Eloxx Pharmaceuticals, Inc.
Form 10-K
March 16, 2018
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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, 2017

OR

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

For the transition period from_____ to _____

Commission file number: 001-31326

ELOXX PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**84-1368850**
(State or Other Jurisdiction of	**(I.R.S. Employer**
Incorporation or Organization)	**Identification No.)**

950 Winter Street

Waltham, Massachusetts 02451

(Address of Principal Executive Offices and Zip Code)

(781) 577-5300

(Registrant s Telephone Number, Including Area Code)

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.01 par value	**The OTCQB 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 15(d) of the Act. YES NO

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed 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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant s knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post 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 definitions of accelerated filer , large accelerated

filer , smaller reporting company and emerging growth company in Rule 12b-2 of the Exchange Act. (Check one):

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 is a shell company (as defined in Rule 12b-2 of the Act). Yes No

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the closing price for such stock as reported on the OTCQB Market on June 30, 2017, the last business day of the registrant s most recently completed second quarter, was: $7,092,700.

As of December 31, 2017, there were 27,527,738 shares of the Registrant s common stock, par value $0.01 per share, outstanding.

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Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K, or this report and the other documents we have filed with the SEC that are incorporated herein by reference, contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, potential, will, would, could, should, continue, and similar expressions are intended to identify forward-looki statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. In particular, you should consider the numerous risks described in the Risk Factors section in this Report on Form 10-K.

Although we believe the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, level of activity, performance or achievements. You should not rely upon forward-looking statements as predictions of future events. Unless required by law, we will not undertake and we specifically disclaim any obligation to release publicly the result of any revisions which may be made to any forward-looking statements to reflect events or circumstances after the date of such statements or to reflect the occurrence of events, whether or not anticipated. In that respect, we wish to caution readers not to place undue reliance on any such forward-looking statements, which speak only as of the date they are made.

This report and the other documents incorporated by reference herein includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third party research, surveys and studies are reliable, we have not independently verified such data.

The following are some risks and uncertainties, among others, that could cause actual results to differ materially from those expressed or implied by forward looking statements in this prospectus:

- risks related to the reverse merger and potentially significant, unexpected costs and liabilities arising with respect to the historic Sevion business and operations;
- risks related to our ability to obtain adequate financing in the future through product licensing, public or private equity or debt financing or otherwise; general business conditions; competition; business abilities and judgment of personnel; and the availability of qualified personnel;
- risks related to the ability to obtain the capital necessary to find our operations;
- risks related to our ability to progress any product candidates in preclinical or clinical trials;

risks related to the scope, rate and progress of our preclinical studies and clinical trials and other research and development activities;

the uncertainty of clinical trial results and the fact that positive results from preclinical studies are not always indicative of positive clinical results;

risks that our product candidates may not prove to be safe and efficacious;

risks relating to the cost of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights; and

risks related to the competition for patient enrollment from drug candidates in development.

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PART I

ITEM 1. BUSINESS

Merger of Sevion Therapeutics, Inc. and Eloxx Pharmaceuticals, Limited

On December 19, 2017, the Sevion Therapeutics, Inc. (Sevion) acquired Eloxx Pharmaceuticals, Limited (Private Eloxx) pursuant to a merger between the companies (the Transaction). Upon consummation of the Transaction (the Closing), Sevion adopted the business plan of Private Eloxx and discontinued the pursuit of Sevion s business plan pre-Closing. In connection with the Transaction, Sevion agreed to acquire all of the outstanding capital stock of Private Eloxx in exchange for the issuance of an aggregate 20,316,656 shares of the Sevion s common stock, par value $0.01 per share (the Common Stock), after giving effect to a 1-for-20 reverse split effected immediately prior to the Transaction. As a result of the Transaction, Private Eloxx became a wholly-owned subsidiary of Sevion. While Sevion was the legal acquirer in the transaction, Private Eloxx was deemed the accounting acquirer. Immediately after giving effect to the Transaction, on December 19, 2017, Sevion changed its name to Eloxx Pharmaceuticals, Inc. (Eloxx or the Company). Our current trading symbol is ELOX. Our principal executive offices are located in Waltham, Massachusetts and we have a research and development center in Rehovot, Israel. Our telephone number is (781) 577-5300.

Company Overview

We are a global biopharmaceutical company focused on discovering and developing novel therapeutics for the treatment of rare and ultra-rare premature stop codon diseases. We are harnessing the science of genetic read-through to develop novel drug product candidates that interact with the ribosome to overcome these premature stop codons. Our revolutionary small molecule approach is designed to unleash the potential to restore production of full length functional proteins with the goal of enabling a return toward normal cellular function. We believe there is a broad application of this approach to the over 1800 rare and ultra-rare diseases where nonsense mutation has been implicated in the cause or pathway of human disease.

Our research and development strategy is to target rare or ultra-rare diseases where a high unmet medical need, nonsense mutation bearing patient population has been identified. We focus on clinical indications where there is a high unmet medical need, established preclinical read-through or personalized medicine experiments that are predictive of clinical activity, and a definable path for Orphan Drug development, regulatory approval, patient access and commercialization. We believe patient advocacy to be an important element of patient focused drug development and seek opportunities to collaborate with patient advocacy groups throughout the discovery and development process. Our current clinical focus is on cystic fibrosis (or CF) and cystinosis where we are advancing our lead drug product candidate, ELX-02.

We intend to be the global leader in the application of the science of translational read through and the associated pathway of nonsense mediated messenger ribonucleic acid (mRNA) decay. We believe that expanding our expertise across these basic science areas of mRNA regulation, ribosomal function, and protein translation forms a solid foundation to support our discovery and development activities. Our compounds modulate the activity of the ribosome, the organelle within living cells responsible for protein production, a process also known as translation. These novel small molecule compounds are designed to allow the ribosome to read-through a nonsense mutation in mRNA (which is transcribed from the DNA sequence), to restore the translation process to produce full length, functional proteins and increase the amount of mRNA that would otherwise be degraded as part of a phenomenon called nonsense mediated mRNA decay. As our compounds target the general mechanism for protein production in the cell, we believe they have the potential to treat hundreds of genetic diseases where nonsense mutations have

impaired gene function. Our subcutaneously injected small molecules have the potential to be self-administered and to be active at most tissue locations across the body.

We believe that our library of related novel small molecules hold the potential to be disease-modifying therapies that may change the course of hundreds of genetic diseases and improve the lives of patients. Our early

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preclinical data in animal models of nonsense mutations suggests that drug product candidates from our read through compound library may have potential beneficial effects for each of the following diseases: cystic fibrosis, cystinosis, mucopolysaccharidosis type 1, Duchenne muscular dystrophy and Rett syndrome, and have demonstrated the potential for beneficial effects in multiple organs such as the brain, kidney, muscles and others. We intend to advance one or more additional molecules from our drug product candidate library toward clinical development by initiating the required investigational new drug (IND)-enabling studies in 2018.

Currently our lead program ELX-02 is focused on development for cystic fibrosis and cystinosis patients with diagnosed nonsense mutations. To advance the program, we have held pre-IND pre-clinical trial application (CTA) discussions with the Federal Agency for Medicines and Health Products (the FAMHP) in Brussels Belgium and pre-IND discussions with the U.S. Food & Drug Administration (the FDA) for cystic fibrosis and cystinosis, respectively. We are on-track for an expected mid-2018 submission of our IND and CTA. Approval of these submissions will be required for initiation of Phase 2 studies in cystic fibrosis and cystinosis in 2018.

As part of our clinical program, we have completed a Phase 1 single ascending dose (SAD) study in a total of 60 healthy volunteers at sites in Israel (ClinicalTrials.gov Identifier: NCT02807961) and Belgium (ClinicalTrials.gov Identifier: NCT03292302). Currently ongoing is the Phase 1 multiple ascending dose (MAD) study in 45 healthy volunteers in Belgium (ClinicalTrials.gov Identifier: NCT03309605). We anticipate that the Phase 1 MAD study will be completed in 2018. The results from the completed Phase 1 study will be included in the planned IND and CTA submissions.

We believe there is a significant unmet medical need in the treatment of cystic fibrosis patients carrying nonsense mutations on one or both alleles of the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene. Cystic fibrosis is the most prevalent genetic disease in the western world and there are no currently approved therapies that target the impairment associated with Class 1 CFTR mutations. We believe that nonsense mutations may impact a similar proportion of patients diagnosed with cystinosis. There are no currently approved therapeutics that target the nonsense mutation mediated impairment of cystinosin the cystine-selective transport channel in the lysosomal membrane that is attributed as the cause for the accumulation of cystine in this disease state. Given the high proportion of pediatric patients in each of these rare orphan diseases we intend to apply for relevant Orphan Drug incentives in the US and Europe, including the Rare Pediatric Disease Priority Review Voucher in the U.S.

Currently, the European Medicines Agency (the EMA) has designated ELX-02 as an orphan medicine for the treatment of mucopolysaccharidosis type I (MPS I), and the FDA has granted orphan drug designation to ELX-02 for the treatment of MPS I and for the treatment of Rett Syndrome.

We hold worldwide development and commercialization rights to ELX-02 and novel compounds in our read-through library, for all indications, in all territories, under a license from the Technion Research and Development Foundation Ltd. Professor Timor Baasov, the inventor of our compounds, has served as our senior consultant since our incorporation.

Our Technology

Nonsense mutations, also known as premature termination or stop codons, are single point mutations within the DNA sequence which are either inherited or acquired that result in premature termination of the translational process leading to truncated or absent proteins. Nonsense mutations are the cause of a large number of genetic diseases such as cystic fibrosis, cystinosis, mucopolysaccharidosis type 1 (nmMPS-1), Duchenne muscular dystrophy (nmDMD), Rett syndrome, and a variety of cancers. According to the human gene mutation database (http://www.hgmd.cf.ac.uk/ac/index.php), nonsense mutations account for approximately twelve percent (12%) of

patients with a given genetic disease. The disease phenotypes caused by nonsense mutations are frequently more severe than those caused by other kinds of mutations because these mutations often lead to a complete loss of protein production or function. In general, these diseases do not have specific therapies beyond symptomatic and palliative interventions.

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In eukaryotic cells, the cytoplasmic ribosome is responsible for the production of proteins by a process called translation. As part of the translation process, the genetic information is transcribed to the mRNA arranged as codons that specify the corresponding amino acid, the building block of a protein. The ribosome pairs a specific mRNA codon with an aminoacyl transfer RNA (aa-tRNA) containing an anticodon sequence causing elongation of the nascent protein.

Normal translation termination in eukaryotic cells occurs when a natural (canonical) termination codon enters the ribosomal A site, the protein production site within the ribosome, and no complementary aa-tRNA is found. Termination codon recognition is not carried out by codon-anticodon interactions, since no tRNA anticodon is complementary to any of the mRNA termination codons. Rather, a complex of releasing factors recognize the termination codons and interact with the ribosome to release the completed protein, resulting in termination of the translation process.

Translation terminates efficiently when the termination codon (TC) is in physical proximity to the 3 poly(A) tail (AAAAAAAA) and/or the 5 7-methylguanosine (m7G) cap of the mRNA. Efficient translation termination prevents nonsense-mediated delay (NMD) of the mRNA.

In the presence of a nonsense mutation the ribosome cannot pair the mRNA with a corresponding aa-tRNA and protein elongation stops and terminates, giving rise to a truncated protein.

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When the ribosome stalls after finding a premature termination codon, upstream protein factor 1 (UPF1), UPF2 and UPF3 are recruited. UPF1 binds nonspecifically to the mRNA, ribosome-associated eRF3 interacts with UPF1, thereby recruiting UPF2 and/or UPF3 (assisted by an exon junction complex (EJC) bound to the 3 untranslated region (UTR) or independently) and thus enables NMD. Some mRNAs may escape NMD for one or more rounds of translation, due to the inefficient recruitment of UPF1, UPF2 and/or UPF3 to the terminating ribosome.

The assembly of a protein complex including UPF1, UPF2, UPF3, suppressor of morphogenetic effect on genitalia 1 (SMG1), SMG8, SMG9, DEAH box polypeptide 34 (DHX34) and the EJC signals that the TC is a PTC. At this point, translation may terminate, ultimately leading to the dissociation of the individual ribosomal subunits, the release factors and the nascent protein.

