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6 OVERVIEW OF NICOX'S ACTIVITIES

6.1 Main activities

6.1.1 Summary of the main activities of the Company

We are an international ophthalmology company developing innovative solutions to help maintain vision and improve ocular health. Our lead products and product candidates leverage our proprietary expertise in generating novel patentable molecules or new chemical entities, or NCEs, that release nitric oxide, or NO. NO is a small signaling molecule that plays a key role in the regulation of intraocular pressure, or IOP. Adding NO to well-known molecules, such as prostaglandin analogs, which is the most commonly prescribed class of IOP-lowering drugs, adds a second mechanism of action, or MOA and allows certain of our products and product candidates to lower IOP further than the parent molecule alone. VYZULTA®, based on our proprietary NO-donating research platform, has been approved by the U.S. Food and Drug Administration, or FDA, and is indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. VYZULTA is exclusively licensed worldwide to Bausch + Lomb, a Bausch Health Companies Inc. company, and has been commercialized in the U.S. since December 2017.

NCX 470, which is our lead proprietary development stage product candidate, was also developed through our proprietary NO-donating research platform. In preclinical studies, NCX 470 has demonstrated superior IOP lowering of up to 3.5 mmHg compared to its parent molecule, bimatoprost, which is an FDA-approved prostaglandin analog and the current market leader by sales in the U.S. If repeated in human studies, we believe that NCX 470 would be a clinically meaningful improvement over the current standard of care with the potential to become the leading firstline therapy for glaucoma. NCX 470 is in a Phase 2 clinical trial for the IOP lowering in patients with open-angle glaucoma or ocular hypertension, and we expect to report top-line data from this study in the fourth quarter of 2019.

NCX 4251, which is our second most advanced proprietary development stage asset, is in development for the treatment of acute exacerbations of blepharitis. Based on fluticasone, which is an FDA-approved corticosteroid with established efficacy and safety, we believe NCX 4251 to be the first targeted topical treatment for blepharitis in development that is designed to be applied directly to the eyelid, the location where the blepharitis disease and its related inflammation originates. With this novel route of delivery, NCX 4251 has the potential to minimize ocular adverse events often seen with steroid eye drops. The U.S. Investigational New Drug, or IND is in effect and a Phase 2 clinical trial for patients with acute exacerbations of blepharitis is planned, which is expected to report top-line data in the Q4 of 2019.

ZERVIATE™, previously AC-170, our second FDA-approved product, is indicated for the treatment of ocular itching associated with allergic conjunctivitis and has been exclusively licensed in the U.S.to Eyevance Pharmaceuticals LLC, or Eyevance, with a commercial launch in the U.S. by the partner expected for summer 2019 .

Our pipeline also includes the product candidate NCX 4280, previously AC-120, for relief of ocular redness and eyelid swelling due to morning ocular congestion, and the research programs targeting future generation NO donors, including NO-donating phosphodiesterase-5 (or PDE5) inhibitors and NO-donating soluble guanylate cyclase (or sGC) stimulators that combine NO-release with other mechanisms of actions (MOAs) to potentially lower IOP.

NO is a small signaling molecule that targets an enzyme, soluble guanylate cyclase, or sGC. NO plays a key role in the regulation of IOP either as a stand-alone molecule or linked with an another pharmaceutical agent. Release of NO and the subsequent activation of sGC is one of the mechanisms that leads to IOP lowering by these novel molecules. We believe that by designing our proprietary molecules with a dual mechanism-of-action, or MOA, we may be able to achieve improved IOP lowering compared to the parent compound alone.

Product candidates

NCX 470, generated from our proprietary NO-donating research platform, is our lead product candidate. NCX 470, which we believe is a new NCE, is a novel, second generation NO-donating prostaglandin analog formulated as an ophthalmic solution, which is currently in development for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Molecules from the first (VYZULTA) and second (NCX 470) generations of this technology lower IOP with dual MOA, which combines NO donation that activates sGC with prostaglandin analogs that activate

Prostaglandin F, or FP, receptors, to enhance their performance relative to the parent active compound. In NCX 470, our NO-donating research platform was applied to add an NO-donating group to bimatoprost. Bimatoprost (known by the brand name LUMIGAN) is a prostagladin analog and is the current market leader by sales value among all glaucoma therapies in the U.S. NCX 470's dual MOA is believed to lower IOP by improving the outflow of fluid from the eye through the primary, or conventional outflow route via trabecular meshwork by the NO activation of sGC as well as through secondary, or unconventional uveoscleral outflow route by bimatoprost activation of FP receptors. NCX 470 is currently in a Phase 2 clinical trial powered for both non-inferiority and superiority comparison to latanoprost. We expect to report top-line data from this study in the fourth quarter of 2019.

In-house research on novel future generation NO-donors is being conducted where NO is linked to pharmacologically active molecules with different MOAs including novel NO-donating PDE5 inhibitors, and we are also collaborating externally with Ironwood Pharmaceuticals, Inc., or Ironwood, regarding novel NO-donating sGC stimulators. Our research platform produced first and second generation NO-donating compounds, VYZULTA and NCX 470 respectively, that demonstrated greater IOP lowering than the parent prostaglandin analog, or PGA, compounds which is due to the additional lowering in IOP from the NO-donating MOA. We are therefore actively researching NO-donating compounds of different non-PGA pharmacological classes where we add NO donation to another MOA and thus potentially enhance their IOP lowering activity.

In addition to our NO-donating approved product and product candidates in research and development, our pipeline includes product candidates based on novel and proprietary formulations of well-established molecules that have previously been used in other indications and therapeutic areas, with the potential to offer novel treatments for various eye conditions.

NCX 4251, our novel patented ophthalmic suspension of fluticasone propionate nanocrystals, is being developed as the first targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis, a common eye condition characterized by eyelid inflammation. Fluticasone propionate, the active ingredient in NCX 4251, is a leading corticosteroid which has been marketed for more than 20 years for a number of indications, including asthma and allergic rhinitis, and it has an affinity for the glucocorticoid receptor approximately ten times greater than dexamethasone, a corticosteroid commonly used in ophthalmology. The U.S. IND is in effect and a first-in-human, randomized, placebo-controlled, Phase 2 clinical trial for patients with acute exacerbations of blepharitis is planned, which is expected to report top-line data in the fourth quarter of 2019.

NCX 4280, previously AC-120, is an ophthalmic solution that targets relief of ocular redness and lid swelling (also known as "puffy eyes") due to morning ocular congestion, and is being developed by Ora Inc., or Ora,under an exclusive worldwide license granted to Ora by us. Morning eyelid swelling is a common complaint of aging individuals, particularly women, and is a condition with a range of different causes. Ora plans to advance the clinical development of NCX 4280 and to subsequently sub-license this compound to a third party for future commercialization.

Products

Our lead commercial product, VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, represents the first FDA-approved drug developed through our proprietary NO-donating research platform. VYZULTA adds an NO-donating group to latanoprost, also known by the brand name XALATAN, a prostaglandin analog, which is a chemical structurally related to prostaglandins. Prostaglandin analogs are in a class of molecules used in ophthalmology to lower IOP and do so by activating FP receptors located on the surface of cells. In the U.S., prostaglandin analogs are the first line and the most prescribed pharmacotherapy class for the lowering of IOP in glaucoma patients. VYZULTA is the first prostaglandin analog approved by the FDA for the lowering of IOP with one of its metabolites being NO. NO further lowers IOP by increasing the outflow of fluid from the eye by a different mechanism from prostaglandin analogs via activation of sGC. Thus, VYZULTA possesses a dual MOA in a single molecule. We believe that prior to the FDA approval of VYZULTA, there were no other NO-donating products approved for the lowering of IOP in the U.S. In March 2012 we granted Bausch + Lomb the exclusive worldwide rights of VYZULTA which is commercialized in the U.S. by partner since December 2017.

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ZERVIATE™ (cetirizine ophthalmic solution), 0.24%, our second FDA-approved product, is a novel formulation of cetirizine developed and approved for the first time for topical application in the eye. ZERVIATE, which is indicated for the treatment of ocular itching associated with allergic conjunctivitis, is the first product for the topical treatment of ocular allergies to use cetirizine, the active ingredient in ZYRTEC, which has been marketed for over 20 years. We believe that the proven safety and efficacy of oral cetirizine currently recognized by physicians will encourage the adoption of ZERVIATE ophthalmic solution. In 2017, we granted Eyevance exclusive rights to commercialize ZERVIATE in the U.S. and transferred the New Drug Application, or NDA, to Eyevance Pharmaceuticals. The commercial launch of ZERVIATE by Eyevance in the U.S. is expected in summer 2019.

Ophthalmic Products Market

The current treatment landscape for open-angle glaucoma is dominated by two drug classes, topical prostaglandin analogs and topical beta-blockers, with various combinations introduced over the past 20 years. Since prostaglandin analogs began to replace topical beta-blockers as first line IOP-lowering agents in glaucoma in 1996, several have been approved and generic competition in the category is significant. In the U.S., prostaglandin analogs have nearly completely replaced beta-blockers as the the first line therapy. We believe that prior to the approval of VYZULTA, there had been no drugs with new MOAs approved in U.S. and European Union for the lowering of IOP since the launch of the first prostaglandin analog. This is a situation which we believe has resulted in a significant demand from eyecare providers for new MOAs to lower IOP in patients with glaucoma.

Allergic conjunctivitis is currently treated by both oral and topical antihistamines, with more serious cases requiring topical or even oral corticosteroids. The treatment regimens and molecules are well established and most oral antihistamines are now available as generics in the U.S., frequently without prescription, along with some topical antihistamines. Nevertheless new products in the field are necessary to expand the choices available to doctors and patients.

The blepharitis market is not well-defined as there are no products approved to specifically treat blepharitis. Topical steroids, antibiotics and their combinations are often prescribed to treat acute and chronic blepharitis. In addition to the pharmacotherapy, current standards of care include swabbing the eyelids with diluted soap solution.

Worldwide sales of pharmaceutical ophthalmic treatments reached $18.6 billion in 2017 and have grown at a rate of 3% annually since 2013, according to IQVIA Health Analytics. In the U.S. alone, ophthalmology sales reached $8.1 billion in 2017, growing at an average rate of 5% annually since 2013. With respect to our markets of focus, sales of drugs used to lower IOP in patients with glaucoma or ocular hypertension generated approximately $2.6 billion in the U.S.in 2017, growing at an annual rate of 9% since 2013 and representing 32% of the $8.1 billion total ophthalmic drug sales in the U.S. for 2017. While there are no approved treatments solely indicated for blepharitis, the combined sales of topical glucocorticoids and anti-infective treatments, both separately and as fixed dose combinations, which may be used to treat blepharitis are more than $500 million annually. Additionally, prescription topical treatments for ocular allergies generate approximately $600 million annually in the U.S.and do not include substantial sales of non-prescription and over-the-counter products used to alleviate symptoms of ocular allergies.

Our intellectual property portfolio consists of patents and pending patent applications related to composition of matter, pharmaceutical compositions and methods of use for our product candidates. We have patent protection for VYZULTA and ZERVIATE and our product candidates, NCX 470, NCX 4280 and NCX 4251, in the U.S.through 2025, 2032, 2029, 2030 and 2033, respectively. These dates do not include potential patent extensions which may be available to us. Specifically, we expect the U.S. patent for VYZULTA to be extended to 2030.

