10%	0.40%
Expected dividend yield	0.00%	0.00%
Expected term	4.00 years	5.00 years

Changes in the fair value of our financial liabilities for the years ended December 31, 2021 and 2020 were as follows:

(in thousands)	Notes Payable	Derivative Instrument	Preferred Stock Warrant Liability	Common Stock Warrant Liability	Clene Nanomedicine Contingent Earn-out	Initial Stockholders Contingent Earn-out
Balance - December 31, 2019	$ 640	$ —	$ 3,213	$ —	$ —	$ —
Issuance of convertible promissory notes	—	705	—	705	—	—
Initial fair value of instrument	—	—	—	—	64,712	7,371
Change in fair value	656	(29)	14,615	(29)	(12,659)	(1,465)
Extinguishment of preferred stock warrant liability in connection with the conversion of redeemable convertible preferred stock	—	—	(17,828)	—	—	—
Extinguishment of derivative liability in connection with extinguishment of the 2020 Convertible Notes (Note 12)	—	(676)	—	(676)	—	—
Balance - December 31, 2020	$ 1,296	$ —	$ —	$ —	$ 52,053	$ 5,906
Initial fair value of instrument	—	—	—	1,457	—	—
Change in fair value	(560)	—	—	(983)	(33,953)	(3,589)
Balance - December 31, 2021	$ 736	$ —	$ —	$ 474	$ 18,100	$ 2,317

17. Redeemable Convertible Preferred Stock

Prior to the Reverse Recapitalization, we issued Series A, B, C, and D preferred stock to various investors. Preferred stock was convertible into Clene Nanomedicine common stock at the option of the holder at the conversion price. We evaluated the preferred stock and concluded that it did not meet the criteria for being classified as a liability. However, we determined the preferred stock should be classified as temporary equity, as we might be required to redeem the outstanding preferred stock in cash. We concluded that a redemption event was not probable, accordingly, the value of preferred stock was not adjusted to its redemption amount.

In connection with the closing of the Reverse Recapitalization, the preferred stock was converted into 36,893,894 shares of Common Stock based on the Exchange Ratio (see Note 3). As of December 31, 2021 and 2020, there was no redeemable convertible preferred stock outstanding.

18. Common Stock

As of December 31, 2021 and 2020, our certificate of incorporation, as amended and restated, authorized us to issue 150,000,000 and 100,000,000 shares of Common Stock, respectively, par value $0.0001 per share, and 1,000,000 shares of Preferred Stock, par value $0.0001 per share. At our 2021 Annual Meeting of Stockholders on May 18, 2021, our stockholders approved an amendment to the Amended and Restated Certificate of Incorporation to increase the number of authorized shares of Common Stock from 100,000,000 to 150,000,000 shares.

Our common stockholders are entitled to one vote per share and to notice of any stockholders' meeting. Voting, dividend, and liquidation rights of the holders of Common Stock are subject to the prior rights of holders of all classes of stock and are qualified by the rights, powers, preferences, and privileges of the holders of Preferred Stock. No distributions shall be made with respect to Common Stock until all declared dividends to Preferred Shares have been paid or set aside for payment to the holders of Preferred Stock. Common Stock is not redeemable at the option of the holder.

Upon consummation of the Reverse Recapitalization, the total outstanding 2,303,495 Tottenham common stock was converted into the same number of Common Stock, and 644,164 shares of Common Stock were issued to LifeSci as financial advisor to the Reverse Recapitalization (see Note 3).

Prior to the completion of the Reverse Recapitalization, we entered into subscription agreements with various investors in December 2020 for the sale and issuance of 2,239,500 shares of Common Stock at $10.00 per share, generating net proceeds of $22.2 million. In addition, investors in the 2020 PIPE also received warrants to purchase a number of shares equal to one-half of the number of 2020 PIPE shares, totaling 1,119,750 shares of Common Stock, at $0.01 per share and subject to a 180-day holding period (see Note 10). Between July 1, 2021 and December 20, 2021, the PIPE Warrants were exercised in full for 1,119,750 shares of Common Stock. We received cash proceeds of $11,198.

In May 2021, we entered into subscription agreements with various investors in the 2021 PIPE for the sale and issuance of 960,540 shares of Common Stock at a price of $9.63 per share, generating net proceeds of $9.3 million. The closing of the 2021 PIPE occurred substantially concurrently with, and was conditioned upon, the closing of the 2021 Avenue Loan (see Note 8).

In July 2021, Chardan exercised the Chardan Unit Purchase Option for 220,000 units, each unit consisting of one and one-tenth shares of Common Stock and one warrant to purchase one-half of one share of Common Stock at an exercise price of $11.50 per share. Chardan elected to perform a cashless or net exercise, which resulted in a net issuance of 54,083 shares of Common Stock and 49,166 warrants to purchase one-half of one share of Common Stock at $11.50 per share. We received no cash proceeds. As of December 31, 2021, none of the warrants had been exercised, and as of December 31, 2020, the Chardan Unit Purchase Option had not been exercised.