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Translation read-through across a premature termination codon (nonsense mutation) is a process in which the ribosome inserts related (near cognate) tRNAs which compete with the releasing factor complex and enable the insertion of a near cognate amino acid in the protein leading to translation of the full protein. Translation read-through across a nonsense mutation is a natural process that occurs at the rate of 1%. In such instances, the ribosome will not terminate the translational process prematurely regardless of a premature termination. ELX-02 is designed to enhance this natural process by increasing the read-through activity and the frequency of near cognate aa-tRNA binding within the A site of the ribosome. ELX-02 enables the production of sufficient amounts of full-length protein to restore activity of the mutated protein.

Current Data Indicating the Mechanism of Action of ELX-02

ELX-02 is an advanced aminoglycoside with poor antibiotic activity and markedly decreased affinity for the prokaryotic and mitochondrial ribosomes. Aminoglycosides, such as gentamicin, are potent antibiotics that bind to the decoding site in the prokaryotic ribosome and prevent protein translation in bacteria. In eukaryotic cells, aminoglycosides induce a conformational change that reduces the codon-anticodon recognition, enhancing the ability of an aa-tRNA to compete with the release factor complex for binding to the premature termination codon and increasing the probability that translational read-through of premature termination codons occurs. Despite promising results, aminoglycoside use as a read through therapy is restricted since they cause damage to the kidney and ear after prolonged administration. In addition, prolonged administration of antibiotic aminoglycosides may cause antibiotic resistance and may damage the natural microflora. Because it stabilizes the ribosomal RNA (or rRNA), ELX-02 prevents the assembly of the NMD factors required to initiate decay of mRNA. In this manner the PTC is not recognized and the insertion of the near cognate amino acid to the nascent polypeptide drives translation to produce a full-length, functional protein.

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ELX-02 is an investigational new chemical entity (NCE) advanced aminoglycoside optimized by successive rounds of medicinal chemistry to separate the sections of the molecule interacting with the prokaryotic ribosome responsible for the antibiotic activity from those portions of the molecule inducing translational read-through. ELX-02 has poor antibiotic activity and binds preferentially to the eukaryotic ribosome and is thereby designed to improve translational read-through. ELX-02 s low affinity for the bacterial ribosome decouples the antibacterial activity from the read-through activity. When compared in laboratory tests to gentamicin, a classic aminoglycoside, ELX-02 thus far has shown a 100-fold lower antibacterial activity and nine-fold higher read-through activity for nonsense mutations; this has been attributed to higher selectivity towards the cytoplasmic eukaryotic ribosome. Consequently, ELX-02 could potentially be used to treat hundreds of genetic diseases caused by nonsense mutations.

Our Disease Focus

We believe that the segment of cystic fibrosis and cystinosis patients with diagnosed nonsense mutations on one or both alleles represents a high unmet medical need as there are currently no approved therapeutics targeting the impairment caused by these mutations. There are existing in vitro assays, animal models and/or biomarker screens that have been demonstrated to be useful in assessing the potential therapeutic benefit of development compounds for these disease states. The design of clinical trials and the endpoints for measuring clinical benefit have been established for the currently approved therapeutics for these disorders. We believe these to be attractive development targets based on the potential use of these precedents to de-risk the program.

We believe that our library of related novel small molecules hold the potential to be disease-modifying therapies that may change the course of hundreds of genetic diseases and improve the lives of patients. Our early preclinical data in animal models of nonsense mutations suggest that drug product candidates from our read through compound library may have potential beneficial effects for each of the following diseases: cystic fibrosis, cystinosis, mucopolysaccharidosis type 1, Duchenne muscular dystrophy and Rett syndrome, and have demonstrated the potential for beneficial effects in multiple organs such as the brain, kidney, muscles and others. We intend to advance one or more additional molecules from our drug product candidate library toward clinical development by initiating the required investigational new drug (IND)-enabling studies in 2018.

Nonsense Mutation Cystic Fibrosis

Cystic fibrosis (CF) is the most prevalent genetic disease in the western world and affects an estimated 70,000 to 100,000 patients worldwide, with the vast majority of affected individuals in the United States, Canada, Europe and Australia. CF is the most common fatal inherited disease in Caucasians. The incidence of CF varies across the globe. CF affects one out of 3,500 births in the United States, one out of 2,000 to 3,000 in Europe, and one out of 2,500 in Australia.

Approximately 13% of the CF patients carry a nonsense mutation on the CFTR gene. CF is a progressive disease caused by a deficiency in CFTR activity with insufficient ionic transconductance in the cell membrane, which, in turn, leads to the accumulation of thick mucus in vital organs, particularly the lungs, pancreas and gastrointestinal tract. As a result, CF patients experience respiratory infections, chronic lung inflammation, and poor absorption of nutrients as well as many other conditions, and, in most cases, progressive respiratory failure. Although the life expectancy of CF patients has improved, the median age of death in the United States in 2014 was only 29 years, with a vast majority of such deaths resulting from respiratory failure.

The disease occurs at a rate of 1 in 2,500 6,000 newborns, depending on the region and ethnic origin. Patients with CF caused by nonsense mutations have some of the most severe forms of the disease and, other than palliative therapies, no treatment currently exists for them.

Mutations in the gene that encodes CFTR protein, which play a critical role in regulating the viscosity of the mucus layer that lines human organs, cause CF. The CFTR protein forms an ion channel that regulates the flow of ions in and out of the cells of vital organs such as the lungs, pancreas and gastrointestinal tract. We refer to

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this as ion flow. When CFTR protein expels the ions, osmosis draws water out of the cell and hydrates the cell surface. Through regulation of the location of the ions across the cell membrane, the amount of salts in the fluid both inside and outside the cell remains balanced.

In CF patients, the CFTR gene is defective, and as a result, CF patients lack the functional CFTR protein ion channel necessary to regulate ion flow. An altered ion concentration gradient between the inside and the outside of the cell reduces the amount of water molecules outside the cell, causing the accumulation of thick mucus on the epithelial surface as shown in Figure 1.

Figure 1: Ion Flow in Normal CFTR Protein Compared to Mutant CFTR Protein

The deficiency in CFTR protein activity in CF patients is particularly problematic in the lungs, where the build-up of thick mucus obstructs airflow and impairs proper immune response, which leads to chronic infection and persistent inflammation. In the pancreas and the gastrointestinal tract, the build-up of mucus prevents the release of digestive enzymes that help the body break down food and impairs the absorption of nutrients, resulting in poor growth and development.

Nonsense mutation Cystinosis

Cystinosis is an ultra-rare autosomal recessive lysosomal storage disease. Mutations in the *CTNS* gene (cystinosin), on the short arm of chromosome 17 (17p13), cause the primary defect in the disease. Cystinosin is a ubiquitous cystine-selective transport channel in the lysosomal membrane. Loss-of-function mutations prevent cystine efflux from the lysosome, causing massive accumulation of intra-lysosomal cystine in tissues throughout the body, and lead to apoptotic cell death, impaired physiology and end organ damage.

Affected children may appear fairly well until the age of 4-6 months, when progressive dysfunction and atrophy of the proximal renal tubule cause Fanconi syndrome and failure to thrive. By 10-12 years of age, dialysis or kidney transplantation is required to treat end-stage renal disease. Although the renal allograft is spared, lifespan is diminished by the inexorable dysfunction of other organs.

The most common nonsense mutation in the CTNS gene is W138X which has an overall incidence rate of 1 in every 62,500 live births in Quebec, Canada.

Current treatment includes cysteamine bitartrate (Cystagon® or Procysbi®). Cystagon was approved in the USA and Europe in 1994 and Procysbi was approved in the USA and Europe in 2013. Both therapies delay but

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do not cure the condition and despite treatment, patients eventually require dialysis and renal transplantation and experience significant morbidity in other organ systems.

Nonsense mutation Duchenne muscular dystrophy (nmDMD)

Muscular dystrophies are genetic disorders involving progressive muscle wasting and weakness. DMD is the most common and one of the most severe types of muscular dystrophy. DMD occurs when a mutation in the dystrophin gene prevents the cell from making a functional dystrophin protein. Dystrophin is a muscle membrane associated protein and is critical to the structural and membrane stability of muscle fibers in skeletal, diaphragm and heart muscle. The absence of normally functioning dystrophin results in muscle fragility, such that muscle injury occurs when muscles contract or stretch during normal use. As muscle damage progresses, connective tissue and fat replace muscle fibers, resulting in inexorable muscle weakness.

Because the dystrophin gene is located on the X chromosome, DMD occurs almost exclusively in young boys. According to Parent Project Muscular Dystrophy, DMD occurs in approximately 1 in 3,500 live male births, while information from Moat, et al. (2013) in the European Journal of Human Genetics indicate prevalence of approximately 1 in 5,000 live male births. Genetic tests are available to determine if a patient s DMD is caused by a nonsense mutation. Based on information from Prior, et al. (1995) in the American Journal of Human Genetics, we estimate that a nonsense mutation is the cause of DMD in approximately 13% of patients. Overall, we estimate that there are approximately 7,000 nmDMD patients worldwide, with approximately 85% of such patients outside of the United States, including in Europe, Latin America, Asia Pacific, Middle East and Northern Africa regions. nmDMD is an ultra-rare, life threatening disorder. Without treatment, patients with DMD typically lose walking ability by their early teens, require ventilation support in their late teens and, eventually, experience premature death due to heart and lung failure. The average age of death for DMD patients is in their mid-twenties.

Two main treatments have received approval for DMD, Translarna (ataluren), which has received approval in the European Union (EU) for the treatment of underlying cause of nmDMD, and received a complete response letter from the FDA and is not approved in the US. Another marketed product is EXONDYS 51® (eteplirsen) Injection, approved in the US for the treatment of DMD patients who are amenable for exon 51 skipping.

Nonsense mutation Mucopolysaccharidosis type I (nmMPS I)

Mucopolysaccharidosis type I (MPS I) is a chronic, progressive genetic disorder caused by a deficiency of the enzyme alpha-L-iduronidase (IDUA). The deficiency of this enzyme leads to the accumulation of a class of molecules called glycosaminoglycans (GAGs). The accumulation of GAGs causes disruption in the movement of molecules inside the cell and leads to the subsequent dysfunction of cells, tissues and organs. Globally, MPS I occurs in about 1 in every 100,000 births for the severe form and 1 in 500,000 for the attenuated form. About 70% of MPS I patients carry one of two nonsense mutations, Q70X and W402X. Estimates suggest that 50%- 80% of all MPS I patients present with the severe form.

MPS I is broadly classified in two groups; severe MPS I and the attenuated MPS I. The symptoms of the severe form of MPS I develop after birth and progress rapidly, causing progressive respiratory, cardiac and musculoskeletal manifestations along with coarse facies, hepatosplenomegaly, hernias, deafness, and a shortened life expectancy. Lack of reabsorption of cerebrospinal fluid (CSF) in the severe phenotype leads to communicating hydrocephalus, delayed neuromotor and impaired cognitive development. Patients usually have increased intracranial pressure due to accumulation of macromolecules, which causes optic atrophy, corneal clouding, glaucoma and vision problems including corneal opacity, acute blindness and corneal thickening. Children with severe MPS I often die in the first decade of life due to respiratory failure, cardiac valvulopathy, and cardiorespiratory problems. The attenuated form of

MPS I progresses slowly and usually manifests in early childhood. Patients with the attenuated phenotype have valvular, left ventricular diastolic and systolic abnormalities. Patients typically face cervical spinal cord injury, carpal tunnel syndrome and joint stiffness along with other deformities like kyphosis, scoliosis and spondylolisthesis. Children with attenuated MPS I have

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decreased intelligence quotient and language skills as compared to healthy children. Patients also suffer from recurrent headaches and optic nerve compression due to increased levels of CSF.

Treatment of severe and attenuated forms of MPS I is aimed at slowing the progression of the disease and improving the quality of life. Treatment can be broken into two classifications: supportive, symptom-based treatment and disease-specific treatment. The symptom-based treatment is coordinated by a specialized team to maintain patients health and prevent the comorbidity which may arise due to the progression of the disease. The disease-specific treatments include enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). HSCT is considered the standard of care for children with severe MPS I. HSCT therapy is based on the principle that donor-derived hematopoietic stem cells (HSC) engraft in the recipient and can differentiate into numerous cell types, thus providing enzyme to deficient cells via metabolic cross-correction and clearing GAG storage material from host tissues. Recombinant -L-iduronidase is used for the ERT treatment in the form of Laronidase and is currently licensed in the US, Europe, and Canada for treating non-CNS manifestations of MPS I. In this treatment, drugs are administered exogenously by weekly intravenous infusion. At this time, more effective and affordable strategies are being developed as an alternative approach to treat patients with MPS disorders.