As of December 31, 2019 we had 34 employees, including personnel supporting our development operations in the U.S.and France, and research operations in Italy. Our headquarters is located in Sophia-Antipolis, Valbonne, France, and we have been listed on Euronext Paris (COX.PA) since 1999.

6.1.2 Our Competitive Strengths

We believe the following key competitive strengths are core to our ability to develop novel treatment solutions for our patients and become a leader in ophthalmology:

- Our clinical-stage pipeline, consisting of potential first-in-class and best-in-class therapies, targeting inadequately met or unmet medical needs within ophthalmology, including glaucoma and blepharitis;

- Our proven NO-donating research platform, which we believe provides a competitive advantage for the discovery of innovative product candidates for the lowering of IOP, as demonstrated by VYZULTA and NCX 470;

- Our portfolio of products approved for commercialization in the U.S., VYZULTA and ZERVIATE, both of which may potentially be able to obtain marketing approval in other countries where the data are sufficient for such approval;

- Our ability to identify and effectively advance additional product candidates, both through our internal discovery efforts and through possible in-licensing opportunities or acquisitions of additional ophthalmic products or product candidates that would complement our current product portfolio;

- Our proven ability to attract leading biopharmaceutical companies into successful partnerships, as demonstrated by our worldwide exclusive partnership agreement with Bausch + Lomb for VYZULTA;

- Our ability to successfully enter into commercialization partnerships, as demonstrated by our exclusive licensing agreement with Eyevance; and

- Our significant experience in ophthalmic drug discovery and development as well as extensive operational, financial and public company experience across both our management team and our board of directors. Our key executives and board members have held leadership roles within major pharmaceutical ophthalmology companies, including divisions of Alcon, Inc., Allergan, Inc., Novartis AG, Inspire Pharmaceuticals, Inc., Envisia Therapeutics, Parion Sciences, Inc. and ISTA Pharmaceuticals, Inc.

6.1.3 Our Strategy

Our goal is to become a fully integrated pharmaceutical company focused on the discovery, development and commercialization of novel ophthalmic therapeutics. Key elements of our strategy include:

- ***Rapidly advance our product candidates through clinical development in the U.S.*** Our pipeline includes NCX 470 for glaucoma, NCX 4251 for blepharitis.. We plan to develop and commercialize these product candidates internally in key markets such as the United States

- ***Optimize development through partnerships.*** In certain instances, as we've done with NCX 4280 with Ora, we may partner a program for exclusive development. In addition, we are seeking to optimize development of our product candidates outside of the U.S. through regional collaborations where we can leverage the resources of a partner, such as our partnership on NCX 470 with Ocumension in greater China.

- ***Expand our product candidate pipeline through internal drug discovery efforts and possible in-licensing activities or acquisitions of additional ophthalmic product candidates or products.*** We plan to maintain and expand our internal discovery efforts focused on enhancing our pipeline of novel ophthalmic assets based on NO release including NO-donating sGC stimulators, together with Ironwood, and NO-donating PDE5 inhibitors, as well as evaluating additional in-licensing or acquisition opportunities for additional ophthalmic candidates. We are collaborating with with Novaliq GmbH for the development and characterization of novel formulations for lead molecules of our NO-donating PDE5 inhibitor NCEs using their water-free enabling EyeSol® technology for IOP lowering.

- ***Leverage the royalty revenues from VYZULTA in the field of glaucoma, in partnership with Bausch + Lomb.*** Under the terms of our worldwide exclusive license agreement, Bausch + Lomb is responsible for commercialization activities. We are eligible to receive future net milestones and tiered net royalties from Bausch + Lomb of up to $150 million and 6% to 12%, respectively, after deduction of

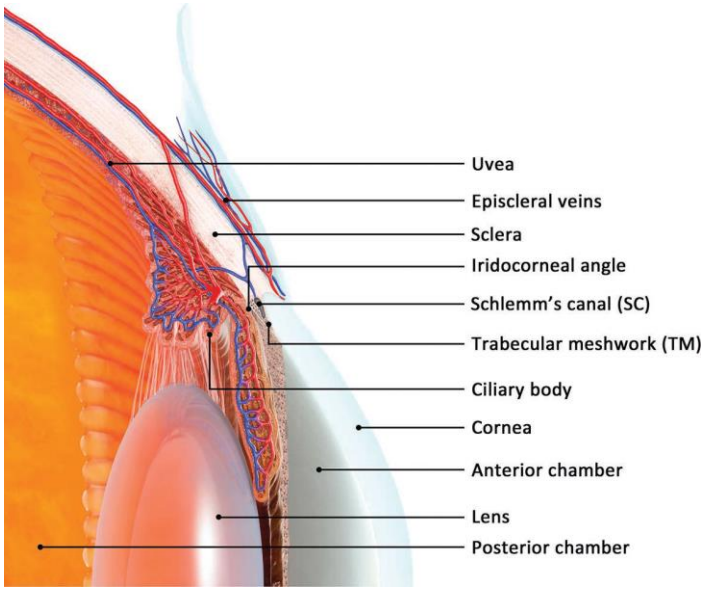
payments due to Pfizer under the 2009 agreement whereby we regained the rights to VYZULTA. We believe Bausch + Lomb's experience in commercialization of ocular products will allow us to realize significant benefits from this partnership.

- ***Maximize the value of ZERVIATE through partnering.*** In September 2017, we entered into an exclusive licensing agreement with Eyevance for the commercialization of ZERVIATE in the U.S. Similar to VYZULTA, we believe this strategy will allow us to efficiently use our internal resources while providing significant financial benefit. We are currently seeking partners capable of pursuing approval for and marketing ZERVIATE in countries outside the U.S..

6.1.4 Description of the Eye

The eye is a fibrous globe that must stay "inflated" with a fluid called aqueous humor on the front side of the eye adjacent to cornea and a gel called vitreous humor on the back side of the eye adjacent to retina, both of which are at the proper pressure to maintain the eye's shape and transparency so that the eye can effectively convey light through the cornea and the lens to the retina. To maintain the pressure inside the eye, and therefore its shape, the aqueous humor is constantly produced inside the eye by a tissue known as the ciliary body and flows forward through the pupil and into the angle defined by the front of the iris and the back of the cornea. Blockages or malfunctions in this drainage system can result in abnormally high IOP.

The picture below shows the cross section of the aqueous humor drainage system of the eye.



There are many diseases that can affect both the front and back of the eye. Diseases and conditions affecting the front of the eye are generally treated either with topical formulations that can be applied directly to the eye as drops or with surgery. Intravitreal injections are typically used to deliver medications to the back of the eye. Our current drug development efforts are focused on ocular diseases treated with topical solutions, with sustained release being investigated in our research efforts, with an emphasis on glaucoma.

6.1.5 Our Pipeline

Our ophthalmic pipeline features two products approved for commercialization by the FDA and product candidates in various stages of development and research. The following table summarizes key information about our approved products and product development programs:

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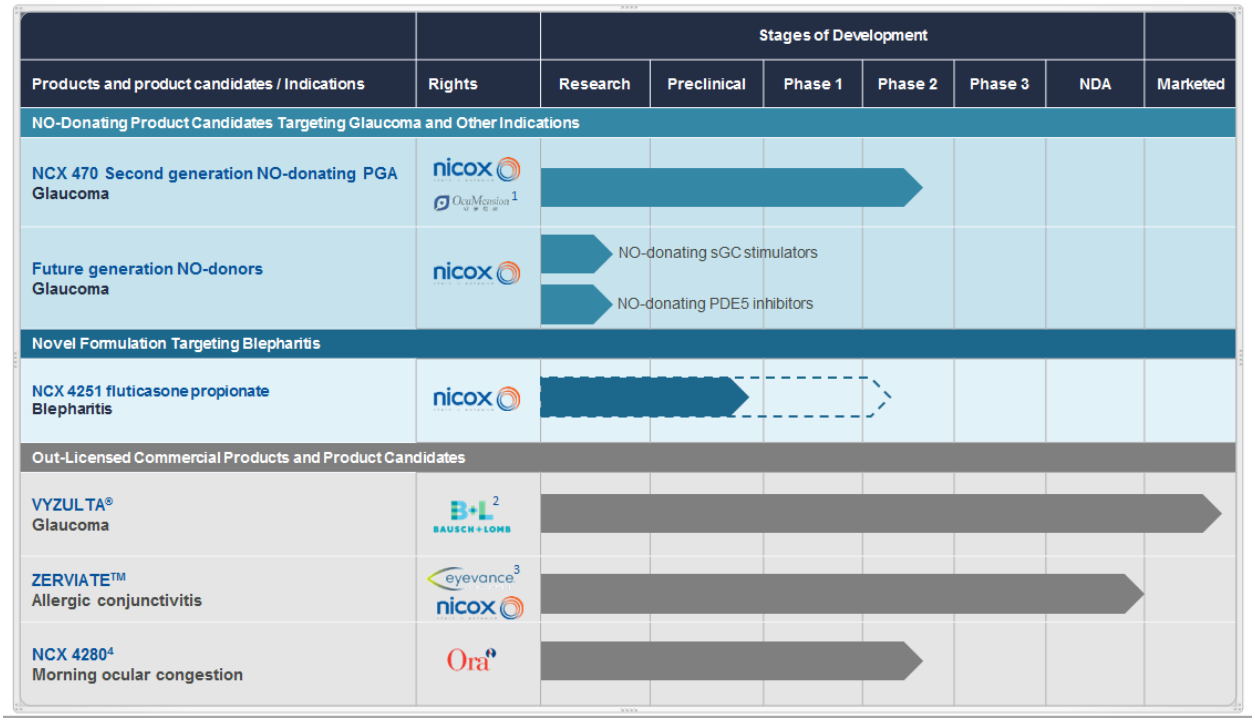

1. Exclusive licence agreement signed with Ocumension Therapeutics for development and commercialization of NCX 470 in the Chinese market. Nicox owns ex-China.
2. Bausch + Lomb, a Bausch Health Companies Inc. company
3. Eyevance has licensed exclusive U.S. rights for commercialization of ZERVIATE. Nicox owns ex-U.S. rights.
4. Previously AC-120

Overview

Our product candidate pipeline features clinical and preclinical stage assets based both on (i) our proprietary NO-donating research platform, principally targeting the lowering of IOP in open-angle glaucoma and ocular hypertension and (ii) novel and proprietary formulations of well-established molecules that have previously been used in other indications and therapeutic areas, with a potential to offer novel treatments in various eye conditions, in addition to two products approved for commercialization by the FDA.

Using NO in ophthalmology

We have developed a leading position in the therapeutic application of NO-donating molecules in ophthalmology. Our compounds are designed to release NO with a pharmacological benefit elicited locally at the tissue level via NO activation of sGC. Consistent with our strategic positioning in ophthalmology, our research platform is focused on eye conditions where NO has been shown to play an important role.