As of December 31, 2021 and 2020, our common shares issued and outstanding were 62,312,097 and 59,526,171, respectively. As of December 31, 2021 and 2020, there were no preferred shares issued or outstanding.

19. Net Loss Per Share Attributable to Common Stockholders

The computation of basic and diluted net income (loss) per share attributable to common stockholders for the years ended December 31, 2021 and 2020 was as follows:

(in thousands, except share and per share data)	2021	2020
Numerator:		
Net loss attributable to common stockholders	$ (9,740)	$ (19,277)
Denominator:		
Weighted average shares outstanding	61,558,455	17,503,992
Net loss per share attributable to common stockholders, basic and diluted	$ (0.16)	$ (1.10)

The following shares of potentially dilutive securities were excluded from the computation of diluted net loss per share attributable to common stockholders for the years ended December 31, 2021 and 2020 because including them would have been antidilutive, or issuance of such shares is contingent upon the satisfaction of certain conditions which were not satisfied by the end of the period, or they were out-of-the money:

	2021	2020
Convertible stock warrants (See Note 11)	482,703	—
Common stock warrants (see Note 10)	4,477,045	4,446,613
Options to purchase common stock	10,395,027	7,032,591
Unvested restricted stock awards	916,603	—
Unit purchase option to purchase common stock (see Note 1)	—	242,000
Earn-out shares (see Note 3 and 12)	6,592,334	9,096,185
Total	22,863,712	20,817,389

20. Related Party Transactions

License and Supply Agreements

In August 2018, we entered into a supply agreement with 4Life in conjunction with 4Life's investment in our Series C preferred stock and warrants. Pursuant to the supply agreement, we granted 4Life an exclusive license to develop dietary supplements using certain of our intellectual property. The term of the exclusive license is five years from the commencement of product sales under the supply agreement, with a deemed commencement date of January 1, 2023 if sales have not commenced by that date, with options to renew for additional five-year terms. We provide non-pharmaceutical product to 4Life for development, and 4Life pays royalties of 3% of incremental sales, as defined in the agreement. 4Life is subject to an annual minimum sales requirement under the supply agreement. If the minimum sales are unmet, 4Life may pay us an additional fee to maintain exclusivity or have the license converted to non-exclusive.

During the years ended December 31, 2021 and 2020, we sold product under the supply agreement totaling $0.5 million and $0.1 million, respectively, and product not under the supply agreement totaling $0.1 million and $0.1 million, respectively. As of December 31, 2021 and 2020, we received advance payments of $0 and $0.1 million, respectively, which we recorded as deferred revenue to be applied against future sales. During the years ended December 31, 2021 and 2020, we received royalty revenue of $0.2 million and $30,000, respectively.

21. Geographic and Segment Information

Geographic Information

Long-lived assets, which were composed of property and equipment, net by location, as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
United States	$ 5,142	$ 3,997
Australia	30	228
Total property and equipment, net	$ 5,172	$ 4,225

Segment Information

Our operating segment profit measure is segment loss from operations, which is calculated as revenue less cost of revenue, research and development, and general and administrative expenses. Profit and loss information by reportable segment for the years ended December 31, 2021 and 2020 was as follows:

(in thousands)	2021	2020
Drugs:		
Revenue from external customers	$ —	$ —
Depreciation expense	(910)	(955)
Stock compensation expense	(12,384)	(761)
Loss from operations	(50,183)	(20,355)
Supplements:		
Revenue from external customers	$ 723	$ 206
Depreciation expense	(45)	(7)
Stock compensation expense	—	—
Income (loss) from operations	205	141
Consolidated:		
Revenue from external customers	$ 723	$ 206
Depreciation expense	(955)	(963)
Stock compensation expense	(12,384)	(761)
Loss from operations	(49,978)	(20,214)

A reconciliation of the total of the reportable segments' loss from operations to consolidated net loss before income taxes for the years ended December 31, 2021 and 2020 was as follows:

(in thousands)	2021	2020
Segment loss from operations	$ (49,978)	$ (20,214)
Total other income (expense), net	39,810	1,343
Net loss before income taxes	$ (10,168)	$ (18,871)

Segment assets exclude corporate assets, such as cash, restricted cash, and corporate facilities. Total assets by reportable segment as of December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Total assets:		
Drugs	$ 12,052	$ 8,066
Supplements	337	504
Corporate	50,674	59,673
Consolidated	$ 63,063	$ 68,243

Additions to long-lived assets for the years ended December 31, 2021 and 2020 were as follows:

(in thousands)	2021	2020
Drugs	$ 1,332	$ 387
Supplements	—	—
Corporate	—	—
Consolidated	$ 1,332	$ 387

22. Subsequent Events

On August 10, 2021, we entered into an operating lease for laboratory space that replaced a previous operating lease for the same facility. The commencement of the lease and the termination of the previous lease was effective as of February 1, 2022.