Nonsense mutation Rett Syndrome

Rett syndrome is a X-linked neurodevelopmental disorder that predominantly affects girls and has a worldwide incidence of 1 in every 10,000-15,000 female births. The condition is characterized by normal development for the first 6-18 months of age, followed by a period of regression in which the girls lose language and motor skills and purposeful hand use is replaced by repetitive stereotyped hand movements. Decelerating head growth and autistic features such as diminished eye contact and emotional withdrawal also occur. Additional characteristics include anxiety, respiratory dysfunctions, impairment of sleeping patterns, cardiac abnormalities, seizures, loss of locomotion, and bone density deficits. Furthermore, girls with Rett syndrome tend to be growth-retarded and have a reduced life-span. Currently, no treatment exists for the underlying cause of the disease. Treatment is symptomatic and palliative. Thus, a high unmet medical need exists for patients with Rett syndrome.

Loss-of-function mutations in the gene encoding the transcriptional regulator methyl-CpG binding protein 2 (Mecp2) account for most cases of Rett syndrome. Mecp2 is a transcriptional repressor that binds to methylated promoters and recruits the histone deacetylases (HDACs) machinery to induce chromatin condensation. In neurons, Mecp2 has been implicated in the modulation of specific neuronal target genes in an activity-dependent manner, such as brain-derived neurotrophic factor (BDNF), but also has been implicated in both repression and activation of a large number of genes, in modulation of RNA splicing, and most recently has been suggested to affect global chromatin structure impacting the entire neuronal genome.

Recent work in mouse models of Rett syndrome suggests that the clinical condition may be reversible, insofar as the reintroduction of functional Mecp2, either ubiquitously or selectively, in the brain of Mecp2-deficient mice significantly improved at least some of their Rett-like behavioral deficits. Collectively, these results indicate that the neurological defects seen in Rett syndrome are amenable to rescue, either by gene or protein reintroduction or by the reactivation of a silenced or dysfunctional Mecp2 allele.

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Nonsense mutations in the Mecp2 gene account for approximately 30% of Rett syndrome cases. The most prominent nonsense mutations found in Rett syndrome, R168X, R255X, R270X and R294X, are all caused by a change of arginine to the stop codon, UGA.

Currently, no cure for Rett Syndrome exists. Treatment of Rett syndrome focuses on the management of symptoms, e.g., physical, occupational and speech-language therapy. Medicines can be used for seizure control and movement disorders along with treatments for breathing and gastrointestinal symptoms. The long-term prognosis of Rett patients is unknown. Patients have numerous comorbidities that are thought to contribute to a shortened lifespan.

Status of Clinical Programs

We are conducting a Phase 1 program in healthy volunteers that is designed to support studies of ELX-02 in patient populations in any indication caused by nonsense mutations and assess the safety of ELX-02. This initial phase of testing includes a small number of healthy volunteers. The studies assess the effects of ELX-02 on humans and measure bioavailability, excretion, safety and side effects, as well as the pharmacokinetics (what the body does to the drug) with increasing doses. Phase 1 studies include single ascending dose SAD, or Phase 1a, and multiple ascending dose MAD, or Phase 1b, studies.

We conducted a SAD study at the Tel Aviv Sourasky Medical Center in Israel (TASMC) between July 12, 2016 and March 15, 2017 and between November 2017 and December 2017 at SGS in Antwerp, Belgium. The study was designed as a Phase 1a, randomized, double-blinded, placebo-controlled, single dose escalation study to evaluate the safety, tolerability and pharmacokinetics of ELX-02 in healthy adult volunteers. The study was designed and executed in compliance with the International Conference of Harmonisation Good Clinical Practices E6 guideline and in compliance with applicable regulatory requirements in Israel, the United States and the European Union. Subjects were allocated to one of seven cohorts and received doses of ELX-02 ranging between 0.3 mg/kg and 7.5 mg/kg injected either IV (only in the 0.3 mg/kg) or SC. A total of 60 subjects participated in the study. The study did not show acute or chronic changes in vital signs, chemistry, hematology, biomarkers of early tubular injury, changes in serum creatinine, evidence of aberrant translational read-through of housekeeping genes or impact in auditory function using a battery of tests that included pure tone audiometry (PTA), high frequency audiometry (HFA), tympanometry, and Speech Reception Threshold (SRT), or vestibular function, using electronystagmography (ENG), the Dizziness Handicap Inventory (DHI) and the Tinnitus handicap Inventory (THI). No significant adverse events (SAEs), or serious adverse events of interest (AEOIs) or deaths occurred in the study. We did report an AEOI of unclear physiological significance when we observed high frequency pure tone fluctuations outside the normal hearing range in a single subject at 5 mg/kg in the Israeli cohort.

We are also conducting a multiple ascending dose MAD study in healthy volunteers. The study has been designed as a Phase 1b, randomized, double-blinded, placebo-controlled, multiple dose escalating study in healthy male and female subjects. The study consists of 5 cohorts of 9 subjects each. Subjects will be randomized to receive nine doses of ELX-02 or placebo at a ratio of 2:1 in each cohort. The study has been reviewed and approved by the Federal Agency for Medicines and Health Products (FAMHP) in Belgium, and by the Institutional Review Board in August 2017 in Antwerp, Belgium. The screening began in October 2017 and the study commenced in November 2017.

In November 2017, we submitted a Pre-IND package to the FDA to initiate regulatory discussions around our submission of an IND supporting our Phase 2 study of cystinosis in the U.S. In December 2017, we received FDA s very productive written response, and we are on track for a mid-2018 IND submission in the U.S., and, subject to regulatory review of the IND and the IND becoming effective, we are targeting the 4th quarter 2018 for the first FPFV for our phase 2 cystinosis study in the U.S.

In January 2018, we held a Pre-CTA regulatory meeting with the FAMHP to discuss our submission of a CTA supporting our Phase 2 study of cystic fibrosis in Belgium. Based upon our very productive regulatory

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dialogue with FAMHP, we are on track for a mid-2018 CTA submission in Belgium, and, subject to regulatory review and approval of the CTA, we are targeting the 4th quarter 2018 for the first patient first visit (FPFV) for our phase 2 cystic fibrosis study in Belgium.

Status of Preclinical Programs

We have completed a comprehensive series of preclinical studies to assess the safety, pharmacokinetics and pharmacology of ELX-02.

Safety and Pharmacokinetic Studies of ELX-02

A comprehensive toxicology program in accordance with the ICH guideline M3 (R2) was completed for ELX-02 to support clinical studies.

We conducted repeated subcutaneous-dose toxicity studies in rats and beagle dogs for up to 28 days at dose levels significantly higher than those intended for humans. Both of these species are routinely selected for toxicology testing. Both species exhibited renal toxicities that were monitorable and reversible at doses higher than those intended for humans. The toxicology data generated thus far in these species suggest the kidney and urinary bladder may be a target organ at higher exposures. In addition, local injection site reactions were observed at all dose levels in both animal species. These injection site reactions are likely due to the unique anatomy of the cutaneous musculature in animals compared to humans and available literature suggests that injection site reactions in animals bear a poor concordance between animal and humans. Based on the 28-day rat study, the expected safety margin is more than 50X at the starting dose in the MAD study (0.1 mg/kg/dose) and 30X times the starting dose to be tested in subjects with CF (0.3 mg/kg/dose). At the anticipated efficacious clinical doses of 1 or 2.5 mg/kg the safety margin based on steady state plasma AUC values in the rat study are anticipated to be approximately 10 or 4X, respectively. The rat 28-day data is used to define the safety margin since the rat was determined to be the most sensitive species. We believe these data provide support for human clinical trials with durations up to 4 weeks, but we plan to complete long-term toxicity studies prior to initiation of our Phase 3 clinical trials. In definitive repeat-dose toxicity studies in rats and dogs, ELX-02 given as intermittent (twice weekly) SC doses over a 28-day period had little or no effect on body weight, food consumption, clinical signs of toxicity, ophthalmology, cardiovascular parameters, hematology or coagulation parameters. ELX-02 has no cochlear toxicity as evidenced in anatomic and functional hearing studies in 28-day rat studies at exposures where renal toxicity was noted (240 mg/kg/day). We are currently conducting 3-month toxicology studies in juvenile rats and in young dogs, as well as chronic toxicology studies in these 2 species for 6- and 9-months, respectively. The 3-month studies have both completed the in-life phase with no mortality and no significant in-life toxicity noted. Both studies are in reporting phase and pathology review. ELX-02 was not genotoxic in the core battery of in vitro and in vivo genotoxicity assays. As an aminoglycoside, ELX-02 has poor oral bioavailability but is 100% bioavailable following SC administration. In rats and dogs, ELX-02 s pharmacokinetic profile is comparable to that of conventional aminoglycosides. Additionally, ELX-02 does not undergo metabolization and is excreted unchanged almost exclusively via the urine.

Pharmacology Studies of ELX-02

We have conducted a series of preliminary studies to demonstrate the primary pharmacodynamics of ELX-02 in several genetic disease indications. We have tested the translational read-through capabilities of ELX-02 in vitro and in vivo, in cells and in animal models of nonsense mutations.

We have shown the in vitro read-through activity of ELX-02 in an array of plasmids engineered to contain nonsense mutations of genetic diseases and in cell-based models of CF, cystinosis, DMD, MPS 1, and Rett syndrome.

In CF, ELX-02 induced about 30% of wild type CFTR levels after 48 h in heterozygous G542/F508del human bronchial epithelial cells. In the G542X transgenic mouse, ELX-02 showed a ~5-fold increase in CFTR activity compared to control after twice weekly treatment for four weeks with 60 mg/kg.

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In DMD, ELX-02 induced a 35-fold increase in read-through in the R3381X mutation in the dystrophin gene in vitro, and in a preliminary study in the mdx mouse increased muscle force (forelimb grip strength tests) and motor activity (rotarod performance) and showing a trend of decreased serum creatine kinase (a measure of muscle injury).

In MPS 1, ELX-02 induced a 48-fold and a 98-fold increase in read-through of the W392X and Q70X mutations, respectively, in the in vitro assay of the Idua gene. In primary mouse embryonic fibroblasts carrying the Idua W392X mutation, ELX-02 led to a dose-dependent increase in -L-iduronidase activity up to 24-fold and a concomitant reduction in stored GAGs to control levels. In Idua-W392X ($Idua^{tm1Kmke}$) mice, ELX-02 treatment for 4-week resulted in elevated levels of -L-iduronidase activity and reduced GAG storage in the brain, spleen, heart, liver, kidneys, lungs, and femoral bone in a dose-dependent manner. In brain and spleen tissues of the Idua-W392X mouse model, ELX-02 treatment reduced the compensatory increases seen in the activity of the lysosomal enzymes ß-glucuronidase and ß-hexosaminidase.

In Rett syndrome, ELX-02 increased translational read-through of multiple nonsense mutations of the *MECP2* gene, R168X (14-fold), R255X (32-fold), R270X (83-fold), and R294X (25-fold) in vitro. In fibroblasts derived from a human male Rett syndrome patient carrying the R294X mutation, ELX-02 increased Mecp2 protein translation and expression levels in nuclei. In neurons and glial cells derived from stem cells overexpressing Mecp2 R168X-GFP and Mecp2 R255X-GFP, ELX-02 induced a dose-dependent increase in Mecp2-GFP protein. In $Mecp2^{R168X}$ cells, ELX-02 increased BDNF mRNA levels by ~ 4-fold, suggesting a downstream effect of the increased Mecp2 protein. In female $Mecp2^{R168X/x}$ mice, ELX-02 was measurable in and increased Mecp2 in the brain and lengthened the latency period of time to fall and in distance traveled on a rotarod test.

In cystinosis, ELX-02 increased read-through of the W138X mutation in the CTNS gene by 30-fold in vitro. In primary homozygous W138X fibroblasts, ELX-02 led to a dose-dependent increase in normalized CTNS mRNA levels, suggesting a decrease in nonsense mediated mRNA decay, and a corresponding reduction in cystine levels to wild-type levels, suggesting translation of a functional CTNS channel.