NO is a small signaling molecule whose target is an intracellular enzyme, sGC, which converts guanosine triphosphate to the second messenger, cyclic guanosine monophosphate (cGMP). The cellular machinery to synthesize endogenous NO is present in ocular tissues, together with other components involved in the NO-signaling cascade via the activation of sGC. The NO stimulated increase in the concentration of cGMP in the trabecular meshwork leads to the relaxation of the trabecular meshwork and, consequently, an increase in the outflow of the aqueous humor from the anterior segment of the eye through the conventional outflow pathway (i.e., via the trabecular meshwork, Schlemm's canal, aqueous veins, and episcleral veins). All of the foregoing events lead to lowering of IOP. The effect of NO in the sGC signaling cascade can be further increased or prolonged by sGC stimulators, which interact synergistically with NO to increase the concentration of cGMP. Additionally, the effect of NO can be further increased or prolonged by PDE5 inhibitors, which inhibit phosphodiesterase type-5, a key enzyme that degrades the second messenger, cGMP, to its inactive metabolite, 5'-guanosine monophosphate (GMP).

Studies have shown that topical administration of traditional NO donors, such as nitroglycerin or isosorbide mononitrate, reduces IOP, reinforcing the role of NO in IOP regulation. Lower plasma levels of NO markers are found in open angle glaucoma patients compared to individuals without glaucoma. Several studies conducted in animal models, as well as in glaucoma patients, have shown that the release of NO activates sGC and lowers IOP.

To-date, it has been established that NO plays a key role in the regulation of IOP either as a stand-alone molecule, or linked with another pharmaceutical agent. Release of NO and the subsequent activation of sGC is one of the mechanisms that leads to IOP-lowering by these novel molecules. We believe that by designing our proprietary molecules with a dual MOA, we may be able to achieve improved IOP lowering compared to the parent compound alone. Based on this approach, our partnered approved product VYZULTA and our product candidate NCX 470 currently in clinical development, are comprised of a parent PGA and a NO donor. The positive clinical Phase 2 and 3 results obtained with latanoprostene bunod, and the subsequent approval of VYZULTA by the FDA, demonstrate the potential of such dual MOA approach with our proprietary NO-donating research platform in ophthalmology. Apart from VYZULTA, there are currently no NO-donating molecules approved for ophthalmic indications in the U.S.

NO-donating research platform

We have developed a leading scientific and strategic position in the therapeutic application of NO-donating compounds, based on our proprietary NO-donating research platform. Using this proprietary expertise in generating novel, patentable molecules (new chemical entities or NCEs) that release NO, our research center has conducted lead generation, lead optimization and evaluation in preclinical studies covering various therapeutic areas such as cardiovascular, inflammation and ophthalmology, creating a significant patent portfolio.

In addition to the product candidates in our pipeline, we are actively researching NO-donating compounds of different chemical and pharmacological classes from those previously evaluated, both in-house and through our collaboration with Ironwood, in order to add NO donation to their existing MOA and thus potentially enhancing the IOP lowering . Some of these are new therapeutic agent classes targeting conventional outflow through the trabecular meshwork by combining NO release with other pharmacological actions. These new therapeutic agent classes include NO-donating sGC stimulators and NO-donating PDE5 inhibitors. We expect to be able to announce a preclinical candidate from one of these programs in the next 18 months.

Mechanism of action of NO and NO-donating prostaglandin analogs

Evidence suggests that prostaglandin analogs, which are indicated for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension, have a MOA via prostaglandin FP receptor activation with a primarily positive impact on the activity of certain enzymes, resulting in a widening of the interstitial spaces of the ciliary muscle and contributing to increased uveoscleral outflow of the aqueous humor. This pathway is referred to as the nonconventional or the secondary pathway. However, the conventional or the primary pathway, wherein aqueous humor exits the eye through the trabecular meshwork into Schlemm's canal (a circumferential vessel in the angle of the eye between the cornea and the iris that collects the aqueous humor from the anterior chamber and delivers it to the venous blood vessels) is believed to be a major limiting factor in aqueous humor outflow, and the flow through the conventional pathway is decreased in glaucoma. Prostaglandin analogs may have only a small impact on this pathway.

Because the conventional or primary pathway is known to be NO-sensitive, we sought to create a compound that would both release a prostaglandin analog to target the uveoscleral and secondary pathway by activating FP receptors and, at the same time, release NO to stimulate sGC to target the conventional or primary pathway in order to achieve a novel dual MOA. Through investigating this mechanism, latanoprostene bunod was discovered in our research center in Italy. Latanoprostene bunod (the active ingredient in VYZULTA) is an NO-donating version of an existing drug, latanoprost, which belongs to the category of prostaglandin F2-alpha analogs. Latanoprostene bunod is metabolized, after application on the ocular surface, into latanoprost acid and another moiety which is then further metabolized to release NO.

The picture below shows the uveoscleral outflow, the secondary or nonconventional outflow pathway that is prostaglandin sensitive, and the trabecular meshwork outflow, also known as the primary or conventional outflow pathway, which is NO-sensitive.

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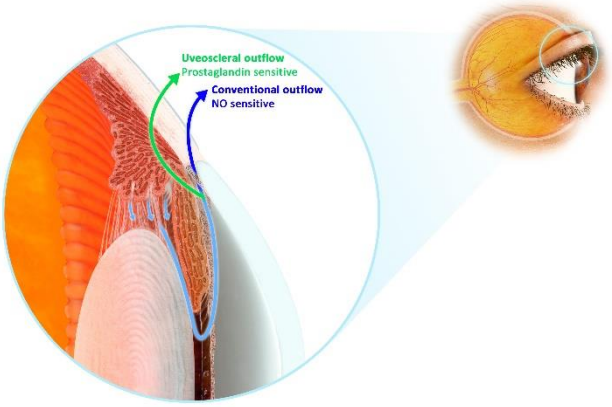

The preclinical and clinical data demonstrate that latanoprostene bunod lowers IOP to a greater extent than latanoprost alone in multiple animal models and in glaucoma patients. Our partner, Bausch + Lomb, conducted preclinical studies to investigate the effect of latanoprostene bunod on primary human trabecular meshwork cell contractility to determine whether latanoprostene bunod might mediate this additional IOP lowering through the conventional outflow pathway. Results from these preclinical studies support the concept that latanoprostene bunod has a dual MOA and may target both aqueous outflow pathways to lower IOP in patients with glaucoma or ocular hypertension. These data have been further substantiated in a Phase 2 clinical trial of latanoprostene bunod versus latanoprost conducted in glaucoma and ocular hypertension patients.

As mentioned above, NCX 470 and VYZULTA are designed to lower IOP in two different ways, or via two MOAs. Upon administration to the eye, NCX 470 and VYZULTA are transformed by certain enzymes present in the eye into the prostaglandin analogs, latanoprost acid and bimatoprost, respectively, and the NO-donating moiety. This NO-donating moiety is then further transformed, breaking down into NO and inactive organic compounds. The prostaglandin analog, one active component of NCX 470 and VYZULTA, is released in the eye and interacts with specific receptors (prostaglandin F2 alpha receptors). This interaction is thought to trigger signaling cascades that ultimately lead to rearrangement of the smooth ciliary muscle in the eye's middle layer, called the uvea, which in turn improves the outflow of the fluid present in the eye, or aqueous humor, from the fluid-filled chamber at the front of the eye backwards through the uvea and sclera (the white fibrous capsule of the eye). This outflow is referred to as the uveoscleral, unconventional or secondary outflow pathway. NO, the second active component released by NCX 470 and VYZULTA, is thought to enhance the outflow of the eye fluid by the conventional or primary outflow pathway, by modulating the eye tissues called the trabecular meshwork and changing the structure of a canal inside the eye known as Schlemm's canal. The released NO triggers signals leading to a decrease in cell contractility and volume and, thus, allowing an enhancement of the conventional outflow pathway.

The figure below illustrates these MOAs:

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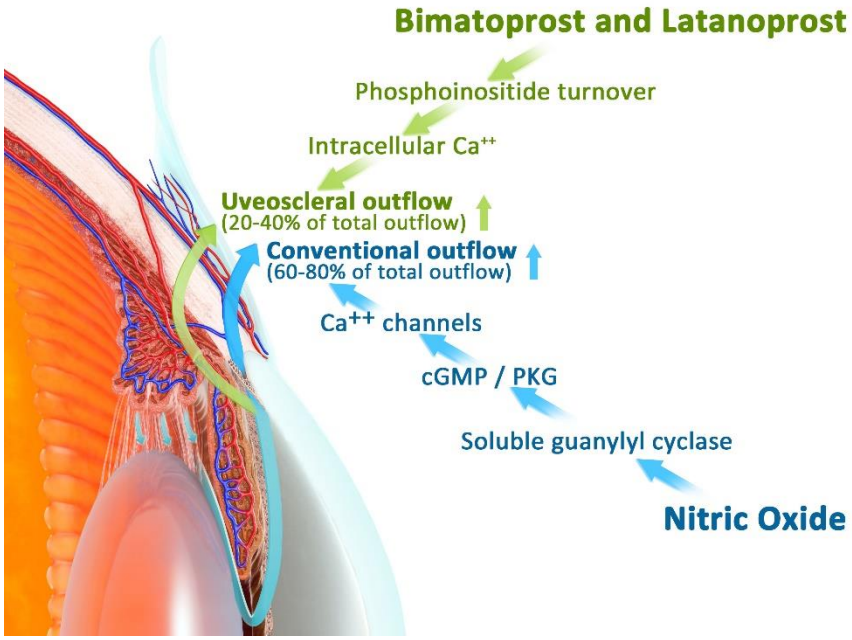

Glaucoma Overview

Glaucoma is a group of ocular diseases in which the optic nerve is injured, leading to peripheral and, ultimately, central visual field loss. Glaucoma can eventually progress to blindness if not treated and is currently considered to be the second leading cause of irreversible blindness worldwide. Glaucoma is frequently linked to abnormally high IOP due to blockage or malfunction of the eye's aqueous humor drainage system in the front of the eye. Current medications are targeted at lowering IOP to slow the progression of the disease. Numerous eye drops are available to either decrease the amount of fluid produced in the eye or improve its flow out of the eye. Nearly half of all patients with open-angle glaucoma require more than one medication to lower their IOP to a target level at which visual field loss is likely to be minimized or halted. The requirement for multiple medications to lower an individual patient's IOP to their target level highlights the need for more effective treatments.

Abnormally high IOP does not usually cause any symptoms, except in cases of acute angle closure where the IOP may rise to three or four times that of normal IOP, but can lead to optic nerve damage and vision loss if left untreated. Optic nerve damage and vision loss can also occur in patients with normal IOP who are also treated with IOP lowering medications. The Normal Tension Glaucoma Study completed in 1998 showed that lowering IOP slowed the progression of normal-tension glaucoma, a form of glaucoma where the patient's IOP is within normal ranges. IOP lowering is associated with a decreased risk in progression to open-angle glaucoma in subjects with ocular hypertension, as well as progression of visual field loss in patients with open-angle glaucoma; every mmHg of IOP-lowering results in a risk reduction in open-angle glaucoma progression of approximately 10% to 20%. Patients with open-angle glaucoma who attain target IOP-lowering have a lower risk of disease progression and vision loss.

In 2017, worldwide sales of treatments targeting glaucoma were $5.0 billion representing 27% of the $18.6 billion worldwide market for ophthalmic drugs. In the U.S., sales of treatments targeting glaucoma totaled $2.6 billion in 2017 (36 million prescriptions) or 32% of the $8.1 billion U.S. market for ophthalmic drugs. Of the U.S. sales of treatments targeting glaucoma, $1.3 billion, or approximately 50%, were sales of prostaglandin analogs, of which more than 90% were the branded products LUMIGAN and TRAVATAN Z. Over 70% of the prostaglandin analog prescriptions are for generic latanoprost.