On February 11, 2022, we entered into an amendment of the Avenue Loan which extended our ability to draw $10 million under Tranche 2 from June 30, 2022 to December 31, 2022.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Under the supervision and with the participation of management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness of our disclosure controls and procedures as of December 31, 2021, as such term is defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. As a result of this evaluation, our principal executive officer and principal financial officer have concluded that, as of December 31, 2021, our disclosure controls and procedures were not effective due to the material weaknesses in internal control over financial reporting described below. Notwithstanding the identified material weaknesses, management, including our principal executive officer and principal financial officer, believes the consolidated financial statements included in this Annual Report fairly represent, in all material respects, our financial condition, results of operations and cash flows as of and for the periods presented in accordance with U.S. Generally Accepted Accounting Principles.

Disclosure controls and procedures are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure.

Management's Annual Report on Internal Control Over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Rules 13a-15(f) and 15d-15(f) of the Exchange Act. Management has evaluated the effectiveness of our internal control over financial reporting based on criteria established in Internal Control — Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. As a result of this assessment, management has concluded that, as of December 31, 2021, our internal control over financial reporting was not effective due to the material weaknesses in internal control over financial reporting described below. As an emerging growth company, we are not required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm in this Annual Report.

Material Weaknesses in Internal Control over Financial Reporting

In connection with the audit of our financial statements as of and for the years ended December 31, 2021 and 2020, our management identified material weaknesses in our internal control over financial reporting. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. The material weaknesses identified relate to the fact that we did not design or maintain an effective control environment commensurate with our financial reporting requirements. This deficiency in our control environment contributed to the following additional material weaknesses related to control activities and information and communication within our internal control over financial reporting:

- we did not design and maintain controls over the preparation and review of reconciliations and the review and segregation of duties over manual journal entries, including controls over the completeness and accuracy of information; and
- we did not design and maintain IT general controls for IT systems that are relevant to the preparation of the financial statements. Specifically, we did not design and maintain: (a) user access controls to ensure appropriate segregation of duties and that adequately restrict user and privileged access to financial applications, programs, and data to our appropriate personnel; (b) program change management controls to ensure that IT program and data changes affecting financial IT applications and underlying accounting records are identified, tested, authorized, and implemented appropriately; (c) computer operations controls to ensure that data backups are authorized and monitored; and (d) testing and approval controls for program development to ensure that new software development is aligned with business and IT requirements.

Each of the control deficiencies described above could result in a misstatement of one or more account balances or disclosures that would result in a material misstatement to the annual or interim consolidated financial statements that would not be prevented or detected. Accordingly, our management has determined that each of the control deficiencies described above constitute material weaknesses.

Material Weakness Remediation

Management continues to be actively engaged and committed to taking the steps necessary to remediate the control deficiencies that constituted the above material weakness. During 2021, we made the following enhancements to our control environment:

- we have strengthened the experience of our internal accounting team, to provide oversight, structure and reporting lines, and to provide additional review over our disclosures, including hiring a new Vice President, Finance and Controller;
- we have engaged external consultants to assist with the evaluation of complex accounting and financial reporting related areas and to assist with the documentation around accounting and financial reporting policies and procedures;
- we engaged external consultants to assist in the design, implementation, and documentation of internal controls that address the relevant risks and provide for appropriate evidence of performance of the internal control; and
- we are in the process of implementing a new Enterprise Resource Planning system that will significantly enhance the information technology general controls environment.

We continue to enhance corporate oversight over process-level controls and structures to ensure that there is appropriate assignment of authority, responsibility, and accountability to enable remediation of our material weaknesses. We believe that our remediation plan will be sufficient to remediate the identified material weakness and strengthen our internal control over financial reporting. As we continue to evaluate, and work to improve, our internal control over financial reporting, management may determine that additional measures to address control deficiencies or modifications to the remediation plan are necessary.

Changes in Internal Control over Financial Reporting

Other than changes described under "*—Material Weakness Remediation*" above, there were no changes in our internal control over financial reporting during the quarter ended December 31, 2021, which were identified in connection with management's evaluation required by paragraph (b) of Rules 13a-15 and 15d-15 under the Exchange Act, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Information required by Item is included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference. The definitive proxy statement will be filed with the SEC within 120 days after the end of the fiscal year to which this Annual Report relates.