Intellectual Property

Patents and Trade Secrets

Our licensed and owned patents and patent applications relate to our lead compounds that exhibit read-through properties and include patent applications directed to new compositions of matter and to methods of treating genetic diseases such as cystic fibrosis, cystinosis, Duchenne s muscular dystrophy, ataxia-telengiectasia, Hurler syndrome, hemophilia A and B, Usher syndrome, Tay-Sachs and Rett syndrome, including combination therapies with existing treatments for these indications, such as CFTR modulators for the CF indication.

As of August, 29 2013, we licensed two pending U.S. provisional patent applications and subsequent Patent Cooperation Treaty (PCT) applications claiming priority from these, from which we have so far gained patent protection in the United States and in Europe, Japan, Canada and Israel for composition of matter, methods of use, and combination therapies relating to our lead compound, ELX-02 (formerly known as NB124) and other compounds (e.g. ELX-03; formerly known as NB84). Additional patent applications are pending in India, as are divisional applications in Europe, Israel and Japan. If we continue to pursue protection, and if any patents issue based on these applications, we expect such patents to expire between 2027 and 2031, depending on any extensions of term for which we may be eligible that we may be granted.

As of June 04, 2015, we own a PCT application for methods of use relating to our lead compound, ELX-02, and other related compounds for treatment of Rett Syndrome and we intend to seek patent protection in the United States and in

selected jurisdictions (Canada, Europe, Hong Kong, India, Israel, and Japan) for such

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methods. If any patents are issued in connection with this application, we expect such patents to expire in 2036, depending on any extensions of term for which we may be eligible that we may be granted.

In addition, we have four pending PCT applications, filed on September 2, 2016, all of which generally relate to new compositions of matter and to methods of treating genetic diseases.

As of March 15, 2018, we have a pending patent application in India related to the large-scale synthesis of our compound, ELX-02, and other related new compounds, and we intend to seek similar patent protection in the United States and in selected jurisdictions worldwide. If any patents are issued based on this application, we expect such patents to expire in 2037, depending on any extensions of term for which we may be eligible that we may be granted.

With respect to our synthetic-aminoglycosides-based technology platform, we primarily rely on trade secrets and know-how to protect the proprietary nature of our platform. However, trade secrets and know-how can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data, know-how and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions.

License Agreements

Research and License Agreement with Technion Research and Development Foundation Ltd.

On August 29, 2013, we entered into a license agreement with the Technion Research and Development Foundation Ltd., or TRDF, which was further amended and addended to reflect, inter alia, the assignment of patents and extension of research periods, with respect to certain technology relating to aminoglycosides and the redesign of aminoglycosides for the treatment of human genetic diseases caused by premature stop mutations and further results of the research of the technology, in order to develop and commercialize products based on such technology. The license agreement provides us with an exclusive, worldwide, non-transferrable license, with a right to grant sublicenses, and royalty-bearing licenses to the TRDF inventions, TRDF patent rights, TRDF s interest in the joint inventions and joint patent rights, and certain materials and research results owned by TRDF, solely with respect to products in the field of prevention, diagnosis or treatment of any human disease or condition therefor. In return for the license we will pay TRDF (i) milestone payments with respect to each licensed product upon the achievement of certain pre-defined goals by us or one of our sublicensees as follows: $100,000 upon first dosing of a patient in Phase II clinical study; $1,000,000 upon first dosing of a patient in pivotal study; $1,000,000 upon first filing on a new drug application (NDA); (ii) certain royalties on a low- to mid- single-digit percentage of all net sales (subject to change in the case of (a) sublicensing to a big pharmaceutical or biotechnology company, or (a) payment of royalties to third parties, or (c) commercialization by a third party of an authorized generic to a licensed product); (iii) a low- to mid-double-digit percentage of any non-royalty sublicense income; (iv) an exit fee in the amount of a one digit percentage of any consideration paid upon an exit event (as defined in the agreement); and (v) in the case of an initial public offering for a number of ordinary shares equal to 3% of our outstanding shares on a fully diluted basis (as defined in the agreement) immediately prior to the closing of such initial public offering. If we distribute any dividends prior to an exit event, TRDF will be entitled to dividends as if it was holding 3% of our outstanding shares. In addition to the milestone payments, we undertook to annually fund the research activities under the license, currently in the amount of $0.1 million per year. The license agreement further provides TRDF with an additional pre-emptive right, in force

until the first exit event, to invest an amount equal to up to 5% of the amount contemplated to be

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raised in a proposed investment. TRDF is also entitled, until the closing of an exit event, to appoint an observer to the board under certain restrictions such as confidentiality or conflict of interest. In addition, we will reimburse TRDF for all patent filing expenses as of the effective date of the license agreement and for past patent filing expenses in the amount of several hundred thousand New Israeli Shekels upon the occurrence of certain conditions.

Under the license agreement, TRDF reserved the right, for itself, the Technion and other not-for-profit research organizations to utilize the technology solely for educational purposes. Furthermore, Professor Bassov, the principal investigator, had ongoing research programs involving covered compounds (as defined in the agreement) that are being funded by the National Institute of Health in the U.S., or the NIH, under sub-awards from the University of Alabama and the University of Michigan and it is possible that such research programs will overlap with the research conducted according to the terms of the agreement. In the case of any such overlap, the work product of such research will be subject to the terms and conditions of such sub-awards, including certain obligations under 35 U.S.C. §§ 200-212 or 37 C.F.R § 401 et seq. in the case of any TRDF inventions that are also subject invention as defined in 35 U.S.C. §201.

The license agreement shall continue in full force and effect on a product-by-product and country-by-country basis until the expiration of all payment obligations for any such licensed product as described above. Upon the expiration, we will have a fully-paid up, worldwide non-exclusive, perpetual, irrevocable license (with the right to grant sublicenses) to use certain materials and the research results, solely with respect to products in the field of prevention, diagnosis or treatment of any human disease or condition.

Manufacturing

ELX-02 is manufactured under current Good Manufacturing Practice (cGMP) conditions and is formulated as a sterile frozen liquid in glass vials for parenteral subcutaneous (SC injection) administration.

We do not own or operate manufacturing or distribution facilities for the production of clinical quantities of ELX-02 or for our other preclinical product candidates. We currently rely, and expect to continue to rely, on third parties for the manufacture, packaging, labeling and distribution of clinical supplies of ELX-02 as well as any other candidate that we may develop.

We engage separate manufacturers for drug substance and drug product. We have a relationship with a manufacturer that is capable of providing fill and finish services for our clinical product at the current scale. To support later clinical trials, transfer of the manufacturing and release to a manufacturer with higher lot scale capacity will be needed for our clinical product.

All of our current drug candidates are organic compounds of low molecular weight. We have selected our lead compounds not only on the basis of their potential efficacy and safety but also for their ease of synthesis and reasonable cost of their starting materials. ELX-02 is manufactured in reliable and reproducible synthetic processes. We currently rely on a single third-party manufacturing source for the production of a key raw material, produced by bacterial fermentation. We do not currently have any agreements with third-party manufacturers for the long-term commercial supply of ELX-02 or the fermentation-derived starting material, although we may seek to establish such arrangements in the future.

We currently obtain supplies of ELX-02 from third-party manufacturers pursuant to agreements that include specific supply timelines and volume expectations. If a manufacturer should become unavailable to us for any reason, we would seek to obtain supply from another manufacturer engaged by us for the applicable product or service. In the event that we were unable to procure the applicable supply from a currently qualified manufacturer, we believe that

there are a number of potential replacements for each of our outsourced services, however we would likely experience delays in our ability to supply ELX-02 in advancing our clinical trials while we identify and qualify replacement suppliers.

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Government Regulation

Drug Development and Approval in the United States

The preclinical studies and clinical testing, manufacture, labeling, storage, record keeping, advertising, promotion, export, and marketing, among other things, of our product candidates are subject to extensive regulation by governmental authorities in the United States, the European Union and other territories. In the United States, pharmaceutical products are regulated by the FDA under the Federal Food, Drug, and Cosmetic Act (the FDCA) and other laws, including, in the case of biologics, the Public Health Service Act. Failure to comply with FDA requirements, both before and after product approval, may subject us and/or our partners, contract manufacturers, and suppliers to administrative or judicial sanctions, including FDA refusal to approve applications, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, fines and/or criminal prosecution.

The process for obtaining regulatory approval to market a medicine is expensive, often takes many years, and can vary substantially based on the type, complexity, and novelty of the product candidates involved. The steps required before a drug may be approved for marketing of an indication in the United States generally include:

(a) preclinical laboratory tests and animal tests;

(b) submission to the FDA of an IND application for human clinical testing, which must become effective before human clinical trials may commence;

(c) adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for its intended use;

(d) submission to the FDA of a NDA;

(e) FDA pre-approval inspection of the manufacturing and clinical study sites identified in the NDA; and

(f) FDA review and approval of the NDA.

Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as toxicological and pharmacological animal studies to assess the potential safety and efficacy of the product candidates. Preclinical safety tests intended for submission to FDA must be conducted in compliance with FDA s Good Laboratory Practice (GLP) regulations and the U.S. Department of Agriculture s Animal Welfare Act. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application that must become effective before human clinical trials may be commenced. The IND will automatically become effective 30 days after receipt by the FDA, unless the FDA before that time raises concerns about the drug candidate or the conduct of the trials as outlined in the IND. The IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed. We cannot assure you that submission of an IND will result in FDA authorization to commence clinical trials or that once commenced, other concerns will not arise. FDA may stop the clinical trials by

placing them on clinical hold because of concerns about the safety of the product being tested, or for other reasons.

Clinical trials involve the administration of the investigational product to healthy volunteers or to patients, under the supervision of qualified principal investigators. The conduct of clinical trials is subject to extensive regulation, including compliance with the FDA s bioresearch monitoring regulations and Good Clinical Practice (GCP) requirements, which establish standards for conducting, recording data from, and reporting the results of clinical trials, and are intended to assure that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study participants are protected.

Clinical trials must be conducted in accordance with protocols that detail the objectives of the study, the criteria for determining subject eligibility, the dosing plan, patient monitoring requirements, timely reporting of adverse events, and other elements necessary to ensure patient safety, and any efficacy criteria to be evaluated.

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Each protocol must be submitted to FDA as part of the IND; further, each clinical study at each clinical site must be reviewed and approved by an independent institutional review board, prior to the recruitment of subjects. The institutional review board s role is to protect the rights and welfare of human subjects involved in clinical studies by evaluating, among other things, the potential risks and benefits to subjects, processes for obtaining informed consent, monitoring of data to ensure subject safety, and provisions to protect the subjects privacy. Foreign studies conducted under an IND application must meet the same requirements that apply to studies being conducted in the United States. Data from a foreign study not conducted under an IND may be submitted in support of a NDA if the study was conducted in accordance with GCP and FDA is able to validate the data.

Clinical trials are typically conducted in three sequential phases, but the phases may overlap, and different trials may be initiated with the same drug candidate within the same phase of development in similar or differing patient populations. Phase I studies may be conducted in a limited number of patients but are usually conducted in healthy volunteer subjects. The drug is usually tested for safety and, as appropriate, for absorption, metabolism, distribution, excretion, pharmacokinetics and pharmacodynamics. Phase II usually involves studies in a larger, but still limited patient population to evaluate preliminarily the efficacy of the drug candidate for specific, targeted indications; to determine dosage tolerance and optimal dosage; and to identify possible short-term adverse effects and safety risks. Phase III trials are undertaken to gather additional information to evaluate the product s overall risk-benefit profile, and to provide a basis for physician labeling. Phase III trials evaluate clinical efficacy of a specific endpoint and test further for safety within an expanded patient population at geographically dispersed clinical study sites. Phase I, Phase II or Phase III testing might not be completed successfully within any specific time period, if at all, with respect to any of our product candidates. Results from one trial are not necessarily predictive of results from later trials. Furthermore, the FDA, sponsor or institutional review board may suspend clinical trials at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk.

We must register each controlled clinical trial, other than Phase I trials, on a website administered by the NIH (http://clinicaltrials.gov). Registration must occur not later than 21 days after the first patient is enrolled, and the submission must include descriptive information (e.g., a summary in lay terms of the study design, type and desired outcome), recruitment information (e.g., target number of participants and whether healthy volunteers are accepted), location and contact information, and other administrative data (e.g., FDA identification numbers). Within one year of a trial s completion, information about the trial including characteristics of the patient sample, primary and secondary outcomes, trial results written in lay and technical terms, and the full trial protocol must be submitted to the FDA. The results information is posted to the website unless the drug has not yet been approved, in which case the FDA posts the information shortly after approval. A NDA, and certain other submissions to the FDA require certification of compliance with these clinical trials database requirements. There are proposals to expand these registration requirements to additional studies.