Currently, it is estimated that 3.5% of the worldwide population between 40 and 80 years of age are affected by the most common forms of glaucoma, and it is estimated that, in 2017, 36.1 million prescriptions were written in the U.S. annually for glaucoma drugs.

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Product Candidates in our Pipeline

NCX 470—Our Lead Product Candidate

NCX 470, which we believe is an NCE, is formulated as an ophthalmic solution of this novel second generation NO-donating prostaglandin analog in development for the lowering of IOP in patients with open-angle glaucoma and ocular hypertension. NCX 470 is designed to release both bimatoprost and NO following instillation into the eye. Bimatoprost, marketed under the brand name LUMIGAN by Allergan, Inc., is the leading product in the class of prostaglandin analogs, the most widely used class of drugs for IOP-lowering in patients with open-angle glaucoma and ocular hypertension. Bimatoprost is generally considered to be slightly better at lowering IOP than latanoprost. We believe that NCX 470 has the potential for greater IOP lowering activity than either bimatoprost or VYZULTA, given bimatoprost's efficacy profile and the NO-mediated activity.

In rabbit, dog and non-human primate preclinical models of IOP, our data demonstrate that NCX 470 is able to lower IOP more than bimatoprost alone (up to 3.5 mmHg greater lowering of IOP with NCX 470 as compared with bimatoprost 0.03% in dog and non-human primate preclinical models) when tested with equimolar solutions (or solutions containing equivalent numbers/concentrations of molecules). Additionally and notably, in the preclinical model of ocular hypertension in rabbits in which bimatoprost did not have an effect on IOP, NCX 470 appeared to lower IOP, with up to 8.4 mmHg IOP lowering due to NO alone, suggesting that its NO-donating part of the molecule produces an IOP-lowering action. We believe translation of this treatment effect from preclinical to clinical domain would result in a disruptive and differentiated IOP lowering therapy.

Based on the positive Phase 3 results, the recent FDA approval and commercialization of VYZULTA, and the increased interest in the potential of NO donors in ophthalmology, we have selected NCX 470 as the lead follow-on glaucoma candidate for internal development.

We initiated a Phase 2 clinical trial of NCX 470 in the third quarter of 2018, which consists of a multi-center, double-masked, 28-day, parallel group, dose-response study in patients with open-angle glaucoma or ocular hypertension. Multiple doses of NCX 470 are being compared to latanoprost 0.005%. In this study patients at clinical sites across the U.S.will be randomized in a 1:1:1:1 ratio to receive one of the three concentrations of NCX 470 (0.021%, 0.042% or 0.065%) or the active comparator latanoprost 0.005%, with approximately 105 patients per each of the four arms. The primary efficacy endpoint of the study is the change from baseline in mean diurnal IOP after 28 days of treatment, with the overall objective being to identify the appropriate dose of NCX 470 to be advanced into Phase 3 studies. The study is powered for non-inferiority and superiority comparison versus latanoprost. We expect to report top-line data from the study in the fourth quarter of 2019.

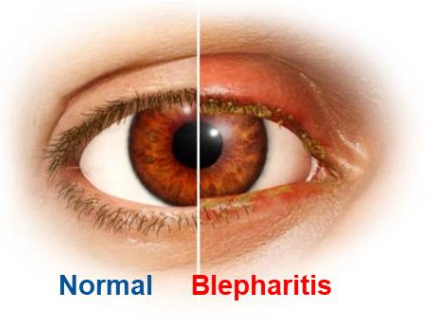
NCX 4251

Another of our product candidates, which leverages an established molecule is NCX 4251, a novel patented ophthalmic suspension of fluticasone propionate nanocrystals which is being developed as the first targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis. Blepharitis is a common eye condition characterized by eyelid inflammation. It is being developed for application via a swab at the eyelid margin, applied directly to the site of inflammation thereby minimizing potential penetration of the drug through the cornea which can lead to the damaging side effects such as IOP increase found with current topical steroids.

Blepharitis Overview

Blepharitis is a condition in which the margins of the eyelids become red and swollen and may contain dandruff-like matter, as shown in the picture below, and occurs in two forms. Anterior blepharitis affects the outside front of the eyelids, where the eyelashes are attached, and is most commonly caused by bacteria, demodex (a tiny mite that lives in or near hair follicles) and scalp dandruff. Posterior blepharitis affects the inner edge of the eyelids, the moist part which makes contact with the tear film of the eye, and is most commonly caused by problems with certain eyelid oil glands, or meibomian glands. Acne, rosacea and scalp dandruff can also cause posterior blepharitis.

An example of the condition is shown in the picture below:



Blepharitis often coexists with other related conditions, such as dry eye, with an incidence that is similar to or higher than dry eye in evaluations of symptomatic patients (24% incidence of blepharitis versus 21% incidence of dry eye). It is believed that in patients with both blepharitis and dry eye, an improvement in blepharitis may lead to an improvement of the dry eye disease. Blepharitis is difficult to study and there is little consensus on the prevalence of the disease. Studies show, however, that blepharitis is one of the most common conditions encountered in clinical practice. Of patients seen by ophthalmologists and optometrists, 37% and 47%, respectively, present with signs of the disease.

There is currently no FDA-approved prescription product solely indicated for blepharitis, which limits our ability to estimate prevalence and market size. Treatment options include lid scrubs, topical ophthalmic steroids, topical ophthalmic antibiotics and topical ophthalmic antibiotic/steroid combinations. The annual U.S. revenues for products prescribed for blepharitis among these three categories total more than $500 million according to IQVIA Health Analytics. Surveys reveal that ophthalmologists consider anti-inflammatory activity to be the most important product attribute when selecting a treatment for blepharitis, which supports the development of NCX 4251.

Fluticasone propionate, the active ingredient in NCX 4251, which has not previously been approved in a topical formulation for use in ophthalmology, has an affinity for the glucocorticoid receptor which is approximately ten times greater than dexamethasone, a corticosteroid commonly used in ophthalmology. Fluticasone propionate is a glucocorticoid with potent anti-inflammatory properties that has been approved in numerous drug products over the past 20 years for the treatment of various indications including dermatology, rhinitis and asthma.

Similar to ZERVIATE, we intend to seek regulatory approval for NCX 4251 using the FDA's Section 505(b)(2) regulatory pathway, which enables us to rely, in part, on the FDA's prior findings of safety and efficacy for fluticasone propionate, or published literature, in support of our NDA.

The IND is in effect and a first-in-human, randomized, placebo-controlled, Phase 2 clinical trial evaluating the safety and efficacy of NCX 4251 versus a placebo in subjects with acute exacerbations of blepharitis is planned. This multi-center, dose-response study will be conducted in the U.S. The overall objective of the study is to identify the dose we will advance into further development. We expected to report top-line data in the fourth quarter of 2019.

Research programs

Future generation NO-donors

We are focusing our research efforts on ocular disorders where NO plays a major role as a modulator, including glaucoma and ocular hypertension. Our research platform produced first and second generation NO-donating compounds, VYZULTA and NCX 470, that demonstrated greater IOP lowering than the parent PGA compounds, which is due to the additional lowering in IOP from the NO-donating MOA. We are applying key learnings, based on Nicox stand-alone NO-donors, to NO-donating moieties attached to other non-PGA therapeutic classes of compounds.

We are therefore actively researching NO donating compounds of different, non-PGA chemical and pharmacological classes to add NO donation to another MOA and thus to potentially enhance their IOP lowering activity.

Some of these are new therapeutic agent classes directly target primary outflow by combining NO release with other pharmacological actions. These new therapeutic agent classes include NO donating sGC stimulators, in collaboration with Ironwood, and NO donating PDE5 inhibitors.

In December 2018 we refocused our research activities on these compounds, including entering into a research collaboration on our NO-donating PDE5 inhibitors with Novaliq. We expect to be able to announce a preclinical candidate from one of these programs in the next 18 months.

Our Out-Licensed Commercial Products and Product Candidate

VYZULTA®—Our Lead Commercial Product

Overview

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024% is a prostaglandin analog with one of its metabolites being NO. VYZULTA is the first eye drop approved in the past twenty years with a novel approach to reduce intraocular pressure (IOP). VYZULTA was approved by the U.S. FDA in November 2017 for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Bausch + Lomb, a leading eye health company, has exclusive worldwide rights to develop and market VYZULTA and has been commercializing it in the U.S.since December 2017. VYZULTA was approved in Canada in late December 2018.

VYZULTA has demonstrated a greater IOP lowering and a comparable safety profile compared with two currently available medications, latanoprost and timolol, for the lowering of IOP in open-angle glaucoma or ocular hypertension in a Phase 2 clinical trial and two Phase 3 clinical trials.

We believe there is an unmet need for products with improved IOP lowering in the glaucoma market. We believe that VYZULTA offers a differentiated treatment based on:

- **Superior IOP-Lowering**—In the Phase 3 clinical trials, VYZULTA dosed once daily demonstrated statistically significant greater IOP lowering than twice-daily dosed timolol maleate ophthalmic solution 0.5% throughout the day at three months of treatment. Based on analysis of the pooled results of these trials, the IOP lowering from baseline was in the range of 7.5-9.1 mmHg across three months of treatment. In the 413 subject Phase 2 randomized trial, VYZULTA demonstrated statistically significantly greater IOP lowering than latanoprost ophthalmic solution, 0.005% after four weeks of treatment.

- **Novel Dual Mechanism of Action**—VYZULTA is the first prostaglandin analog approved by the FDA for the lowering of IOP with one of its metabolites being NO and the only once-daily single-agent IOP-lowering product to provide activity through two distinct MOAs that are mediated by a prostaglandin and NO.

- **Favorable Tolerability Profile**—In the Phase 3 clinical trials, 562 patients were exposed to the drug. VYZULTA administered once a day in the evening was well tolerated with no serious adverse events.

With VYZULTA, increased pigmentation of the iris and eyelid can occur with iris pigmentation likely to be permanent. Gradual changes to eyelashes, including increased length, increased thickness and number of eyelashes, can occur and are usually reversible upon discontinuation of treatment. The most common ocular adverse reactions are conjunctival hyperemia, eye irritation, eye pain and instillation site pain.

Summary results from the pivotal Phase 3 trials conducted by Bausch + Lomb

In January 2013, Bausch + Lomb initiated a program of Phase 3 trials, including two separate randomized, multicenter, double-masked, parallel-group non-inferiority clinical trials. These two studies, LUNAR and APOLLO, were designed to compare the efficacy and safety of VYZULTA administered once daily in the evening, against timolol maleate ophthalmic solution 0.5%, a non-selective beta-adrenergic receptor blocking agent, administered twice daily, in lowering IOP in subjects with open-angle glaucoma or ocular hypertension. Subjects were randomized, two to one, to either

VYZULTA or timolol. The primary efficacy endpoint of both trials, which included a combined total of 840 subjects, was the mean IOP in the subjects' study eye measured at specified time points during three months of treatment. Specifically, IOP was measured at nine time points: 8 a.m., 12 p.m. and 4 p.m. at two weeks, six weeks and three months post-randomization. Secondary efficacy endpoints included the proportions of subjects with IOP less than or equal to 18 mmHg consistently at all nine time points and IOP lowering greater than or equal to 25% from baseline consistently at all nine time points. The Phase 3 trials were intended to support the basis for FDA approval and were conducted in North America and Europe.