Item 11. Executive Compensation

Information required by Item is included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference. The definitive proxy statement will be filed with the SEC within 120 days after the end of the fiscal year to which this Annual Report relates.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

Information required by Item is included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference. The definitive proxy statement will be filed with the SEC within 120 days after the end of the fiscal year to which this Annual Report relates.

Item 13. Certain Relationships and Related Transactions, and Director Independence

Information required by Item is included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference. The definitive proxy statement will be filed with the SEC within 120 days after the end of the fiscal year to which this Annual Report relates.

Item 14. Principal Accountant Fees and Services

Information required by Item is included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders and is incorporated herein by reference. The definitive proxy statement will be filed with the SEC within 120 days after the end of the fiscal year to which this Annual Report relates.

PART IV

Item 15. Exhibit and Financial Statement Schedules

(a) Documents filed as part of this Annual Report:

(1) Financial Statements:

Report of Independent Registered Public Accounting Firm
Consolidated Balance Sheets
Consolidated Statements of Operations and Comprehensive Loss
Consolidated Statements of Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)
Consolidated Statements of Cash Flows
Notes to Consolidated Financial Statements

(2) Financial Statement Schedules:

All schedules have been omitted because the required information is included in the consolidated financial statements or the notes thereto, or because it is not required.

(3) Exhibits:

See exhibits listed under Part (b) below.

(b) Exhibits:

Exhibit Number	Exhibit Description
2.1	Merger Agreement, dated September 1, 2020 (incorporated by reference to Annex A-1 to the Proxy Statement/Consent Solicitation Statement/Prospectus on Form S-4 filed by Chelsea Worldwide Inc. on September 10, 2020).
3.1	Third Amended and Restated Certificate of Incorporation of Clene Inc. (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed by the Registrant on July 16, 2021).
3.2	Bylaws of Clene Inc. (incorporated by reference to Exhibit 3.2 to the Current Report on Form 8-K filed by the Registrant on January 5, 2021).
4.1*	Description of Securities of the Registrant.
4.2	Warrant Agreement, dated August 1, 2018, by and between Continental Stock Transfer & Trust Company and the Registrant (incorporated by reference to Exhibit 4.1 to the Current Report on Form 8-K filed by Tottenham on August 7, 2018).
4.3	Specimen TOTA Warrant Certificate (incorporated by reference to Exhibit 4.3 to the Registration Statement on Form S-1 filed by Tottenham on July 5, 2018).
10.1#	Clene Inc. Board of Directors Compensation Program (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on April 22, 2021).
10.2#	2020 Equity Incentive Plan (incorporated by reference to Exhibit 10.4 to Current Report on Form 8-K filed by the Registrant on January 5, 2021).
10.3#	Form of Indemnification Agreement between the Registrant and its directors and executive officers (incorporated by reference to Exhibit 10.18 to the Registration Statement on Form S-4 filed by Chelsea Worldwide Inc. on December 15, 2020).
10.4#	Form of Executive Employment Agreement (incorporated by reference to Exhibit 10.3 to the Current Report on Form 8-K filed by the Registrant on February 2, 2022).
10.5	Form of Registration Rights Agreement (incorporated by reference to Exhibit 10.10 to the Registration Statement on Form S-4 filed by Chelsea Worldwide Inc. on December 15, 2020).
10.6	Form of Subscription Agreement (incorporated by reference to Exhibit 10.12 to the Registration Statement on Form S-4 filed by Chelsea Worldwide Inc. on December 15, 2020).
10.7	Form of Subscription Agreement (incorporated by reference to Exhibit 10.4 to the Current Report on Form 8-K filed by the Registrant on May 24, 2021).
10.8##	License Agreement, effective August 31, 2018, between Clene Nanomedicine, Inc. and 4Life Research, LLC (incorporated by reference to Exhibit 10.14 to the Registration Statement on Form S-4 filed by Chelsea Worldwide Inc. on December 15, 2020).
10.9	Exclusive Supply Agreement, dated August 31, 2018, between Clene Nanomedicine, Inc. and 4Life Research, LLC (incorporated by reference to Exhibit 10.15 to the Registration Statement on Form S-4 filed by Chelsea Worldwide Inc. on December 15, 2020).
10.10†	Clinical Research Support Agreement, dated September 27, 2019, between Clene Nanomedicine, Inc. and The General Hospital Corporation (incorporated by reference to Exhibit 10.17 to the Registration Statement on Form S-4 filed by Chelsea Worldwide Inc. on December 15, 2020).