The results of the preclinical studies and clinical trials, together with other detailed information, including information on the manufacture and composition of the product and proposed labeling for the product, are submitted to the FDA as part of a NDA requesting approval to market the product candidate for a proposed indication. Under the Prescription Drug User Fee Act, as amended, the fees payable to the FDA for reviewing a NDA, as well as annual fees for commercial manufacturing establishments and for approved products, can be substantial. The NDA review fee alone can exceed $2.4 million subject to certain limited deferrals, waivers and reductions that may be available. Each NDA submitted to the FDA for approval is typically reviewed for administrative completeness and reviewability within sixty days following submission of the application. If the FDA finds the NDA sufficiently complete, the FDA will file the NDA, thus triggering a full review of the application. The FDA may refuse to file any NDA that it deems incomplete or not properly reviewable at the time of submission. Current FDA performance goals provide for action on an application within 12 months of submission. The FDA, however, may not approve a drug within these established timeline goals and its review clock for a particular NDA is subject to change from time to time because the

review process is often significantly extended by FDA requests for additional information or clarification. As part of its review, the FDA may refer the NDA to an advisory committee composed of outside experts for evaluation and a recommendation

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as to whether the application should be approved. Although the FDA is not bound by the recommendation of an advisory committee, the agency usually has followed such recommendations.

Further, the outcome of the review, even if generally favorable, may not be an actual approval but instead a complete response letter communicating the FDA s decision not to approve the application at that time, outlining the deficiencies in the NDA that need to be addressed in order to be eligible for approval, and identifying what information and/or data (including additional preclinical or clinical data) is required before the application can be approved. Even if such additional information and data are submitted, the FDA may decide that the NDA still does not meet the standards for approval. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we do.

The FDA will typically inspect one or more clinical sites to assure compliance with GCP before approving an NDA. The FDA also will inspect the facility or the facilities at which the product is manufactured before the NDA is approved to assure compliance with cGMP. The FDA will not approve the product unless GCP and cGMP compliance is satisfactory. The FDA may also take into account results of inspections performed by certain counterpart foreign regulatory agencies in assessing compliance with GCP or cGMP. The FDA has entered into international agreements with foreign agencies, including the EMA, in order to facilitate this type of information sharing. If the FDA determines the application, clinical sites, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information.

The FDA may deny approval of a NDA if applicable statutory or regulatory criteria are not satisfied, or may require additional testing or information, which can delay the approval process. FDA approval of any application may include many delays or never be granted. If a product is approved, the approval will impose limitations on the indicated uses for which the product may be marketed, may require that warning statements be included in the product labeling, and may require that additional studies be conducted following approval as a condition of the approval. FDA also may impose restrictions and conditions on product distribution, prescribing or dispensing in the form of a Risk Evaluation Mitigation Strategy (REMS), or otherwise limit the scope of any approval. A REMS may include various elements, ranging from a medication guide to limitations on who may prescribe or dispense the drug, depending on what the FDA considers necessary for the safe use of the drug. To market a product for other indicated uses, or to make certain manufacturing or other changes, requires FDA review and approval of a NDA Supplement or new NDA and the payment of applicable review fees. Further post-marketing testing and surveillance to monitor the safety or efficacy of a product may be required. In addition, new government requirements may be established that could delay or prevent regulatory approval of our product candidates under development.

Under the Pediatric Research Equity Act of 2003 (PREA), NDAs or supplements to NDAs must contain data to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the drug is determined by the FDA to be safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. As the FDA has not issued regulations applying PREA to orphan-designated indications, submission of a pediatric assessment is not presently required for an application to market a product for an orphan-designated indication. However, PREA compliance may be required if approval is sought for other indications for which the drug has not received orphan designation.

Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

The testing and approval process requires substantial time, effort and financial resources, and each may take years to complete. Data obtained from clinical trials are not always conclusive and may be susceptible to varying

interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all.

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We may encounter difficulties or unanticipated costs in our efforts to secure necessary FDA approvals, which could delay or preclude us from marketing our products. The FDA may refer applications for novel drug products or drug products that present difficult questions of safety or efficacy to an advisory committee for review, evaluation and recommendation as to whether the application should be approved and under what conditions. The advisory committee process may cause delays in the approval timeline. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations carefully, particularly any negative recommendations or limitations, when making drug approval decisions.

The FDA may limit the indications for use, approve narrow labeling relegating a drug to second- line or later-line use, add limitations of use to the labeling or place other conditions on approvals, which could restrict the marketing of an approved product. Further, FDA may require that certain contraindications, warnings or precautions be included in the product labeling. After approval, some types of changes to the approved product, such as adding new indications, which may themselves require further clinical testing, or changing the manufacturing process are subject to further FDA review and approval.

Post-approval Requirements

After FDA approval of a product is obtained, we may be required to comply with a number of post-approval requirements, including, among other things, establishment registration and product listing, record-keeping requirements, reporting certain adverse reactions and production problems to the FDA, providing updated safety and efficacy information, and complying with requirements concerning advertising and promotional labeling. As a condition of approval of an NDA, the FDA may require the applicant to conduct additional clinical trials or other post-market testing and surveillance to further monitor and assess the drug s safety and efficacy.

The FDA also has the authority to require a REMS to ensure the safe use of the drug. In determining whether a REMS is necessary, the FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate health care providers of the drug s risks, limitations on who may prescribe or dispense the drug, or other measures that the FDA deems necessary to assure the safe use of the drug. In addition, the REMS must include a timetable to assess the strategy at 18 months, three years, and seven years after the strategy s approval. The FDA may also impose a REMS requirement on an approved drug if the FDA determines, based on new safety information, that a REMS is necessary to ensure that the drug s benefits outweigh its risks.

The FDA regulates strictly the marketing, labeling, advertising and promotion of drug products that are placed on the market. Although physicians may prescribe a drug for off-label uses, manufacturers may only promote for the approved indications and in accordance with the approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with the laws and regulations governing advertising and promotion can have negative consequences, including adverse publicity, warning and untitled letters from the FDA, requests for corrective advertising or communications with doctors, and civil penalties or criminal prosecution.

In addition, the distribution of approved prescription pharmaceutical products is subject to the Prescription Drug Marketing Act (PDMA), which regulates the distribution of drugs and drug samples at the federal level and sets minimum standards for the registration and regulation of drug distributors by the states. Similarly, the Drug Supply Chain Security Act (DSCSA), regulates the distribution of prescription pharmaceutical drugs, requiring passage of a pedigree to track and trace each prescription drug at the saleable unit level through the distribution system. The

DSCSA also imposes obligations on drug manufacturers related to suspect product identification/removal, verification, dealing only with authorized trading partners, and other elements. The DSCSA will be effective incrementally over a 10-year period, with serialization of prescription drug products

distributed in the United States effective November 27, 2017 for drug manufacturers. The PDMA, DSCSA, and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Also, quality control and manufacturing procedures must continue to conform to cGMP after approval. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes certain procedural and recordkeeping requirements. Accordingly, manufacturers must continue to expend time, money and effort in the area of process and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical and any future commercial quantities of our product candidates. Future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution or require substantial resources to correct. In addition, discovery of problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

Once approval is granted, FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if issues bearing on the product s safety or efficacy are discovered. Newly discovered or developed safety or effectiveness data or other information may also require changes to a product s approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. New government requirements, including those resulting from new legislation, may be established that could delay or prevent FDA approval of our products under development or negatively impact the marketing of any future approved products.

Orphan Drug Designation

We have received orphan drug designation from the FDA for ELX-02 for the treatment of MPS I for the treatment of Rett syndrome. The FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, which is defined as a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for this type of disease or condition will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. Orphan drug designation can provide opportunities for grant funding towards clinical trial costs, tax advantages and FDA user-fee benefits. In addition, if a product which has an orphan drug designation subsequently receives the first FDA approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors may receive approval of different drugs or biologics for the indications for which the orphan product has exclusivity.

Rare Pediatric Disease Designation and Priority Review Voucher

Some orphan drugs may also qualify for designation as a rare pediatric disease under Section 529 of the FDCA. Section 529 is similar to the Orphan Drug Act, as both require that the rare disease or condition affect fewer than 200,000 persons in the United States. In the Advancing Hope Act of 2016, Section 529 was changed so that the rare pediatric disease must also meet the additional criteria of being a serious or life-threatening disease in which the

serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents. Under Section 529 of the

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FDCA, FDA will award priority review vouchers to sponsors of rare pediatric disease product applications that meet these criteria. Under this program, a sponsor who receives an approval for a drug or biologic for a rare pediatric disease may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product.

Hatch-Waxman Exclusivity

Market and data exclusivity provisions under the FDCA can delay the submission or the approval of certain applications for competing products. The FDCA provides a five-year period of non-patent data exclusivity within the United States to the first applicant to gain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety. During the exclusivity period, the FDA generally may not accept for review an abbreviated new drug application (ANDA) or a 505(b)(2) NDA submitted by another company that references the previously approved drug. An ANDA or 505(b)(2) NDA may be submitted after four years if it contains a certification of patent invalidity or non-infringement.

For some applications that do not qualify for five-year exclusivity, the FDCA provides a shorter three-year period of market exclusivity. Three-year exclusivity applies to an NDA, 505(b)(2) NDA, or supplement to an existing NDA or 505(b)(2) NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant, are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages, strengths or dosage forms of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for generic versions of the original, unmodified drug product. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent market exclusivity in the United States and, if granted, provides for the attachment of an additional six months of market protection to the term of any existing Orange Book-listed patents or regulatory exclusivity, including the non-patent exclusivity periods described above. This six-month exclusivity may be granted based on the voluntary completion of a pediatric study or studies in accordance with an FDA-issued Written Request for such a study or studies.

Regulation Outside the United States

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of any future approved products. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Regulation in the European Union

We have obtained an orphan medicinal product designation from the European Commission, following an evaluation by the EMA s Committee for Orphan Medicinal Products, for ELX-02 for the treatment of nmMPS I.

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The European Commission can grant orphan medicinal product designation to products for which the sponsor can establish that it is intended for the diagnosis, prevention, or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in 10,000 people in the European Union, or (2) a life threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that sales of the drug in the European Union would generate a sufficient return to justify the necessary investment. In addition, the sponsor must establish that there is no other satisfactory method approved in the European Union of diagnosing, preventing or treating the condition, or if such a method exists, the proposed orphan drug will be of significant benefit to patients. Orphan drug designation is not a marketing authorization. It is a designation that provides a number of benefits, including fee reductions, regulatory assistance, and the possibility to apply for a centralized EU marketing authorization, as well as 10 years of market exclusivity following a marketing authorization. During this market exclusivity period, neither the European Medicines Agency, nor the European Commission nor the Member States can accept an application or grant a marketing authorization for a similar medicinal product. A similar medicinal product is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may be reduced to six years if, at the end of the fifth year, it is established that the orphan designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, a competing similar medicinal product may in limited circumstances be authorized prior to the expiration of the market exclusivity period, including if it is shown to be safer, more effective or otherwise clinically superior to our product. Our product can lose orphan designation, and the related benefits, prior to us obtaining a marketing authorization if it is demonstrated that the orphan designation criteria are no longer met.

Overview of Application Process

To obtain regulatory approval of a drug under the European Union s regulatory systems and authorization procedures, an applicant may submit a Marketing Authorization Application (MAA) under a centralized, decentralized, or national procedure. The centralized procedure is compulsory for certain medicinal products, including orphan medicinal products, like ELX-02 and medicinal products produced by certain biotechnological processes, and optional for certain other innovative products. The centralized procedure enables applicants to obtain a marketing authorization that is valid in all EU member states based on a single application. Under the centralized procedure, the EMA s Committee for Human Medicinal Products (CHMP), is required to adopt an opinion on a valid application within 210 days, excluding clock stops, during which additional written or oral information is to be provided by the applicant in response to questions. More specifically, on day 120 of the procedure, once the CHMP has received the preliminary assessment reports and opinions from the rapporteur and co- rapporteur, the CHMP prepares a list of potential outstanding issues, referred to as other concerns or major objections. These are sent to the applicant together with CHMP s recommendation. The CHMP can make one of two recommendations: (1) the marketing authorization could be granted provided that satisfactory answers are given to the other concerns and/or major objections identified and that all conditions outlined in the list of outstanding issues are implemented and complied with; or (2) the product is not approvable since there are major objections.