The primary efficacy objective of statistical non-inferiority of VYZULTA to timolol maleate 0.5%, based on mean IOP, was achieved in both Phase 3 trials. This mean IOP-lowering also met the studies' criteria for statistical superiority over timolol at most timepoints in both trials, with the exception of the first assessment time point in LUNAR. Additionally, in a combined analysis of both studies, VYZULTA showed a lowering in IOP over the three months in the range of 7.5 to 9.1 mmHg from baseline. VYZULTA also showed positive results on a number of secondary endpoints. There were no treatment-related serious adverse events in either study for VYZULTA. Results for the individual studies are described below.

Results of the pooled analysis of the Phase 3 LUNAR and APOLLO studies conducted by Bausch + Lomb

A pooled analysis of the LUNAR and APOLLO, randomized, multicenter, double-masked, parallel-group, non-inferiority studies, each with open-label safety extension phases has been published (Weinreb, 2018). Patients with open-angle glaucoma or ocular hypertension were randomized 2:1 to treatment with latanoprostene bunod, or LBN, once daily or timolol twice daily for 3 months followed by open-label LBN treatment for 3 (LUNAR) or 9 (APOLLO) months. Of the 840 subjects randomized, 92% completed the efficacy phase, and 88% completed the safety extension phase. Mean IOP was significantly lower with LBN versus timolol at all 9 evaluation timepoints during the efficacy phase ($P< 0.001$). A significantly greater proportion of LBN-treated subjects attained a mean IOP $\leq$ 18mmHg and IOP lowering $\geq$ 25% from baseline versus timolol-treated subjects ($P< 0.001$). The IOP lowering with LBN was sustained up to one year; subjects crossed over from timolol to LBN experienced additional significant IOP lowering ($P\leq0.009$). Both treatments were well tolerated, and there were no safety concerns with long term LBN treatment.

Results of the APOLLO Phase 3 study conducted by Bausch + Lomb

Of 420 randomized subjects, 387 completed the three-month efficacy follow-up (VYZULTA, n=264; timolol 0.5%, n=123). At all nine timepoints, the mean IOP in the study eye was significantly lower with VYZULTA (range 17.8-18.7 mmHg) than with timolol (range 19.1-19.8 mmHg) ($p\leq0.002$). This was the primary endpoint. At all nine time points, the mean change from baseline in mean IOP was also significantly greater with VYZULTA (range, −7.7 to −9.1 mmHg) than with timolol (range, −6.6 to −8.0 mmHg; all $p\leq 0.002$) and the difference in mean IOP between treatments exceeded 1 mmHg at all time points. The percent of subjects with average IOP less than or equal to 18 mmHg or IOP lowering greater than or equal to 25% at all nine time points was higher in the VYZULTA group than in the timolol group (mean IOP $\leq$18 mmHg: 22.9% vs. 11.3%, p=0.005; IOP lowering $\geq$25%: 34.9% vs. 19.5%, p=0.001). Of the VYZULTA treated subjects, 13.4% had one or more ocular treatment-emergent adverse events in the study eye during the double-masked period, with the most common ocular event being eye irritation (3.9%). The most common ocular treatment-emergent adverse events in the study eye for the timolol treated subjects were eye irritation and eye pain (2.2% each). No clinically relevant findings were reported for tolerability, visual acuity or vital signs.

In this study, following three months of once-daily administration, VYZULTA demonstrated statistical superiority under the study's superiority criteria to timolol 0.5% administered twice a day in subjects with open-angle glaucoma or ocular hypertension based on the mean IOP in the study eye at all time points.

Results of the LUNAR Phase 3 study conducted by Bausch + Lomb

Of 420 randomized subjects, 387 completed the three-month efficacy phase (VYZULTA, n=259; timolol 0.5%, n=128). The mean IOP in the study eye was significantly lower in the VYZULTA group than in the timolol 0.5% group at the majority of timepoints measured. This was the primary endpoint. At eight out of the nine time points, the change from baseline in IOP was greater with VYZULTA (range, −7.5 to −8.8 mmHg) than with timolol (range, −6.6 to −7.9 mmHg)

and statistically significant ($p \leq 0.025$) at all but the first time point in the study (the second week, at 8 a.m., p=0.216). The percentage of subjects with IOP lowering greater than or equal to 25% at all nine time points was significantly higher in the VYZULTA group than in the timolol group (31.0% vs. 18.5%, p=0.007). However, the percentage of subjects with mean IOP less than or equal to 18 mmHg was not significantly different between the two groups (17.7% vs. 11.1%, p=0.084). Of the VYZULTA subjects, 23.8%, versus 13.3% of timolol subjects, had one or more ocular treatment-emergent adverse events in the study eye during the double-masked treatment period. The most common adverse event for VYZULTA was conjunctival hyperemia (9.0%) whereas the most common adverse event with timolol was eye irritation (4.4%). No clinically relevant findings were reported for ocular signs, tolerability, visual acuity or vital signs.

In this study, VYZULTA administered once a day in the evening was well tolerated and generally demonstrated statistical superiority under the study's superiority criteria, to timolol 0.5% administered twice a day in subjects with open-angle glaucoma or ocular hypertension based on the mean IOP in the study eye.

Results of the Phase 2 study conducted by Bausch + Lomb

Bausch + Lomb conducted a randomized, investigator-masked Phase 2 study called VOYAGER to determine most effective drug concentrations of latanoprostene bunod in the treatment of elevated IOP to facilitate further clinical development and to compare VYZULTA head-to-head with latanoprost ophthalmic solution, 0.005%.

The study enrolled 413 subjects across 23 sites in the U.S. and Europe. Subjects were randomized to receive either latanoprostene bunod at various concentrations or latanoprost ophthalmic solution, 0.005% once a day in the evening for 28 days.

The Phase 2 study met its primary efficacy endpoint and showed positive results on certain secondary endpoints for the two higher doses tested. The primary efficacy endpoint was the reduction from baseline in average daytime IOP on day 28. The 0.024% and 0.040% doses showed statistically significant $p<0.01$ greater day time IOP lowering from baseline compared with latanoprost at a dose of 0.005% at day 28, with the difference for the 0.024% dose reaching greater than 1 mmHg (statistical significance: $p<0.01$).

The most efficacious dose, the 0.024% dose, of latanoprostene bunod also showed positive results on certain secondary endpoints, including significantly greater reduction of mean daytime IOP at two out of three timepoints on day 28, translated by 42% of the patients with a better diurnal IOP reduction of at least 2mmHg compared to lanatoprost 0.005%,as well as a statistically significant greater percentage of responders than latanoprost ophthalmic solution 0.005%, defined as subjects achieving a mean daytime IOP of 18 mmHg or less. The responder rate was nearly 70% for the 0.024% dose of latanoprostene bunod on day 28, compared to less than 50% for latanoprost 0.005% (p=0.05).

The safety assessment indicated that latanoprostene bunod at concentrations from 0.006% to 0.040% dosed once daily for 28 days was well tolerated in patients, although associated with slightly more treatment-emergent ocular adverse events overall in the 0.040% treatment group compared to lower concentrations and the latanoprostene bunod groups, regardless of dose, compared to latanoprost. Hyperemia, or eye reddening, a common adverse event of ocular hypotensive treatment, did not appear to differ substantially across treatments. Local ocular pain after instillation, occurring more frequently with latanoprostene bunod treatments, did not affect compliance.

Additional Phase 2 study conducted by Bausch + Lomb

Bausch + Lomb conducted a supplementary Phase 2 study called CONSTELLATION to study the effect of VYZULTA on daytime and nighttime IOP lowering over a 24-hour period, and notably overnight. The objective of the study was to compare the effect of VYZULTA given once daily in the evening with timolol maleate ophthalmic solution 0.5% twice a day in lowering daytime IOP measured over a 24-hour period in subjects with open-angle glaucoma or ocular hypertension. This was a randomized, single-center, open-label, eight-week study with crossover at four weeks, in 25 randomized subjects, of which 21 completed the study, at the University of California, San Diego. Subjects were randomized to receive either VYZULTA once a day or timolol maleate 0.5% twice a day for four weeks and were crossed over to the alternate treatment for another four weeks. IOP and arterial blood pressure were measured every two hours for 24 hours at the baseline, week four and week eight study visits.

While both treatments lowered mean diurnal IOP compared to baseline (p<0.001), VYZULTA lowered mean supine nocturnal IOP compared to baseline (p=0.002). In addition, treatment with VYZULTA resulted in significantly greater ocular perfusion pressure, or OPP, compared to baseline during the diurnal period and compared to timolol during the nocturnal period (p=0.010). The OPP results for VYZULTA were not significant compared to timolol during the diurnal period and compared to baseline during the nocturnal period. Low OPP has been implicated as a risk factor for glaucomatous damages. In this study, VYZULTA lowered IOP without any negative effects on average arterial pressure, leading to a greater OPP compared to baseline during the day. VYZULTA also resulted in greater nocturnal OPP compared to timolol, reflecting the smaller effect of timolol on IOP lowering combined with some lowering in mean arterial blood pressure for the timolol group, though this lowering was not significant. The ability of VYZULTA to improve OPP together with continued IOP lowering over a 24-hour period may be of benefit in the management of patients with open-angle glaucoma or ocular hypertension. Further exploration of these effects in a larger study with adequate statistical powering may be warranted as this was a small study with inadequate statistical power. However, Bausch + Lomb is not currently seeking approval of VYZULTA for the lowering of OPP. Accordingly, they will not be able to promote VYZULTA for this use.

Japanese trials conducted by Bausch + Lomb

Bausch + Lomb has initiated development of VYZULTA in Japan, including completing a Phase 1 clinical trial called KRONUS in 2013. We believe that another, confirmatory efficacy study will be required for the registration of VYZULTA in Japan.

KRONUS was a single-arm, single-center, open-label, clinical study of 24 healthy Japanese male volunteers. The objective of the study was to evaluate the effect of VYZULTA in lowering IOP over 24 hours in healthy Japanese subjects. A baseline 24-hour profile was established by measuring IOP in both eyes every two hours between 8 p.m. and 4 a.m. and again at 8 a.m., 10 a.m., 12 p.m. and 4 p.m. IOP was then measured at the same nine time points after 14 days of treatment with VYZULTA administered once daily in the evening. The measurements indicated that VYZULTA significantly lowered mean IOP in healthy Japanese subjects at all timepoints, and lowered mean 24-hour IOP from 13.6 to 10.0 mmHg in the study eye, corresponding to a 27% lowering in mean 24-hour IOP.

These results suggest the potential of this compound to provide 24-hour IOP lowering to glaucoma patients not only with elevated IOP, but also with normal IOP. Studies of VYZULTA in subjects diagnosed with normal tension glaucoma are warranted.