10.11	Loan and Security Agreement, dated as of May 21, 2021, between Clene Inc., Clene Nanomedicine, Inc. and Avenue Venture Opportunities Fund, L.P. (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on May 24, 2021).
10.12##	First Amendment to the Loan and Security Agreement, dated as of June 30, 2021 between Clene Inc., Clene Nanomedicine, Inc. and Avenue Venture Opportunities Fund, L.P. (incorporated by reference to Exhibit 10.3 to the Quarterly Report on Form 10-Q filed by the Registrant on August 9, 2021).
10.13†	Supplement to the Loan and Security Agreement, dated as of May 21, 2021, among Clene Inc., Clene Nanomedicine, Inc., and Avenue Venture Opportunities Fund, L.P. (incorporated by reference to Exhibit 10.2 to the Current Report on Form 8-K filed by the Registrant on May 24, 2021).
10.14*	Amendment to Supplement to Loan and Security Agreement, dated as of February 11, 2022, among Clene Inc., Clene Nanomedicine, Inc., and Avenue Venture Opportunities Fund, L.P.
10.15	Form of Avenue Venture Opportunities Fund, L.P. Warrant to Purchase Shares of Stock of Clene Inc. (incorporated by reference to Exhibit 10.3 to the Current Report on Form 8-K filed by the Registrant on May 24, 2021).
10.16##	Lease Agreement, dated as of August 10, 2021, between Clene Nanomedicine, Inc. and 100 Chesapeake Blvd LLC. (incorporated by reference to Exhibit 10.1 to the Current Report on Form 8-K filed by the Registrant on August 11, 2021).
10.17##	Lease Agreement, dated as of August 10, 2021, between Clene Nanomedicine, Inc. and Upper Chesapeake Flex One, LLC. (incorporated by reference to Exhibit 10.2 to the Current Report on Form 8-K filed by the Registrant on August 11, 2021).
21.1*	Subsidiaries of the Registrant.
23.1*	Consent of PricewaterhouseCoopers LLP.
23.2*	Consent of Deloitte & Touche LLP.
31.1*	Certification of Chief Executive Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a), promulgated under the Securities and Exchange Act of 1934, as amended.
31.2*	Certification of Chief Financial Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a), promulgated under the Securities and Exchange Act of 1934, as amended.
32.1**	Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2**	Certification of Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.1	Inline XBRL Instance Document.
101.2	Inline XBRL Taxonomy Extension Schema Document.
101.3	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.4	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.5	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.6	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101).

* Filed herewith.
** Furnished herewith.
# Management contract or compensatory plan or agreement.
Schedules and similar attachments to this exhibit have been omitted pursuant to Item 601(a)(5) of Regulation S-K. We agree to furnish supplementally a copy of such omitted materials to the SEC upon request.
† Certain portions of this exhibit have been redacted pursuant to Item 601(b)(10)(iv) of Regulation S-K. We agree to furnish supplementally an unredacted copy to the SEC upon request.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

CLENE INC.

Date: March 11, 2022

By: /s/ Robert Etherington
Robert Etherington
President, Chief Executive Officer and Director

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed by the following persons on behalf of the registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Robert Etherington Robert Etherington	President, Chief Executive Officer and Director (Principal Executive Officer)	March 11, 2022
/s/ Morgan R. Brown Morgan R. Brown	Chief Financial Officer (Principal Financial and Accounting Officer)	March 11, 2022
/s/ David J. Matlin David J. Matlin	Chairman of the Board	March 11, 2022
/s/ Jonathon T. Gay Jonathon T. Gay	Director	March 11, 2022
/s/ Shalom Jacobovitz Shalom Jacobovitz	Director	March 11, 2022
/s/ Vallerie V. McLaughlin Vallerie V. McLaughlin	Director	March 11, 2022
/s/ Alison H. Mosca Alison H. Mosca	Director	March 11, 2022
/s/ John Henry Stevens John Henry Stevens	Director	March 11, 2022
/s/ Chidozie Ugwumba Chidozie Ugwumba	Director	March 11, 2022
/s/ Reed Neil Wilcox Reed Neil Wilcox	Director	March 11, 2022

Exhibit 4.1

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following is a summary of the rights and preferences of the capital stock of Clene Inc. (the "Company," "we," "us," or "our"). While we believe that the following description covers the material terms of our capital stock, the description may not contain all of the information that is important to you. We encourage you to read carefully our Annual Report on Form 10-K (the "Annual Report"), certificates of designation relating to the securities, as applicable, our amended and restated certificate of incorporation (the "certificate of incorporation") and amended and restated bylaws (the "bylaws") and the other documents we refer to for a more complete understanding of our capital stock. Copies of our certificate of incorporation and bylaws are incorporated by reference as exhibits to our Annual Report.

General

We are governed by the certificate of incorporation, as amended and restated from time to time, and the Delaware General Corporation Law ("DGCL"), and the common law of the state of Delaware. The following summary of certain provisions of our securities does not purport to be complete and is subject to our amended and restated certificate of incorporation, our amended and restated bylaws and the provisions of the DGCL. Copies of our amended and restated certificate of incorporation or our amended and restated bylaws are attached to our Annual Report as Exhibits 3.1 and 3.2, respectively.