Applicants have three months from the date of receiving the potential outstanding issues to respond to the CHMP, and can request a three-month extension if necessary. The granting of a marketing authorization will depend on the recommendations and potential major objections identified by the CHMP as well as the ability of the applicant to adequately respond to these findings. An accelerated assessment can be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of major public health interest, in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days. After the adoption of the CHMP opinion, a decision on the MAA must be adopted by the European Commission, after consulting the EU member states, which in total should be completed in 67 days.

An applicant for an MAA may request a re-examination in the event of a negative opinion, in connection with which CHMP appoints new rapporteurs. Within 60 days of receipt of the negative opinion, the applicant

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must submit a document explaining the basis for its request for re-examination. The CHMP has 60 days to consider the applicant s request for re-examination. The applicant may request an oral explanation before the CHMP, which is routinely granted, following which CHMP will adopt a final opinion. The final opinion, whether positive or negative, is published by the CHMP shortly following the CHMP meeting at which the oral explanation takes place.

Conditional Marketing Authorizations

In specific circumstances, EU legislation enables applicants to obtain a marketing authorization on a conditional basis prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional approvals may be granted for products designated as orphan medicinal products, if (1) the risk-benefit balance of the product is positive, (2) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data, (3) the product fulfills unmet medical needs, and (4) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization. The granting of a conditional marketing authorization will depend on the applicant s ability to fulfill the conditions imposed within the agreed upon deadline.

Variations to Conditional Marketing Authorizations

After the granting of a conditional marketing authorization, the marketing authorization holder may submit an application to vary the conditional marketing authorization under a variation procedure. In the case of the introduction of an additional therapeutic indication, the timeframe for the variation procedure for the initial assessment of the dossier is generally 90 days (plus up to 20 days for validation).

In the framework of a variation application assessment procedure, however, the EMA may send one or more requests for supplementary information to the marketing authorization holder, requiring that additional information be provided by the marketing authorization holder to support its variation application. Such supplementary requests will be sent together with a timetable stating the date by when the marketing authorization holder must submit the requested data and, where appropriate, the extended evaluation period to be applied to such variation procedure. The 90-day variation procedure may be suspended for up to three months for the marketing authorization holder to submit its responses to such supplementary requests. The marketing authorization holder will be notified of the outcome of the CHMP s assessment of the variation procedure within 15 days from the adoption of the CHMP opinion. If unfavorable, the CHMP opinion may be subject to a re-examination procedure upon the marketing authorization holder s request. This may imply an additional minimum two-month procedure. If the CHMP opinion is favorable, the European Commission will vary the marketing authorization to introduce the additional therapeutic indication within approximately two months from the receipt of the final CHMP opinion.

Additional Requirements and Considerations

Prior to obtaining a marketing authorization in the European Union, applicants have to demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan (PIP), covering all subsets of the pediatric population, unless the EMA has granted (1) a product-specific waiver, (2) a class waiver, or (3) a deferral for one or more of the measures included in the PIP. In the case of orphan medicinal products, completion of an approved PIP

can result in an extension of the aforementioned market exclusivity period from ten to twelve years.

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In the European Union, independently generated data submitted as part of a full marketing authorization application dossier are protected by regulatory data protection (data exclusivity) for a period of eight years from the granting of a marketing authorization for a reference product . This means that for a period of eight years, competent authorities may not accept marketing authorization applications that rely on the independently generated data in the marketing authorization dossier of the reference product. Generic medicinal products that rely on the independently generated data of the reference product may not be placed on the market for 10 years from the granting of the initial marketing authorization for the reference medicinal product. These periods of data exclusivity and market exclusivity do not prevent other companies from obtaining a marketing authorization based on their own independently generated data.

Were we able to obtain a marketing authorization for ELX-02 for any indication in the European Union, we would be required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. We must, for example, comply with the EU s stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. Other requirements relate to, for example, the manufacturing of products and active pharmaceutical ingredients in accordance with good manufacturing practice standards. Competent authorities of EU member states may conduct inspections to verify our compliance with applicable requirements, and we will have to continue to expend time, money and effort to remain compliant. Non-compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties in the EU Similarly, failure to comply with the EU s requirements regarding the protection of individual personal data can also lead to significant penalties and sanctions. Individual EU member states may also impose various sanctions and penalties in case we do not comply with locally applicable requirements.

Off-label promotion of medicinal products is prohibited in the European Union. The applicable laws at EU level and in the individual EU member states also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the European Union could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict our promotional activities with health care professionals. In addition, legislation adopted at the EU level and by individual EU member states require that promotional materials and advertising in relation to medicinal products comply with the product s Summary of Product Characteristics (SmPC), as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. Promotion of indications not covered by the SmPC is specifically prohibited.

The EMA is responsible for coordinating inspections to verify compliance with the principles of GCP, cGMP, GLP, and good pharmacovigilance practice (GVP). These inspections are also intended to verify compliance with other aspects of the supervision of authorized medicinal products in use in the European Union. The EMA coordinates any inspection requested by the CHMP in connection with the assessment of MAAs or matters referred to these committees. Inspections may be routine or triggered by issues arising during the assessment of the dossier or by other information, such as previous inspection experience. Inspections usually are requested during the initial review of an MAA but could arise post-authorization.

Inspectors are drawn from member states of the European Union and the European Economic Area. Following an inspection, the inspectors provide a written inspection report to the inspected site or applicant and provide an opportunity for response. Some inspection reports require follow-up and may result in additional adverse consequences due to critical or major findings. The inspectors and the CHMP will comment on any response from an inspected site or applicant and may monitor future compliance with any proposed corrective action plan.

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In the GCP area, inspectors grade their findings according to the following scale:

Critical: Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects or the quality and integrity of data. Observations classified as critical may include a pattern of deviations classified as major.

Major: Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Observations classified as major may include a pattern of deviations or numerous minor observations.

Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects or the quality and integrity of data. Minor observations indicate the need for improvement of conditions, practices and processes.

Comments: Suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.

Possible consequences of critical and major findings include rejection of clinical trial data, causing significant delays in obtaining final marketing authorization, or other direct action by national regulatory authorities.

Early Access Programs

Many jurisdictions allow the supply of unauthorized medicinal products in the context of strictly regulated and exceptional early access programs, and some countries may provide reimbursement for drugs provided in the context of such programs. In the European Union, the legal basis for early access programs, also referred to as named-patient and compassionate use programs, is set out in the EU legislation regulating the authorization, manufacture, distribution and marketing of medicinal products. Detailed regulatory requirements applicable to early access programs have been adopted and implemented by EU member states in their national laws. The promotion, advertising and marketing of unauthorized medicinal products is generally prohibited, and authorization for early access programs must generally be obtained from national competent authorities, which might not grant such authorization. Obtaining authorization for an early access program in one country does not ensure that authorization will be obtained in another country. U.S. law permits expanded access (also known as compassionate use and treatment use) for certain patients with serious diseases who have no comparable alternative treatment options. To provide expanded access, sponsors must submit detailed regulatory information to the FDA. FDA authorization depends on several different factors, including whether expanded access will interfere with related clinical trials or drug development. Sponsors may not promote products as safe or effective for expanded-access uses.

Pharmaceutical Pricing and Reimbursement

The containment of healthcare costs has become a priority of federal, state and foreign governments, and the prices of pharmaceuticals have been a focus of this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, the Medicare Prescription Drug, Improvement, and

Modernization Act of 2003 expanded Medicare coverage for drug purchases by the elderly and changed the way Medicare covers and pays for pharmaceutical products. Cost reduction initiatives and other provisions of this law may decrease the coverage and reimbursement rate that we may receive for any approved products. Likewise, healthcare reform measures under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, referred to together as the Affordable Care Act, contain provisions that may reduce the profitability of drug products by increasing the minimum level of Medicaid rebates payable by manufacturers of brand-name drugs from 15.1% to 23.1%, effective 2011, extending the Medicaid rebate to Medicaid managed care plans, changing the Medicaid rebate rates for line

extensions or new formulations of oral solid dosage form, mandating discounts for certain Medicare Part D beneficiaries, and imposing a non-deductible annual fee on pharmaceutical manufacturers or importers who sell branded prescription drugs, effective 2011, expanding the types of entities eligible for the Section 340B discounts for outpatient drugs, requiring manufacturers to participate in a coverage gap discount program, under which they must agree to offer 50% point-of-sale discounts off negotiated prices of applicable branded 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 and creating a process for approval of biologic therapies that are similar or identical to approved biologics. There are numerous steps required to implement the Affordable Care Act, and implementation remains ongoing. Congress also has enacted, and may continue to seek, legislative changes that alter, delay, or eliminate some of its provisions. On February 1, 2016, the Centers for Medicare and Medicaid Services released a long-awaited new rule, the Medicaid Program Covered Outpatient Drug Final Rule, effective April 1, 2016, implementing various provisions of the Affordable Care Act related to covered outpatient drugs, including revising the calculation of average manufacturer price and addressing other issues relating to Medicaid price reporting and reimbursement. These and other changes contribute to the uncertainty of the ongoing implementation and impact of the Affordable Care Act; they also underscore the potential for additional reform going forward. Certain provisions of enacted or proposed legislative changes may negatively impact coverage and reimbursement of healthcare items and services.

Increasing pricing pressure continues from managed care organizations, government agencies and programs, particularly for new and innovative therapies, that could negatively affect the company s sales and profit margins. In the United States, these include practices of managed care groups, federal and state exchanges, and institutional and governmental purchasers. Changes to the health care system enacted as part of health care reform in the United States, as well as increased purchasing power of entities that negotiate on behalf of Medicare, Medicaid, and private sector beneficiaries, could negatively impact the company s sales and profit margins. Such pressures may also increase the risk of litigation or investigations by the government regarding pricing calculations. There has also been recent negative publicity and Congressional scrutiny around pharmaceutical drug pricing in the United States. These dynamics may give rise to negative reactions to pricing decisions for products for which we may receive regulatory approval in the future, possibly limiting our ability to generate revenue and attain profitability. Moreover, the pharmaceutical industry will likely face greater regulation and political and legal action in the future. In this healthcare regulatory climate, there may be significant delays in and impediments to obtaining coverage and reimbursement for newly approved drugs. Any regulatory approval of our products is limited to specific diseases and indications for which our products have been deemed safe and effective by the FDA. Coverage by federal healthcare programs may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities coverage of the same products. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the extent to which the costs of the products will be covered and reimbursed by third-party payors, including government healthcare programs such as Medicare and Medicaid, private health insurers and other organizations. Obtaining reimbursement for orphan drugs may be particularly difficult because of the higher prices typically associated with drugs directed at smaller populations of patients. In addition, third-party payors are likely to impose strict requirements for reimbursement in the use of a higher priced drug. Net prices for products 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 products from countries where they may be sold at lower prices than in the United States.

The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA approved products for a particular indication. Third-party payors are increasingly challenging the price and examining the cost-effectiveness of medical products and services. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost-effectiveness of our products. Our product candidates may

not be considered cost-effective. In the future, we may need to conduct

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direct head-to-head studies to demonstrate clinical superiority and cost-effectiveness. Our product candidates may not be considered clinically superior and cost-effective to competitor products.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and other third-party payors fail to provide adequate coverage and reimbursement. In addition, there is an increasing emphasis on managed care in the United States that may negatively impact pharmaceutical pricing.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing and reimbursement negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. In some countries, governments can set conditions that must be satisfied for prices to be set at a certain value. Political, economic and regulatory developments may further complicate pricing and reimbursement negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel distribution (arbitrage between low-priced and high-priced member states), can further reduce prices. In some countries we may be required to conduct a clinical trial or other studies that compare the cost-effectiveness of our product candidate to other available therapies in order to obtain reimbursement or pricing approval.

Freedom of Information Requests

We are also subject, in the United States and many other countries, to various regulatory schemes that require disclosure of clinical trial data or allow access to our data via freedom of information requests. We have been and may, from time to time, be notified by regulators, such as the EMA or the competent authorities of EU member states that they have received a freedom of information request for documents that they hold relating to our company, including information related to our product or our product candidates.

Fraud and Abuse Laws

Any present or future arrangements with third-party payors, healthcare providers and professionals and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may restrict certain marketing and contracting practices. These laws include, and are not limited to, anti-kickback and false claims statutes.