Bausch + Lomb also completed a long-term safety Phase 3 clinical trial called JUPITER in Japanese subjects with open-angle glaucoma or ocular hypertension, the results of which were submitted as supportive safety data in the NDA. In this study, VYZULTA was well-tolerated with no serious treatment-related adverse events. Overall, 58.5% of the subjects experienced at least one treatment-emergent ocular adverse event in the study eye, and 47.7% subjects experienced at least one treatment-related ocular adverse event in the study eye. Common ocular treatment-emergent adverse events in the study eye included conjunctival hyperemia (17.7%), growth of eyelashes (16.2%), eye irritation (11.5%), eye pain (10.0%), iris hyperpigmentation (3.8%) and blepharal pigmentation (3.1%). During this study, no subjects had severe conjunctival hyperemia at any time point. In addition to evaluating safety, IOP lowering was assessed in this single-arm, open-label study of Japanese subjects with open-angle glaucoma or ocular hypertension. Results showed that the mean baseline IOP of 19.6 mmHg for the study eye was significantly lowered by 22% to 15.3 mmHg by week 4 of treatment with VYZULTA administered once daily in the evening. Reductions in IOP of greater than 22% were maintained at every subsequent visit through 12 months with a mean IOP of 14.4 mmHg at 12 months (N=121).

ZERVIATE™

Overview

ZERVIATE, the brand name for our cetirizine ophthalmic solution, 0.24%, is a novel formulation of cetirizine developed and approved for the first time for topical application in the eye. Cetirizine, the active ingredient in ZYRTEC, is a second generation antihistamine (H1 receptor antagonist) that binds competitively to histamine receptor sites. Cetirizine, in approved oral formulations, has a well-characterized systemic efficacy and safety profile with world-wide

exposure resulting from 20 years of oral use. We developed ZERVIATE as the first and only formulation of cetirizine for topical application in the eye. In May 2017, the FDA approved the NDA for ZERVIATE for the treatment of ocular itching associated with allergic conjunctivitis.

In September 2017, we entered into an exclusive licensing agreement with Eyevance for the commercialization of ZERVIATE in the U.S. where a commercial launch by Eyevance is expected ine summer 2019 subject to completion of the pre-commercial launch manufacturing activities and regulatory approval, certain elements of which are managed and paid for by us.

The efficacy of ZERVIATE was established in three Phase 3 trials that were randomized, double-masked, placebo-controlled, conjunctival antigen challenged clinical trials in subjects with a history of allergic conjunctivitis. Onset and duration of action were evaluated in two of these trials, and patients treated with ZERVIATE demonstrated statistically and clinically significantly less ocular itching compared to its vehicle at 15 minutes and 8 hours after treatment ($p<0.05$).

Regulatory approval for ZERVIATE was obtained via the FDA's Section 505(b)(2) regulatory pathway, which enabled us to rely, in part, on the FDA's prior findings of safety and efficacy for cetirizine and the published literature in support of our NDA.

Allergic Conjunctivitis Overview

Allergic conjunctivitis occurs when an allergic reaction causes conjunctivitis. Conjunctivitis is an inflammation of the thin layer of tissue that lines the outside of the white surface of the eye and the inner surface of the eyelids. It may affect one or both eyes. The signs and symptoms may include eye redness, excessive watering, itchy burning eyes, discharge, blurred vision and increased sensitivity to light.

It is estimated that more than 75 million people suffer from allergic conjunctivitis in the U.S. and the estimated prevalence of allergic conjunctivitis may be between 15% and 40%. The annual U.S. market for prescription treatment of allergic conjunctivitis totals approximately $600 million according to IQVIA Health Analytics, which does not include substantial sales of over-the-counter eye drops that we believe are less effective. Branded prescription products represent around 70% market share by value.

Clinical Data

As summarized above, the efficacy of ZERVIATE was established in three Phase 3 trials that were randomized, double-masked, placebo-controlled clinical trials in subjects with a history of allergic conjunctivitis, using the Ora Conjunctival Allergan Challenge, or CAC, model to evaluate ocular itching. Onset and duration of action were evaluated in two of these trials in which subjects were randomized to receive ZERVIATE or vehicle ophthalmic solutions. Subjects were evaluated with an ocular itching severity score ranging from 0 (no itching) to 4 (incapacitating itch) at several time points after CAC administration.

The following table displays data from the mean ocular itching ZYRTEC severity scores after ocular administration of an antigen using the CAC model. Approximately a one-unit difference compared to the vehicle is considered a clinically meaningful change in the ocular itching severity score.

	Study 1				Study 2			
	15 minutes post-treatment		8 hours post-treatment		15 minutes post-treatment		8 hours post-treatment	
Statistics	**ZERVIATE N=50**	**Vehicle N=50**	**ZERVIATE N=50**	**Vehicle N=50**	**ZERVIATE N=51**	**Vehicle N=50**	**ZERVIATE N=51**	**Vehicle N=50**
3 Minute Post-CAC Mean	1.00	2.38	1.76	2.69	1.01	2.54	1.94	2.86
Treatment Difference (95% CI)(1)	−1.38 (−1.72, −1.05)*		−0.93 (−1.26, −0.61)*		−1.53 (−1.92, −1.15)*		−0.92 (−1.25, −0.58)*	
5 Minute Post-CAC Mean	1.18	2.43	1.85	2.74	1.17	2.51	2.03	2.94
Treatment Difference (95% CI)(1)	−1.25 (−1.58, −0.91)*		−0.89 (−1.24, −0.54)*		−1.34 (−1.71, −0.97)*		−0.90 (−1.23, −0.57)*	
7 Minute Post-CAC Mean	1.11	2.11	1.54	2.53	1.15	2.23	1.82	2.66
Treatment Difference (95% CI)(1)	−1.00 (−1.35, −0.65)*		−0.99 (−1.40, −0.59)*		−1.07 (−1.46, −0.69)*		−0.84 (−1.21, −0.48)*	

(1) Treatment difference values shown are the group mean active minus the group mean vehicle at each post-CAC time point.

* $p<0.05$

Subjects treated with ZERVIATE demonstrated statistically and clinically significantly less ocular itching compared to vehicle at 15 minutes and 8 hours after treatment. In seven clinical trials conducted in subjects with allergic conjunctivitis or those at risk of developing allergic conjunctivitis, the most commonly reported adverse reactions occurred in approximately 1% to 7% of subjects treated with either ZERVIATE or vehicle. These reactions were ocular hyperemia, instillation site pain and reduced visual acuity.

NCX 4280

NCX 4280 is an ophthalmic solution that targets relief of ocular redness and lid swelling (also known as "puffy eyes") due to morning ocular congestion. Morning ocular congestion is a common complaint of aging individuals, particularly women, and a condition with a variety of causes. In a Phase 2 clinical program, NCX 4280 led to a reduction in morning ocular congestion with results that showed statistical significance against the control group. NCX 4280 demonstrated acceptable tolerability, with no treatment-related adverse effects noted. NCX 4280 is being developed by Ora pursuant to an exclusive worldwide license agreement in order to continue the program and ultimately identify a commercial partner. Ora plans to advance NCX 4280 to further build the Phase 2 package and refine the clinical-regulatory pathway to guide the design of potential Phase 3 clinical trials.

6.2 Commercial, Industrial and financial contracts and Intellectual Property

6.2.1 Our Collaboration Agreements

Bausch + Lomb

In March 2010, we signed an exclusive worldwide licensing agreement with Bausch + Lomb, a leading eye health company and wholly owned subsidiary of Bausch Health Companies Inc., granting Bausch + Lomb exclusive worldwide rights to develop and market latanoprostene bunod.

CHAPTER 6 OF NICOX'S 2018 ANNUAL REPORT
FREE TRANSLATION FOR INFORMATION PURPOSES ONLY

Bausch + Lomb is responsible for funding development and marketing activities, and we jointly manage the collaboration with them through a joint executive committee. The agreement also grants Bausch + Lomb the exclusive worldwide rights to develop and market other products containing latanoprostene bunod, such as fixed-dose combinations, for the reduction of intraocular pressure and/or the treatment of glaucoma.

Under the terms of the agreement signed in 2010, Bausch + Lomb made an initial license payment of $10 million to us upon execution of the agreement. Bausch + Lomb made an additional $10 million milestone payment to us in April 2012 following the decision to pursue further development of latanoprostene bunod after the Phase 2 study completion in late 2011.

As a result of the U.S. FDA's approval of VYZULTA in November 2017, we received a $17.5 million milestone payment from Bausch + Lomb at this date and we made a $15 million milestone payment to Pfizer under the 2009 agreement. In March 2018, we and Bausch + Lomb amended the agreement signed in 2010. The amendment provides that, from January 1, 2019 the royalties due to us according to the original agreement will increase by 1% over the original royalty on net sales above $300 million per year. Royalties will now be 10% to 16% over four tiers, reaching the maximum tier if and when global net sales exceed $500 million annually. Taking into account our royalty payments to Pfizer, the net royalties to us will be 6% to 12%, compared to 6% to 11% originally. In addition, the potential milestones payable to us by Bausch + Lomb have been increased by $20 million, added to and split among three existing milestones at increasing annual net sales levels. The first additional amount payable will be added to the milestone on achievement of $300 million annual net sales and the last additional amount payable will be added to the milestone on achievement of $700 million annual net sales. The total potential milestones due to us have therefore been increased from $145 million to $165 million. The next sales milestone due from Bausch + Lomb remains as originally agreed at $20 million upon VYZULTA net sales reaching $100 million, with $15 million of this milestone paid to Pfizer.

Pursuant to our agreement with Bausch + Lomb, we had an option to co-promote latanoprostene bunod products in the United States. In August 2014, we informed Bausch + Lomb of our decision to exercise the option. However, we have since agreed with Bausch + Lomb that we will not promote latanoprostene bunod in the United States.

Additionally, Bausch + Lomb had the option, pursuant to our agreement, to develop additional NO-donating compounds for the reduction of intraocular pressure and/or the treatment of glaucoma, including other NO-donating prostaglandin F2-alpha analogs from our research. During the third quarter of 2013, Bausch + Lomb decided to forego this option.

Our licensing agreement with Bausch + Lomb will remain in effect until all royalty payment obligations from Bausch + Lomb expire or unless terminated earlier by either us or Bausch + Lomb pursuant to the early termination provision in the agreement. The duration of royalty obligations under the agreement exists on a country-by-country and licensed product-by-licensed product basis, and commences on the date of first commercial sale for the particular country and the particular licensed product and terminates on the latest of (i) the date on which there exists no subsisting claim of an unexpired patent or collaborative patent covering latanoprostene bunod or a licensed product; (ii) the date of expiration of any period of marketing exclusivity, data protection or data exclusivity applicable to such licensed product in the relevant country; and (iii) ten years after the date of first commercial sale date. If there has been no launch date for a licensed product prior to the expiration of (i) and (ii), the royalty obligation terminates on the later-expiring of (i) and (ii).

We may terminate the agreement on a country-by-country basis if Bausch + Lomb fails to use commercially reasonable efforts to develop and commercialize the licensed products. We may also terminate the agreement in its entirety in the event that Bausch + Lomb challenges or causes a third party to challenge the validity or ownership of any of our licensed patents or fails or becomes unable to meet its payment obligations under the agreement. Bausch + Lomb may terminate this agreement without cause upon 90 days' notice. In the event of termination, except in the event of expiration of the payment obligations of Bausch + Lomb, licenses granted by us to Bausch + Lomb will terminate and any sublicenses granted by Bausch + Lomb will either be assigned to us or terminated.