Our amended and restated certificate of incorporation authorizes a total number of shares of all classes of stock of 151,000,000 shares, consisting of (i) 1,000,000 shares of preferred stock, par value $0.0001 per share, and (ii) 150,000,000 shares of common stock, par value $0.0001 per share.

Common Stock

Our common stock is listed on the Nasdaq Stock Market LLC ("Nasdaq") under the symbol "CLNN." The holders of our common stock are entitled to one vote for each share held on all matters to be voted on by shareholders and do not have cumulative voting rights. The holders of our common stock are entitled to receive dividends, if and when declared by our Board of Directors ("Board") out of funds legally available therefor. In the event of a liquidation, dissolution or winding up of the Company, our shareholders are entitled to share ratably in all assets remaining available for distribution to them after payment of liabilities and after provision is made for each class of stock, if any, having preference over our common stock. Holders of our common stock have no preemptive or other subscription rights. Our Board is classified.

Preferred Stock

Our preferred stock is currently undesignated and no shares of preferred stock are outstanding. The Board has the authority to issue shares of preferred stock from time to time on terms it may determine, to divide shares of preferred stock into one or more series and to fix the designations, preferences, privileges, and restrictions of preferred stock, including dividend rights, conversion rights, voting rights, terms of redemption, liquidation preference, sinking fund terms, and the number of shares constituting any series or the designation of any series to the fullest extent permitted by the DGCL. The issuance of preferred stock could have the effect of decreasing the trading price of common stock, restricting dividends on our capital stock, diluting the voting power of the common stock, impairing the liquidation rights of our capital stock or delaying or preventing a change in control of us. There is no restriction on the repurchase or redemption of shares by us while there is any arrearage in the payment of dividends or sinking fund installments.

Warrants

As of the date of our Annual Report, we had warrants outstanding that were exercisable into a total of 4,477,045 shares of common stock, as outlined below.

Public Warrants

The warrants originally issued by Tottenham Acquisition I Limited ("Tottenham") are listed on Nasdaq under the symbol "CLNNW" (the "Public Warrants"). Each Public Warrant entitles the holder thereof to purchase one-half (1/2) of one share of our common stock at a price of $11.50 per full share. We will not issue fractional shares. As a result, a Public Warrant holder must exercise warrants in multiples of two, at a price of $11.50 per full share, subject to adjustment, to validly exercise the warrants. The Public Warrants became exercisable upon the completion of the business combination with Tottenham (the "Reverse Recapitalization") and will expire on December 30, 2025. As of the date of our Annual Report, we had 4,815,000 Public Warrants outstanding exercisable into 2,407,500 shares of common stock. The Public Warrants are currently exercisable.

We may redeem the outstanding Public Warrants (excluding the private warrants that are part of the private units), in whole and not in part, at a price of $0.01 per warrant:

- at any time while the warrants are exercisable;
- upon a minimum of 30 days' prior written notice of redemption;
- if, and only if, the last sales price of our common stock equals or exceeds $16.50 per share for any 20 trading days within a 30-trading day period ending three business days before we send the notice of redemption; and
- if, and only if, (i) there is a current registration statement in effect with respect to our common stock underlying the warrants at the time of redemption and for the entire 30-day trading period referred to above and continuing each day thereafter until the date of redemption or (ii) the warrants may be exercised on cashless basis as set forth in the Warrant Agreement and such cashless exercise is exempt from registration under the Securities Act.

If the foregoing conditions are satisfied and we issue a notice of redemption, each warrant holder can exercise his, her or its warrant prior to the scheduled redemption date. However, the price of our common stock may fall below the $16.50 trigger price as well as the $11.50 warrant exercise price per full share after the redemption notice is issued and not limit our ability to complete the redemption.

If we call the Public Warrants for redemption as described above, our management will have the option to require all warrant holders that wish to exercise the warrants to do so on a "cashless" basis. In such event, each warrant holder would pay the exercise price by surrendering the whole warrant for that number of shares of our common stock equal to the quotient obtained by dividing (x) the product of the number of our common stock underlying the warrants, multiplied by the difference between the exercise price of our warrants and the "fair market value" (as defined below) by (y) the fair market value. The "fair market value" means the average reported last sale price of our common stock for the ten trading days ending on the third trading day prior to the date on which the notice of redemption is sent to the warrant holders. Whether we will exercise the option to require all warrant holders to exercise their warrants on a "cashless basis" will depend on a variety of factors, including the price of our common stock at the time the warrants are called for redemption, our cash needs at such time and concerns regarding dilutive share issuances.