Both the federal Foreign Corrupt Practices Act (FCPA), and the UK Bribery Act of 2010 (Bribery Act), are broad in scope and will require companies to make and keep books and records that accurately and fairly reflect the transactions of the company and to devise and maintain an adequate system of internal accounting controls. The FCPA prohibits the offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to improperly influence any act or decision, secure any other improper advantage, or obtain or retain business. Under the Bribery Act, companies which carry on a business or part of a business in the United Kingdom may be held liable for bribes given, offered or promised to any person, including non-UK government officials and private persons, by employees and persons associated with the company in order to obtain or retain business or a business advantage for the company.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, in cash or kind, to induce or reward either the referral of an individual for, or the purchase, or order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid. This statute has been broadly interpreted

to apply to manufacturer arrangements with prescribers, purchasers and formulary managers, among others. Although a number of statutory exemptions and regulatory safe harbors exist to protect certain

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common activities from prosecution, the exemptions and safe harbors for this statute are narrow, and practices that involve compensation intended to induce prescriptions, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not always meet all of the criteria for safe harbor protection. Further, the Affordable Care Act amended the intent requirement of the federal anti-kickback and criminal health care fraud statutes. This amendment provides that a person or entity no longer needs to have knowledge of these statutes or specific intent to violate them. In addition, the government may assert that 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. Several other countries, including the United Kingdom, have enacted similar anti-kickback, fraud and abuse laws and regulations.

The federal False Claims Act imposes civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for 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. Several pharmaceutical and health care 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 free product. Other companies have been prosecuted for causing false claims to be submitted because of these companies marketing of a product for unapproved, and thus non-reimbursable, uses. Potential liability under the federal False Claims Act includes mandatory treble damages and significant per claim penalties, currently set at $5,500 to $11,000 per false claim. The majority of states also have statutes or regulations similar to the federal anti-kickback statute and False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs; furthermore, in several states, these statutes and regulations apply regardless of the payor. Sanctions under these federal and state laws may include civil monetary penalties, exclusion of a manufacturer s product from reimbursement under government programs, debarment, criminal fines, and imprisonment.

The Affordable Care Act included a provision requiring certain providers and suppliers of items and services to Federal Health Care Programs to report and return overpayments within sixty days after they are identified, or the Overpayment Statute. In February 2016, the Centers for Medicare and Medicaid Services (CMS) released long-awaited regulatory guidance (in the form of a final rule) to Medicare Part A and Part B providers and suppliers regarding how to comply with the Overpayment Statute. CMS had previously released a final rule addressing overpayments involving Medicare Part C and Part D providers in May 2014. Although Medicare Part A/B/C/D providers and suppliers have faced federal False Claims Act liability since 2010 for failures to comply with the Overpayment Statute, these final rules interpreting the Overpayment Statute provide guidance to providers and suppliers regarding how to comply appropriately with applicable obligations, and guidance to government regulators and enforcement authorities regarding monitoring and prosecuting suspected violations. This final rule is not directly applicable to manufacturers, but may impact their customers and potential customers who are Medicare providers and suppliers.

The federal Physician Payments Sunshine Act, enacted as part of the Affordable Care Act, and its implementing regulations, require manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to payments and other transfers of value made to covered recipients, such as physicians and teaching hospitals, as well as physician ownership and investment interests. Payments made to physicians and certain research institutions for clinical trials are included within the ambit of this law. Pharmaceutical manufacturers are required to report and disclose payments and ownership and investment interests held by physicians and their immediate family members during the preceding calendar year. Manufacturers were required to make these first reports for information collected in 2013 by March 31, 2014. Such information is publicly available from the Secretary of Health and Human Services in a searchable format, with data collected in each calendar year published the following June. Failure to submit required information may result in civil monetary penalties of up to $150,000 per year (and up to $1.0 million per year for knowing failures) for all payments, transfers of value or ownership or

investment interests not reported in an annual submission. If not preempted by this federal law, several states currently require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and

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payments to individual physicians in those states. Depending on the state, legislation may prohibit various other marketing related activities, or require the posting of information relating to clinical studies and their outcomes. In addition, certain states, such as California, Nevada, Connecticut and Massachusetts, require pharmaceutical companies to implement compliance programs or marketing codes and several other states are considering similar proposals. Manufacturers that fail to comply with these state laws can face civil penalties.

Statutory requirements to disclose publicly payments made to healthcare professionals and healthcare organizations have also been enacted in certain EU member states. In addition, self-regulatory bodies of the pharmaceuticals industry, such as the European Federation of Pharmaceutical Industries and Associations (EFPIA) have published codes of conduct to which its members have agreed to abide by, that require the public disclosure of payments made to healthcare professionals and healthcare organizations.

The Health Insurance Portability and Accountability Act of 1996 (HIPAA), as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal liability for executing a scheme to defraud any healthcare benefit program and for knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services. HIPAA also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information, and imposes criminal and civil liability for violations of these obligations. Recently, the U.S. federal government criminally prosecuted an employee of a pharmaceutical company for an alleged violation of the privacy requirements under HIPAA. Furthermore, certain privacy laws and genetic testing laws may apply directly to our operations and/or those of our collaborators and may impose restrictions on our use and dissemination of individuals health information.

The foregoing discussion should be read in conjunction with the information appearing under Risk Factors Our relationships with customers, healthcare providers and professionals and third-party payors are or will be subject to applicable anti-kickback, fraud and abuse, transparency and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings which contains important information regarding some of the risks to our business arising as a result fraud and abuse laws.

Competition

Our industry is highly competitive and subject to rapid and significant technological change. New therapies and treatments based on innovative discoveries emerge frequently.

Our potential competitors are public and private companies, pharmaceutical companies and biotechnology companies who may be engaged in targeting the same biological processes that our compounds impact and who may be developing products for the same indications as our investigational drug candidates. Potential competitors could also include academic institutions, government agencies, other public and private research organizations and charitable venture philanthropic organizations that conduct research, seek patent protection and/or establish collaborative arrangements for research, development, manufacturing and commercialization.

Many of our competitors have substantially greater financial resources, technical resources, expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials. As a result, our competitors may commercialize products more rapidly or effectively than we do, which would affect our competitive position, the likelihood that our drug candidates, if approved, would achieve and maintain market

acceptance and our ability to generate meaningful revenues from our products.

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Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects, are more convenient or are more affordable than any products that we may develop. The key competitive factors affecting the success of ELX-02 and our other product candidates are their impact on the targeted diseases, superiority over competing products, long-term safety, convenience, price and the availability of coverage and reimbursement from government and other third-party payors.

Several companies are involved in researching and developing molecules targeting suppression of nonsense mutations and enhancement of translational read-through. PTC Therapeutics is developing ataluren (Translarna®) as translational read-through inducing drug. PTC has gained approval of ataluren for Duchenne muscular dystrophy under exceptional circumstances in the European Union. In January 2017, the European Commission renewed the conditional marketing authorization for ataluren to treat certain nonsense mutations of dystrophin. The renewal of the conditional marketing authorization is subject to a requirement to conduct an 18-month, randomized, placebo-controlled study of ataluren in nmDMD patients followed by an 18-month, open-label extension period with results expected by early 2021. Ataluren has not been approved by the FDA for any indication. Ten out of 11 members from a Peripheral and Central Nervous Systems Drugs Advisory Committee on September 28, 2017 stated more data are needed to prove the drug s efficacy. In a Complete Response Letter, the FDA s Office of Drug Evaluation I stated that it is unable to approve the ataluren application in its current form. Specifically, the letter indicated that evidence of effectiveness from one or more additional adequate and well-controlled clinical trials will be necessary to provide substantial evidence of effectiveness.

We believe that ELX-02 is the only drug candidate in clinical development designed to treat nonsense mutations in CFTR the underlying cause of cystic fibrosis and cystinosis, our lead indications. La Jolla Pharmaceuticals is testing a sub-fraction of gentamicin at a preclinical stage and PTC Therapeutics discontinued its CF program as ataluren did not show efficacy in a Phase 3 CF study.

Additional competition to ELX-02 may arise from other programs that do not target a specific CFTR mutation class but work via other mechanisms. Proteostasis Therapeutics is developing PTI-428, a CFTR amplifier in Phase 2; and Apteeus is developing TEE786 (Amlexanox), a NMD manipulator, in Phase 1. Other companies are developing RNA based therapeutics, gene therapy and cell therapy. Most of these products are in preclinical stages and these platforms face great technological challenges.

Employees

We currently have fifteen full-time employees. Of these employees, ten are located at our Rehovot, Israel research and development facility and five, including some executive officers, are located at our Waltham, Massachusetts facility. None of our employees are covered by a collective bargaining agreement and we have never experienced any work stoppage. We consider our relations with our employees to be good.

Additional Information

Our website address is http://www.eloxxpharma.com. Information on our website is not incorporated by reference herein. Copies of our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and all amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act, are available on our website as soon as reasonably practicable after we electronically file those reports with, or furnish them to the SEC. The public may read and copy any materials we file with the SEC at the SEC s Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling 1-800-SEC-0330. The SEC also maintains a website at http://www.sec.gov that contains reports, proxy and information statements, and other information regarding issuers that file electronically. (This

website address is not intended to function as a hyperlink.)

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ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below and all information contained in this report before you decide to purchase our common stock. If any of the possible adverse events described below actually occurs, we may be unable to conduct our business as currently planned and our financial condition and operating results could be harmed. In addition, the trading price of our common stock could decline due to the occurrence of any of the events described below, and you may lose all or part of your investment.

Risks Related to the Reverse Merger

The risks arising with respect to the historic Sevion business and operations may be different from what we anticipate, which could lead to significant, unexpected costs and liabilities and could materially and adversely affect our business going forward.

We may not have appreciated, understood or fully anticipated the extent of the risks associated with the recent reverse merger between Sevion and Ellox Limited. After the reverse merger, Sevion s historic business was discontinued, but prior to the transaction Sevion had a long operating history. As a consequence, we may be subject to claims, demands for payment, regulatory issues, costs and liabilities that were not and are not currently expected or anticipated. Notwithstanding our exercise of due diligence pre-transaction and risk mitigation strategies post-transaction, the risks involved with taking over a business with a long operating history and the costs and liabilities associated with these risks may be greater than we anticipate. Further, we do not have rights of indemnification against the pre-transaction stockholders of Sevion. We may not be able to contain or control the costs or liabilities associated with Sevion s historic business, which could materially and adversely affect our business, liquidity, capital resources or results of operation.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant operating losses since our inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future. We may never achieve or maintain profitability.

Since our inception, we have incurred significant operating losses. Our net loss was $21.2 million and $9.8 million for 2017 and 2016, respectively. As of December 31, 2017, we had an accumulated deficit of $39.0 million. To date, we have financed our operations primarily through equity capital investments, and to a lesser extent from loans and grants from Israeli Innovation Authority of the Ministry of Economy and Industry, or the IIA. We have devoted substantially all of our financial resources and efforts to research and development. We expect that it will be many years, if ever, before we receive regulatory approval and have a product candidate ready for commercialization. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if and as we:

- advance ELX-02 further into clinical trials;

continue the preclinical development of our research programs and advance candidates into clinical trials;

identify additional product candidates and advance them into preclinical development;

pursue regulatory approval of product candidates;

seek marketing approvals for our product candidates that successfully complete clinical trials;

establish a sales, marketing and distribution infrastructure to commercialize any product candidates for which we obtain marketing approval;

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maintain, expand and protect our intellectual property portfolio;

hire additional clinical, regulatory and scientific personnel;

add operational, financial and management information systems and personnel, including personnel to support product development;

acquire or in-license other product candidates and technologies; and

operate as a public company.

We have never generated any revenue from product sales and may never be profitable. To become and remain profitable, we and our collaborators must develop and eventually commercialize one or more products with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those product candidates for which we may obtain marketing approval, securing coverage and reimbursement for those product candidates, and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, may never generate revenue that is significant or large enough to achieve profitability. Our failure to become and remain profitable would decrease the value of the company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research and development of, continue and initiate clinical trials of and seek marketing approval for ELX-02, and as we become obligated to make milestone payments pursuant to our outstanding license agreements. In addition, if we obtain marketing approval for any of our current or future product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution of the approved product.

Our future capital requirements will depend on many factors, including:

the scope, progress, results and costs of drug discovery, clinical development, laboratory testing and clinical trials for ELX-02;

the costs, timing and outcome of any regulatory review of ELX-02;

the cost of any other product candidate programs we pursue;

the costs and timing of commercialization activities, including manufacturing, marketing, sales and distribution, and securing coverage and reimbursement for any product candidates that receive marketing approval;

the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;

our ability to establish and maintain collaborations on favorable terms, if at all; and

the extent to which we acquire or in-license other product candidates and technologies.