Eyevance Pharmaceuticals

In September 2017, we entered into an exclusive license agreement with Eyevance for the commercialization of ZERVIATE in the U.S.

Under the agreement, Eyevance made a one-time non-refundable upfront payment to us of $6.0 million in 2017.. We are eligible to receive up to an additional $40.5 million in future milestones, of which $3 million is related to certain regulatory acceptance provisions and certain near-term manufacturing objectives. The remaining $37.5 million is payable on Eyevance achieving pre-defined sales targets, with $30 million of these milestones being triggered by annual sales targets of $100 million and above. In addition, we will also receive tiered royalties of 8% to 15% based on future net sales of ZERVIATE. We also are committed to paying Eyevance variable consideration related to certain manufacturing costs that resulted from a delay in the completion of certain manufacturing activities which is estimated to be $627,000. This amount will become payable only when Nicox receives royalty payments from Eyevance and will be directly deducted from these royalty payments.

Eyevance has the exclusive right to commercialize ZERVIATE in the U.S. We have agreed to provide pre-commercial launch manufacturing support to Eyevance including scale-up activities for the manufacturing of the commercial product and the professional samples necessary for the commercial launch, certain elements of which are managed and paid for by us. The commercial launch of ZERVIATE in the U.S. by Eyevance is expected for summer 2019.

The license agreement with Eyevance will remain in force until the later of the fifteenth anniversary of the commercial launch of ZERVIATE or until the expiry of the last licensed patent in the United States. Eyevance has the right to renew the agreement for two additional five-year periods with three months' advance notice. Additionally, with 90 days' prior written notice, Eyevance can terminate the agreement for convenience and either party can terminate the agreement upon a material breach by the other party following a 90-day cure period. In the event of expiry or termination of the agreement, Eyevance and certain related parties may complete and sell any work-in-process and product inventory that exists as of the date of termination. Upon termination, all rights granted to Eyevance terminate.

Fera Pharmaceuticals

In November 2015, we entered into an exclusive license agreement with Fera Pharmaceuticals, or Fera, granting Fera exclusive rights to develop and commercialize naproxcinod in the United States. The agreement was amended in September 2018. Naproxcinod is a Cyclooxygenase-Inhibiting Nitric Oxide-Donating, a CINOD, anti-inflammatory product candidate. The development will focus on an undisclosed rare disease.

Under the terms of the amended agreement, we may be eligible to receive up to $40 million in a single, one-time only, sales-based milestones if annual sales of naproxcinod reach $1 billion (in any indication), plus 7% royalties based on net sales of naproxcinod in the U.S. Fera will be responsible for, and will fully finance, all clinical development, manufacturing and commercialization activities. The agreement covers all indications excluding ophthalmology-related conditions and Duchenne Muscular Dystrophy, or DMD, and we will retain all rights for naproxcinod outside of the U.S. Fera is eligible to receive an undisclosed royalty should we sell or license rights to sell naproxcinod or related products in any ex-U.S. territory to a third party if the third party uses any Fera intellectual property, regardless of the therapeutic indication and territory. A joint steering committee will be put in place with representation from both companies to ensure that development of naproxcinod proceeds in accordance with the agreement.

The contract remains in force until the later of the tenth anniversary of the commercial launch or the expiration of the last patent included in the agreement. Upon termination of the agreement due to expiration of the term or our material breach, the licenses become fully paid and irrevocable and Fera will have all rights to the product in the U.S.. In the case where Fera, despite having used commercially reasonable efforts, has not submitted an NDA for the product before December 31, 2027, Fera must present a plan for such submission, otherwise we may terminate the agreement. Fera may terminate the agreement at any time by giving one month's notice. In such case (or in the case of material breach by Fera), all the rights concerning regulatory authorizations, intellectual property rights concerning the product and all data (including clinical, preclinical, regulatory, formulation and commercial data) shall be assigned or licensed (if assignment is not possible) to us.

Our product candidate naproxcinod is a non-steroidal anti-inflammatory drug, or NSAID, that is an NO-donating naproxen. The NO-donating MOA makes naproxcinod a CINOD, a class of drugs that are hoped to produce similar analgesic efficacy to traditional NSAIDs, but with an improved gastrointestinal and cardiovascular side effect profile. We have completed a broad clinical program for naproxcinod in osteoarthritis, including three Phase 3 trials with over 2,700 patients. We submitted an NDA for naproxcinod for osteoarthritis in 2009 and received a Complete Response Letter in 2010 in which the FDA requested substantial additional long-term safety data on the product.

Ironwood Pharmaceuticals

In June 2018 Nicox entered into a research collaboration with Ironwood focused on combining Ironwood's expertise in sGC and our proprietary NO-donating research platform to generate novel compounds in order to identify potential new therapeutics for the treatment of certain ophthalmic conditions.

Under the terms of the research collaboration agreement, each company will be responsible for their own costs associated with activities carried out as part of the collaboration. Depending on the outcome of our research collaboration, we may then enter into discussions regarding Nicox's further development of any identified product candidate.

Novaliq

In December 2019 we entered into a research collaboration with Novaliq GmbH for the development of novel topical ophthalmic formulations of our NO-donating PDE5 inhibitors based on Novaliq's water-free enabling EyeSol® technology, for lowering intraocular pressure (IOP). In this collaboration, Novaliq is developing and characterizing novel formulations for lead series of the NO-donating PDE5 inhibitor new chemical entities using its EyeSol® technology. If successful, we will be testing the novel topical ophthalmic formulations of NO-donating PDE5 inhibitors for IOP lowering activity in established pre-clinical models. Newly developed intellectual property from the collaboration will be jointly owned.

Ocumension Therapeutics

In December 2019 we entered into an exclusive license agreement with Ocumension Therapeutics for the development and commercialization of Nicox's product candidate, NCX 470, targeting patients with glaucoma or ocular hypertension for a territory comprising mainland China, Hong Kong, Macau, and Taiwan. Ocumension is expected to have to conduct additional clinical studies for the regulatory approval of NCX 470 in the Chinese market. All development activities will be overseen by a Joint Development Committee comprising representatives of both companies, with Ocumension responsible for undertaking all the activities at its own cost.

Ocumension received exclusive rights to develop and commercialize NCX 470, at its own cost, in the agreed territory. Under the terms of the agreement, we received a one-time upfront payment of €3 million from Ocumension and a further €2.5 million when we initiates a Phase 3 clinical study with NCX 470 outside the territory of this agreement. Under this agreement, we are also eligible to receive up to an additional €14.5 million in milestones associated with Ocumension's progress with NCX 470, up to and including regulatory approval, and up to €16.25 million split over three separate sales milestones associated with potential sales in the territory of up to €200 million, as well as tiered royalties from 6% to 12% on sales.

Ora

In January 2016, we entered into a license agreement with Ora, the world's leading ophthalmic clinical research and product development firm, granting Ora exclusive worldwide rights for the development and commercialization of NCX 4280, our innovative product candidate for relief of ocular redness and lid swelling due to morning ocular congestion.

Under the terms of the exclusive worldwide license agreement, Ora will be responsible for all development activities and will fund this program through its investment arm with which products from clients and partners are incubated and advanced with the goal to help find a final development and commercial partner. Ora plans to to continue the clinical development of NCX 4280 before sub-licensing this compound to a third party for future commercialization. We are

eligible to receive a $10 million milestone payment from Ora upon approval of NCX 4280 by the FDA. We are also eligible to receive 12.5% of any proceeds received by Ora under a potential sub-license agreement. If Ora or its affiliates sell licensed products, we are eligible to receive a percentage of net sales from such products. Upon Ora's submission to a drug approval agency in Germany, UK, France, Italy and Spain to market a licensed product, we have a right of first negotiation to exclusively commercialize and sell licensed products in that country. We have no additional financial obligations under this agreement.

The license agreement with Ora will remain in force, on a country-by-country basis, until the later of the tenth anniversary of the commercial launch of NCX 4280 or until the expiry of the last patent included under the agreement in the relevant country. Except in the case of early termination, at expiry of the agreement, the licenses become fully paid and irrevocable. Ora can terminate the agreement at any time by giving 90 days' notice. Either party may terminate for uncured material breach of the agreement with 90 days' notice. In case of early termination of the agreement, Ora may complete the ongoing work, subject to the payment of all royalties or sublicense fees due under the agreement. In the event of early termination of the agreement or termination due to material breach of the agreement by Ora, Ora must return all licensed rights and data. In the event of termination for our material breach, rights to all improvements made by Ora are retained by Ora. In all cases, Ora retains its pre-existing intellectual property and inventions related to clinical models, scales and trial processes, which we may use in regulatory filings but not in clinical trials without contracting with Ora. In the case of termination for all reasons other than material breach by Ora, the sub-licenses granted by Ora remain in force provided such sub-licenses do not place obligations on us which are greater than those in the main agreement.

Pfizer

In August 2009, we signed an agreement with Pfizer terminating our previous collaboration agreements dated August 2004 and March 2006. Under the terms of the 2009 agreement, we recovered all the development and marketing rights for latanoprostene bunod, and in particular the right to sub-license, as well as all the data and development information. This compound is currently out-licensed to Bausch + Lomb (see above). Moreover, we also have access to certain information regarding development of XALATAN (latanoprost ophthalmic solution) 0.005% belonging to Pfizer, in particular the regulatory files for XALATAN (latanoprost ophthalmic solution) 0.005%. In return, we are obligated to pay Pfizer two milestone payments of $15 million each linked to approval of VYZULTA in the U.S.(or a lower amount if approved only in Europe or Japan) and $15 million linked to reaching predefined sales levels. The first milestone payment was made in December 2017. Pfizer is also entitled to receive royalties on potential future sales. Pfizer's royalties are in the low single digit percentages for sales in the U.S.and sales made directly by us outside the United States. For sales made by our licensees outside the U.S, Pfizer's royalty is the greater of our royalty rate for sales outside the U.S.or a low double-digit percentage of the income that we receive from such licensee. We also recovered the rights to a certain number of new NO donors at the research stage for the potential treatment of diabetic retinopathy and glaucoma.

VISUfarma

Pursuant to our August 2016 partnership with VISUfarma, a founded private pan-European ophthalmic specialty pharmaceutical company created by GHO Capital, we transferred the commercial entities Nicox Pharma SNC (and its affiliates), Nicox Farma S.r.l. and Laboratoires Nicox, and certain assets and rights of Nicox SA to VISUfarma. Our European and international commercial operations, product portfolio and related late-stage development programs were valued at up to €26 million in this transaction. We transferred the related products and trademark rights to VISUfarma (or, as the case may be, the corresponding agreements with third parties) including rights to our commercial portfolio of ophthalmology products and rights to some development candidates in Europe. In exchange for these assets, we received €9 million in cash and a combination of ordinary shares and interest-bearing notes receivable valued at an aggregate of €12 million.