Founder Warrants

Prior to the Reverse Recapitalization, in April 2013, we issued Series A preferred stock warrants in connection with certain note purchase agreements. The warrants expire 10 years from issuance and became exercisable upon completion of a previous equity financing of Clene Nanomedicine. At the close of the Reverse Recapitalization and as of the date of our Annual Report, these warrants are exercisable and entitle the holder thereof to purchase one share of our common stock at a fixed exercise price of $1.97 into 1,608,670 aggregate shares of common stock.

Prior to the Reverse Recapitalization, in April 2013, Clene Nanomedicine issued warrants to purchase units of its most senior equity equal to 0.25% of the company's fully diluted equity at the time of exercise in connection with certain note purchase agreements. The warrants expire 10 years from issuance and became exercisable upon issuance. At the close of the Reverse Recapitalization and as of the date of our Annual Report, these warrants are exercisable and entitle the holder thereof to purchase one share of our common stock at a fixed exercise price of $1.97 into 320,441 aggregate shares of our common stock.

Option Warrants

In July 2021, Chardan Capital Markets, LLC ("Chardan") exercised a unit purchase option originally issued in connection with Tottenham's initial public offering in August 2018 for 220,000 units, each unit consisting of one and one-tenth shares of common stock and one warrant to purchase one-half of one share of common stock at an exercise price of $11.50 per share. Chardan elected to perform a cashless or net exercise, which resulted in a net issuance of 49,166 warrants to purchase one-half of one share of common stock. The warrants became exercisable upon issuance and are subject to the same expiration and redemption terms as the Public Warrants. As of the date of our Annual Report, the Option Warrants are exercisable into 24,583 shares of common stock at a fixed exercise price of $11.50 per share.

Avenue Warrant

In May 2021, we issued a warrant to purchase shares of our common stock in connection with a loan agreement by and among the Company and our wholly owned subsidiary, Clene Nanomedicine, Inc., and Avenue Venture Opportunities Fund, L.P. ("Avenue"), a Delaware limited partnership within the Avenue Capital Group, and its affiliates. The exercise price per share of the warrant is equal to the lower of (i) $8.63, or (ii) the lowest price per share paid by cash investors for our common stock issued in the next bona fide round of equity financing prior to March 31, 2022. The warrant became exercisable upon issuance and expires on May 21, 2026. As of the date of our Annual Report, the warrant is exercisable into 115,851 shares of common stock.

Dividends

We currently intend to retain all available funds and any future earnings to fund the growth and development of our business. We have never declared or paid any cash dividends on our capital stock. We do not intend to pay cash dividends to our shareholders in the foreseeable future. Our ability to declare dividends is limited by the terms of financing or other agreements that we have entered into. Future debt or other financing arrangements also may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Any future determination to declare dividends will be made at the discretion of our Board and will depend on our financial condition, operating results, capital requirements, general business conditions, and other factors that our Board may deem relevant.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar's address is 6201 15th Avenue, Brooklyn, New York 11219.

AMENDMENT
TO
SUPPLEMENT TO LOAN AND SECURITY AGREEMENT

This Amendment to Supplement to Loan and Security Agreement (the "Amendment") is made effective as of February 11, 2022, by and among Clene Inc., a Delaware corporation ("Company"), Clene Nanomedicine, Inc. ("Nanomedicine"), (Company and Nanomedicine, individually and collectively, "Borrower") and Avenue Venture Opportunities Fund, LP. ("Lender"). The Borrower and Lender are sometimes separately referred to herein as a "Party" and are collectively referred to herein as the "Parties". Capitalized terms used but not defined herein have the meanings assigned to such terms in the LSA or Agreement (as defined below), as the case may be.

WHEREAS, Borrower and Lender are Parties to a Loan and Security Agreement (the "LSA") and Supplement to Loan and Security Agreement dated as of May 21, 2021 (the "Agreement") and have been acting in accordance with the terms thereof since the effective date; and

WHEREAS, the Parties desire to amend the Agreement in accordance with the terms of this Amendment.

NOW THEREFORE, in consideration of the mutual promises and covenants contained in this Agreement, the Borrower and Lender hereby agree as follows:

1. The reference to "June 30, 2022" in the definition of **Additional Equity** in **Part 1 - Additional Definitions** of the Agreement is deleted and replaced with the date "December 31, 2022".

2. The reference to "June 30, 2022" in subsection (ii) of the definition of **Termination Date** in **Part 1 - Additional Definitions** of the Agreement is deleted and replaced with the date "December 31, 2022".

3. The following definition of "**Cash Equivalents**" shall be added (after the definition of "**Amortization Period**") in **Part 1 -Additional Definitions** of the Agreement and shall read in its entirety as follows:

> "**Cash Equivalents**" means any short-term investment securities with maturity periods of 90 days or less at date of purchase. They include bank certificates of deposit, banker's acceptances, Treasury bills, commercial paper, other money market instruments, and commercial bonds with a credit rating of A or higher from Moody's, Standard & Poor's or Fitch."