Identifying potential product candidates and conducting preclinical studies and clinical trials are time consuming, expensive and uncertain processes that take years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales for any of our current or future product candidates. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenue, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all.

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Accordingly, we will need substantial additional funding in connection with our continuing operations and to achieve our goals. We expect that our existing cash and cash equivalents will be sufficient to enable us to meet our current operating plan at least through the end of the first quarter of 2019. However, our existing cash and cash equivalents may prove to be insufficient for these activities. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs, product portfolio expansion or future commercialization efforts. Adequate additional financing may not be available to us on acceptable terms, or at all. In addition, we may seek additional financing due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our operating plans.

Raising additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity and debt financings, as well as entering into new collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaborations, which are limited in scope and duration. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, and may be secured by all or a portion of our assets. If we raise funds by entering into new collaborations, strategic alliances or licensing arrangements in the future with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings or through collaborations, strategic alliances or licensing arrangements when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to Drug Discovery, Development, Regulatory Approval and Commercialization

We depend heavily on the success of our lead product candidate, ELX-02. If ELX-02 fails during development or suffers any material delays, it may adversely impact the commercial viability of ELX-02 and our business.

We currently have no products approved for sale. To date, we have invested substantially all of our efforts and financial resources in the research and development of ELX-02, which is currently our only product candidate in clinical development. Our ability to achieve and sustain profitability depends on obtaining regulatory approvals, and successfully commercializing (if ever), ELX-02 and any future product candidates, either alone or with third parties. Before obtaining regulatory approval for the commercial distribution of our therapeutic product candidates, we or a collaborator must conduct extensive preclinical studies and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. The clinical trials, manufacturing and marketing of ELX-02, and any future product candidates, will be subject to extensive and rigorous review and regulation by numerous government authorities in the United States, the European Union and other jurisdictions where we intend to test and, if approved, market our current and future product candidates. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through preclinical studies and clinical trials that the product candidate is safe and effective for use in each target indication, and potentially in specific patient populations, including the pediatric population. This process can take many years and may include post-marketing studies and surveillance, which would require the expenditure of substantial resources. Of the large number of drugs in development for approval in the United States and the European Union, only a small percentage successfully complete the FDA or

EMA regulatory approval processes, as applicable, and are commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our research, development and clinical programs, we cannot assure you that ELX-02 or any of our future product candidates will be successfully developed or commercialized.

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Preclinical studies and clinical trials are expensive, difficult to design and implement, can take many years to complete and are uncertain as to outcome. The start or end of a clinical trial is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparative therapeutic or required prior or combination therapy, clinical outcomes or financial constraints. For instance, delays or difficulties in patient enrollment or difficulties in retaining trial participants can result in increased costs, longer development times or termination of a clinical trial. Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the eligibility criteria for the clinical trial, the age and condition of the patients, the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites and the availability of effective treatments for the relevant disease.

We and our collaborating partners may be subject, directly or indirectly, to federal and state healthcare fraud and abuse and false claims laws and regulations. If we or our collaborating partners are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

All marketing activities associated with product candidates that are approved for sale in the United States, if any, will be, directly or indirectly through our customers, subject to numerous federal and state laws governing the marketing and promotion of pharmaceutical products in the United States, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act and HIPAA. These laws may adversely impact, among other things, our proposed sales, marketing and education programs.

The federal Anti-Kickback Statute prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, to induce either the referral of an individual, or the furnishing, recommending, or arranging for a good or service, for which payment may be made under a federal healthcare program, such as the Medicare and Medicaid programs. The term remuneration has been broadly interpreted to include anything of value, including for example, gifts, discounts, the furnishing of supplies or equipment, credit arrangements, payments of cash, waivers of co-payments and deductibles, ownership interests and providing anything at less than its fair market value. The reach of the Anti-Kickback Statute was also broadened by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or the PPACA, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. § 1320a-7b, effective March 23, 2010. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, PPACA provides that the government may assert that 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 civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent. The federal Anti-Kickback Statute is broad, and despite a series of narrow safe harbors, prohibits many arrangements and practices that are lawful in businesses outside of the healthcare industry. Penalties for violations of the federal Anti-Kickback Statute include criminal penalties and civil sanctions such as fines, imprisonment and possible exclusion from Medicare, Medicaid and other state or federal healthcare programs. Many states have also adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs, and do not contain identical safe harbors.

The federal False Claims Act imposes liability on any person who, among other things, knowingly presents, or causes to be presented, a false or fraudulent claim for payment by a federal healthcare program. The qui tam provisions of the False Claims Act allow a private individual to bring civil actions on behalf of the federal government alleging that the defendant has submitted a false claim to the federal government, and to share in any

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monetary recovery. In addition, various states have enacted false claims laws analogous to the False Claims Act. Many of these state laws apply where a claim is submitted to any third-party payer and not merely a federal healthcare program. When an entity is determined to have violated the False Claims Act, it may be required to pay up to three times the actual damages sustained by the government, plus civil penalties of $5,500 to $11,000 for each separate false claim.

HIPAA created several new federal crimes, including health care fraud, and false statements relating to health care matters. The health care fraud statute prohibits knowingly and willfully executing a scheme to defraud any health care benefit program, including private third-party payers. The false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services.

We are unable to predict whether we could be subject to actions under any of these or other fraud and abuse laws, or the impact of such actions. Moreover, to the extent that any of our product candidates, if approved for marketing, will be sold in a foreign country, we and our future collaborators, may be subject to similar foreign laws and regulations. If we or any of our future collaborators are found to be in violation of any of the laws described above and other applicable state and federal fraud and abuse laws, we may be subject to penalties, including civil and criminal penalties, damages, fines, exclusion from government healthcare reimbursement programs and the curtailment or restructuring or our operations, any of which could have a material adverse effect on our business, results of operations and financial condition.

Positive results from preclinical or in vitro and in vivo testing of ELX-02 are not necessarily predictive of the results of future clinical trials of ELX-02. If we cannot achieve positive results in our clinical trials for ELX-02, we may be unable to successfully develop, obtain regulatory approval for and commercialize ELX-02.

Positive results from our preclinical testing of ELX-02 in vitro and in vivo may not necessarily be predictive of the results from our planned clinical trials in humans. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical trials after achieving positive results in preclinical and in vitro and in vivo studies, and we, or the third parties whose product candidates we expect to be co-administered with ELX-02, may face similar setbacks. Preclinical and clinical data are often susceptible to varying interpretations and analyses, and the FDA or EMA or other regulatory agencies may require changes to our protocols or other aspects of our clinical trials or require additional studies. Additionally, many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or EMA approval. If we fail to secure positive results from our clinical trials of ELX-02, the development timeline and regulatory approval and commercialization prospects for our lead product candidate, and, correspondingly, our business and financial prospects would be materially adversely affected.

Our product candidates, including ELX-02, may cause adverse effects or have other properties that could delay or prevent their regulatory approval or limit the scope of any approved label or market acceptance.

Undesirable side effects caused by our product candidates, such as ELX-02, could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other comparable foreign regulatory authorities. It is possible that, during the course of the clinical development of ELX-02, results of our clinical trials could reveal an unacceptable severity and prevalence of this or other side effects. For example, in preclinical testing of ELX-02, we observed renal toxicities in the animals we tested following administration of this compound at doses in excess of the doses we expect to administer in our clinical trials. As a result of this or any other side effects, our clinical trials could be suspended or terminated or not even allowed to commence, and the FDA or comparable foreign regulatory authorities could order us to cease further development, or

deny approval, of our product 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 trial or result in potential product liability claims.

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Additionally if one or more of our product candidates receive marketing approval, and we or others later identify undesirable side effects caused by such products, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approvals of such product or impose restrictions on its distribution in a form of a modified risk evaluation and mitigation strategy;
- regulatory authorities may require additional labeling, such as additional warnings or contraindications;
- we may be required to change the way the product is administered or to conduct additional clinical studies;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Our clinical trials may be costly and lengthy, time-consuming and difficult to design and implement, may result in unforeseen costs and could be delayed or terminated, which may have a material adverse effect on our business, results of operations and financial condition.

For human trials, patients must be recruited and each product candidate must be tested at various doses and formulations for each clinical indication. In addition, to ensure safety and effectiveness, the effect of drugs often must be studied over a long period of time, especially for the chronic genetic diseases that we will be studying. Many of our programs focus on diseases with small patient populations making patient recruitment and enrollment difficult. Insufficient patient enrollment in our clinical trials could delay or cause us to abandon a product development program. We may decide to abandon development of a product candidate or a study at any time due to unfavorable results, or we may have to spend considerable resources repeating clinical trials or conducting additional trials, either of which would increase costs and delay any revenue from those product candidates, if any.

Failure or delay in the commencement or completion of our clinical trials may be caused by several factors, including:

- slower than expected rates of patient recruitment, particularly with respect to trials of rare diseases such as nmCF;
- determination of dosing issues;
- unforeseen safety issues;

lack of effectiveness during clinical trials;

inability to monitor patients adequately during or after treatment;

inability or unwillingness of medical investigators and institutional review boards to follow our clinical protocols; and

lack of sufficient funding to finance the clinical trials.

We may find it difficult to recruit and enroll patients in our clinical trials, which could cause significant delays in the completion of such trials or may cause us to abandon one or more clinical trials.

Some of the diseases that our product candidates are intended to treat are rare and ultra-rare and we expect only a subset of the patients with these diseases will be eligible for our clinical trials. Because ELX-02 targets small populations and patient numbers have not been determined definitively, we must be able to identify patients in order to complete our development programs and commercialize ELX-02 successfully.

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In addition, the protocol for our clinical trials generally mandates that a patient cannot be involved in more than one clinical trial for the same indication. Therefore, subjects that participate in ongoing clinical trials for products that are competitive with our product candidates are not available to participate in our clinical trials. We cannot guarantee that any of our programs will identify a sufficient number of patients to complete clinical development and market our product candidates if approved. The combined number of patients in the United States, Japan and Europe and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with ELX-02, or new patients may become increasingly difficult to identify, all of which would adversely affect our results of operations and our business. An inability to recruit and enroll a sufficient number of patients for any of our current or future clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether, which could impact our ability to develop our product candidates and may have a material adverse effect on our business, results of operations and financial condition.

Because our clinical trials depend upon third-party researchers, scientists and consultants the results of our clinical trials and such research activities are subject to delays and other risks that are, to a certain extent, beyond our control, which could impair our clinical development programs and our competitive position.

We depend on independent investigators, consultants, researchers, medical experts, collaborators, chemists, toxicologist and a small number of medical institutions and third-party contract organizations to assist with our research efforts and conduct our preclinical and clinical trials and related activities. These collaborators, scientists, consultants and other third parties have provided, and we expect that they will continue to provide, valuable advice regarding our clinical development programs and product candidates. These collaborators, scientists, consultants and other third parties are not our employees, may have other commitments that would limit their future availability to us and typically will not enter into non-compete agreements with us. We cannot control the amount or timing of resources that they devote to our preclinical and or clinical development programs and they may not assign as great a priority to our preclinical or clinical development programs or pursue them as diligently as we would if we were undertaking such programs directly. If outside collaborators fail to devote sufficient time and resources to our preclinical and clinical development programs, or if their performance is substandard, the approval of anticipated NDAs and other marketing applications, and our introduction of new drugs, if any, may be delayed, which could impair our clinical development programs and would have a material adverse effect on our business and results of operations. The collaborators may also have relationships with other commercial entities, some of whom may compete with us and we may be unable to prevent them from establishing competing businesses or developing competing products. For example, if a key scientist acting as a principal investigator in any of our clinical trials identifies a potential product or compound that is more scientifically interesting to his or her professional interests, his or her availability to remain involved in our clinical trials could be restricted or eliminated, which may have a material adverse effect on our business, results of operations and financial condition.

We are subject to extensive governmental regulation including the requirement of FDA or comparable foreign regulatory authorities for approval of our product candidates before they can be marketed.

We, our product candidates, our suppliers, our contract manufacturers, our contract testing laboratories and our clinical trial sites and clinical trial researchers are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. Failure to comply with applicable requirements of the FDA or comparable foreign regulatory authorities could result in, among other things, any of the following actions:

warning letters;