In September 2017, we amended the terms of the partnership agreement. Under the terms of the amended agreement, we agreed to amend the terms and conditions related to the €5 million potential milestone payments, which would have been made in a combination of ordinary shares and interest-bearing loan notes. As a result of the amended agreement, we received an additional €1.65 million in upfront consideration in a combination of ordinary shares and interest-bearing loan notes, making the total consideration for the assets equal to an aggregate of €22.65 million, increased from the €21 million initially. We are now eligible to receive a milestone payment of up to €3.35 million in a combination

of ordinary shares and interest-bearing loan notes if certain business objectives are achieved by VISUfarma. We will also no longer be responsible for completing development and regulatory approval for NCX 4240 in Europe, but will retain rights to develop NCX 4240 in the U.S.and Japan. However, we currently have no such development plans, and there is no guarantee that this program will be developed further. Subsequently, we agreed with VISUfarma that we will no longer be responsible for completing development and regulatory approval for AzaSite in Europe. Finally, we made a one-time cash payment of € 479,000 to VISUfarma. As a minority shareholder, we have a right to occupy one seat on the board of directors of the new company, which we do not currently occupy and reserve the ability to exercise this right.

6.2.2 Other Strategic Partnerships

We have other strategic partnerships that are not active at this time. For instance, under our collaboration with Portola Pharmaceuticals, Inc., we have exclusive rights to jointly develop certain of their preclinical small molecules for topical ophthalmic indications, but no compound has been selected for development under this agreement. Under our collaboration with Merck, Merck can elect to develop certain of our NO-donating compounds in the cardiovascular field. We do not expect these partnerships to impact our future financial status at this time.

6.2.3 Manufacturing and Supply

We do not have any in-house manufacturing facilities or logistics platforms. Therefore, we need to secure agreements with third parties for the manufacturing and supply of our product candidates under development. These third parties either manufacture and assemble in-house or outsource one or more processes to other external service providers.

Our business is subject to risks associated with our reliance on third-party suppliers. These risks are discussed more fully in the section of this prospectus titled "Risk Factors."

6.2.4 Intellectual Property

Our intellectual property is critical to our business and we strive to protect it, including by obtaining and maintaining patent protection in the U.S.and internationally for our product candidates and other inventions that are important to our business. We also rely on trade secrets to protect and maintain the confidentiality of proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. In addition, we rely on trademarks, copyrights and contractual obligations to establish and protect our intellectual property rights.

Our activities rely on our intellectual property and our business is subject to risks associated with the uncertain protection provided by patents and other intellectual property rights. The patent positions of pharmaceutical companies like ours are generally uncertain and involve complex legal, scientific and factual questions. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we may not obtain or maintain adequate patent protection for any of our product candidates. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties. These risks are discussed more fully in the section of this prospectus titled "Risk Factors."

Our portfolio of patents and patent applications cover a number of products. We have been issued product patents covering a wide range of NO-donating drugs and our key product-candidates. We have also filed patent applications on compositions of matter covering a wide range of drug classes including steroids, non-steroidal anti-inflammatory drugs, prostaglandins, angiotensin inhibitors and NO donors. Our intellectual property portfolio also includes licenses to patents for commercialized or development assets. In addition, we have filed applications for the registration of a number of trademarks in several countries, including France and the U.S.

As of December 31, 2018, our patent portfolio included 210 issued patents and 54pending patent applications and two patent applications under the Patent Cooperation Treaty, or PCT. In the U.S., our patent portfolio includes 39 issued patents and 8 pending patent applications and one patent application under the Patent Cooperation Treaty or PCT. We also

have 12 patents granted by the European Patent Office, or EPO, which have been validated in the principal European countries, and 9 pending European patent applications. Expenses related to our patents amounted to €503,361 in 2017 and €365,409 in 2019. The following tables summarize the status of our current patent portfolio for Nicox products and key product candidates.

Patent Terms

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the U.S., the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. As further described in this prospectus, the length of the patent term extension is related to the length of time between the opening of the IND and the submission of a marketing application, and the length of time the drug is under regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if our products receive FDA approval, we expect to apply for patent term extensions on patents covering one or more of those products. However there is no guarantee that the applicable authorities, including the FDA in the U.S., will agree with our assessment of whether such extensions should be granted and, if granted, the length of such extensions.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. Our agreements with employees also provide that all inventions conceived by the employee in the course of employment with us or from the employee's use of our confidential information are our exclusive property.

6.3 Competition

6.3.1 Overview

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We believe that our proprietary NO-donating research platform, knowledge, experience and scientific resources provide us with competitive advantages. However, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Our potential competitors include large pharmaceutical and biotechnology companies, and specialty pharmaceutical and generic drug companies. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Many of our potential competitors have significantly greater financial resources and 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 recruitment for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of each of our product candidates, if approved for marketing, are likely to be its efficacy, safety, method of administration, convenience, price, the level of generic competition and the availability of coverage and adequate reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third party payors seeking to encourage the use of generic products. Our product candidates target markets that are already served by a variety of competing products based on a number of active pharmaceutical ingredients. Many of these existing products have achieved widespread acceptance among physicians, patients and payors for the treatment of ophthalmic diseases and conditions. In addition, many of these products are available on a generic basis, and our product candidates may not demonstrate sufficient additional clinical benefits to physicians, patients or payors to justify a higher price compared to generic products. In many cases, insurers or other third-party payors, particularly Medicare, seek to encourage the use of generic products. Given that we are developing products based on FDA approved therapeutic agents, our product candidates, if approved, will face competition from generic and branded versions of existing drugs based on the same active pharmaceutical ingredients that are administered in a different manner, such as bioerodable drug product formulations.

Because the active pharmaceutical ingredients in some of our product candidates are available on a generic basis, or are soon to be available on a generic basis, competitors may be able to offer and sell products with the same active pharmaceutical ingredient as our products so long as these competitors do not infringe our patents. For example, our patents covering our NO-donating compounds largely claim new composition of matter. However, intellectual property covering certain other products such as ZERVIATE and NCX 4251 relate to the formulation and method of use of these compounds. As such, if a third party were able to design around the formulation and process patents that we hold and to create a different formulation using a different production process not covered by our patents or patent applications, we would likely be unable to prevent that third party from manufacturing and marketing its product.

6.3.2 Competitors of VYZULTA, NCX 470 and other NO-donating product candidates for the lowering of intraocular pressure (IOP)

Prostaglandin analogs account for more than 50% of prescriptions for IOP lowering drugs, where the leading branded product is LUMIGAN (bimatoprost ophthalmic solution) 0.01% and 0.03% from Allergan, the other leading branded product is TRAVATAN Z (travoprost ophthalmic solution) 0.004% from Novartis (Alcon), and the leading generic product is latanoprost. The other products are alpha agonists, beta blockers and carbonic anhydrase inhibitors, most of which are available as generic as well as branded forms. Rhopressa (netarsudil ophthalmic solution) 0.02%, a Rho kinase inhibitor, was recently approved and launched in the U.S.by Aerie Pharmaceuticals. A MAA has been filed in Europe for Rhopressa. XELPROS (latanoprost ophthalmic emulsion) 0.005% was recently approved for IOP lowering in patients with open-angle glaucoma or ocular hypertension and will be launched in the U.S.by a subsidiary of Sun Pharmaceutical Industries Ltd.

Several competitors are developing new formulations, novel chemical compounds and other sustained drug release products for the same ophthalmic indications as our current NO-donating compounds for IOP lowering. The list below sets out the principal programs in Phase 3 or above (excluding generics of existing, approved products):

- *Aerie Pharmaceuticals, Inc.* has filed an NDA for Roclatan, a fixed dose combination of its Rho-kinase inhibitor and latanoprost for IOP lowering. The Prescription Drug User Fee Act date is set for March 14, 2019.

- *Allergan, Inc.* is conducting Phase 3 clinical development of bimatoprost extended release, a biodegradable intraocular insert consisting of bimatoprost and a biodegradable polymer matrix for IOP lowering, in the United States. Allergan recently disclosed positive Phase 3 study results for this extended release injectable formulation of bimatoprost.

- *Glaukos* is conducting Phase 3 clinical development of an iDose insert or implant, which is a non-biodegradable metal insert that secretes travoprost and is placed in the eye during a surgical procedure.

- *Laboratorios Sophia S.A.de C.V.* is conducting Phase 3 clinical development of PRO-067, a cyclodextrin containing formulation of latanoprost that is aimed at improving the stability of currently available latanoprost formulations.

- *Ocular Therapeutix, Inc.* is conducting Phase 3 clinical development of OTX-TP, a sustained release travoprost punctal plug formulation that is aimed at lowering IOP.

- *Santen* is developing DE117, an EP2 agonist for the lowering of IOP. It has been approved in Japan under the brand name EYBELIS.

- *Senju* is conducting Phase 3 clinical development with SJP0125 in Japan.

6.3.3 Competitors to our other pipeline product candidates

We may also be exposed to potentially competitive products which may be under development for our other indications.

Allergic conjunctivitis

The allergic conjunctivitis market is dominated by Alcon Laboratories, Inc.'s PAZEO, PATANOL and PATADAY, three products based on olopatadine at different concentrations. In January 2015, the FDA approved PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7% for the treatment of ocular itching associated with allergic conjunctivitis.

- *Aldeyra Therapeutics, Inc.*, is in Phase 3 studies with reproxalap (ADX102) for allergic conjunctivitis.

- *Ocular Therapeutix, Inc.* is developing Dextenza, a dexamethasone insert. It is currently in Phase 3 trials for allergic conjunctivitis.

Blepharitis

There is currently no treatment approved solely for blepharitis, although certain drugs, notably steroids, are known to be used off-label for steroid-responsive inflammation of the palpebral (eyelid) conjunctiva.

- *Sun Pharma* is developing DexaSite (ISV-305), a dexamethasone gel forming eye drop targeting the treatment of blepharitis, which is currently in a Phase 3 clinical trial.

6.3.4 Other NO-delivery and NO-donating technologies

As far as we are aware, there are at least eight pharmaceutical companies working in the field of NO-donating drugs:

- *Bellerophon Therapeutics, Inc.* is currently developing the INOpulse, an NO device system product in the U.S.for the treatment of various conditions related to pulmonary hypertension.

- *Edixomed* is developing *in-situ* generation of nitric oxide for application in wound care, dermatology, critical care, respiratory and transdermal drug delivery

- *Kowa Pharmaceutical Europe Co. Ltd.* markets HYPADIL Kowa Ophthalmic Solution 0.25% in Japan for the treatment of glaucoma and intraocular hypertension. The active ingredient of this drug is nipradilol, an alpha- and beta-adrenergic blocker with NO-releasing action.

- *Mallinckrodt PLC* markets INOmax in the United States, a gaseous NO product for the treatment of persistent pulmonary hypertension of the newborn.

- *Novan Therapeutics* is developing NO donors for the treatment of acne, viral infections, onychomycosis and inflammatory skin disease. Their most advanced program is in Phase 3.

- *Synzyme Technologies* is developing caged nitric oxide molecules for the treatment of life threatening disruption of blood flow.

- *Topadur* is developing an NO-releasing PDE5 inhibitor to accelerate chronic wound closure.

- *Vast Therapeutics* is developing controlled and local delivery of Nitric Oxide via macromolecules for treatment of severe respiratory infections in patients with Cystic Fibrosis.

- *Zylo Therapeutics* is developing transdermal drug delivery systems including nitric oxide.

It is important to note that once marketed (subject to obtaining marketing approvals on an ad-hoc basis), the products developed by us will be competing with a number of products that are already commercially available. In addition, research conducted by the pharmaceutical industry and by public and private institutions will continue to generate new products that could compete with our existing or future commercial products.