4. Section 6 of the Agreement is deleted and shall read in its entirety as follows:

> "**Financial Covenants**. Borrower shall at all times during the term hereof maintain minimum unrestricted cash and Cash Equivalents, in accounts subject to control agreements in favor of, and in form and content reasonably acceptable to, Lender, of at least Five Million Dollars ($5,000,000); provided that, upon Borrower (1) achieving Performance Milestone 1 and (2) receiving the Additional Equity, Borrower shall no longer be required to comply with this Part 2, Section 6."

5. Borrower understands and agrees that Lender is relying upon Borrower's representations, warranties, and agreements, as set forth in the Loan Documents. Borrower represents and warrants (i) that the representations and warranties contained in the Loan Agreement are true and correct as of the date of this Amendment, and (ii) that no Event of Default has occurred and is continuing. Except as expressly modified pursuant to this Amendment, the terms of the Loan Documents remain unchanged, in full force and effect and are hereby ratified and confirmed in all respects. Lender's agreement to modifications pursuant to this Amendment in no way shall obligate Lender to make any future modifications. It is the intention of Lender and Borrower to retain as liable parties all makers and endorsers of Loan Documents, unless the party is expressly released by Lender in writing. No maker, endorser, or guarantor will be released by virtue of this Amendment. The terms of this paragraph apply not only to this Amendment, but also to any subsequent loan and security modification agreements.

6. Except as expressly set forth herein, the execution, delivery, and performance of this Amendment shall not operate as a waiver of, or as an amendment of, any right, power, or remedy of Lender under the Loan Documents, as in effect prior to the date hereof.

7. Borrower and Lender may execute this Amendment in counterparts and by facsimile signature or via email. Each executed counterpart of this Amendment will constitute an original document, and all executed counterparts, together, will constitute the same agreement. This Amendment shall be governed by, and construed in accordance with, the internal laws of the State of California, without regard to its conflict of laws principles.

[*Remainder of Page Intentionally Left Blank*]

IN WITNESS WHEREOF, the Parties have executed this Amendment as of the date first above written.

Clene Inc.

By: /s/ Rob Etherington
Rob Etherington, President

Clene Nanomedicine, Inc.

By: /s/ Rob Etherington
Rob Etherington, President

Avenue Venture Opportunities Fund, L.P.

By: Avenue Venture Opportunities Partners, LLC

By /s/ Sonia Gardner
Name: Sonia Gardner
Title: Authorized Signatory

Exhibit 21.1

Subsidiaries of Clene Inc.

Name of Subsidiary	Jurisdiction of Organization
Clene Nanomedicine, Inc.	Delaware
Clene Australia Pty Ltd	Australia
dOrbital, Inc.	Delaware
Clene Netherlands B.V.	Netherlands

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-258098) and Form S-8 (No. 333-254810) of Clene Inc. of our report dated March 26, 2021 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Salt Lake City, Utah
March 11, 2022

Exhibit 23.2

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Registration Statement No. 333-258098 on Form S-3 and Registration Statement No. 333-254810 on Form S-8 of our report dated March 11, 2022, relating to the financial statements of Clene Inc. appearing in this Annual Report on Form 10-K for the year ended December 31, 2021.

/s/ Deloitte & Touche LLP
Salt Lake City, Utah
March 11, 2022

Exhibit 31.1

CERTIFICATION

I, Robert Etherington, certify that:

1. I have reviewed this Annual Report on Form 10-K of Clene Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 11, 2022

/s/ Robert Etherington
Robert Etherington
President and Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, Morgan R. Brown, certify that:

1. I have reviewed this Annual Report on Form 10-K of Clene Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 11, 2022

/s/ Morgan R. Brown
Morgan R. Brown
Chief Financial Officer

Exhibit 32.1

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Robert Etherington, President and Chief Executive Officer of Clene Inc. (the "Company"), hereby certifies that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 11, 2022

/s/ Robert Etherington
Robert Etherington
President and Chief Executive Officer

A signed original of this written statement required by Section 906 of 18 U.S.C. § 1350 has been provided to the Company, and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.

Exhibit 32.2

CERTIFICATION

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Morgan R. Brown, Chief Financial Officer of Clene Inc. (the "Company"), hereby certifies that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2021, to which this Certification is attached as Exhibit 32.2 (the "Annual Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 11, 2022

/s/ Morgan R. Brown
Morgan R. Brown
Chief Financial Officer

A signed original of this written statement required by Section 906 of 18 U.S.C. § 1350 has been provided to the Company, and will be retained by the Company and furnished to the Securities and Exchange Commission or its staff upon request.

This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing.