CHAPTER 5 OF NICOX'S 2020 DOCUMENT D'ENREGISTREMENT UNIVERSEL
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5 BUSINESS

5.1 Overview

5.1.1 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. Nicox has two programs in late stage clinical development -- one in glaucoma (two Phase 3 trials) and one in blepharitis (one Phase 2b trial) -- a pre-clinical development candidate, and two licensed and commercialized products with exclusive partners.

- NCX 470, a novel nitric oxide (NO) donating prostaglandin analog, is currently in two Phase 3 clinical trials, Mont Blanc and Denali, for the lowering of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Top-line results from the Mont Blanc trial are currently expected in H1 2022 and those from the Denali trial in Q4 2022.

- NCX 4251, an innovative and patented suspension of nanocrystals of fluticasone propionate, is currently in Phase 2b clinical trial, Mississippi, for the treatment of acute exacerbations of blepharitis. Top-line results are currently expected in Q4 2021.

- NCX 1728, a development candidate selected from a new class of NO-mediated IOP lowering agents, for glaucoma.

- VYZULTA®, indicated for the reduction of IOP in patients with open angle glaucoma or ocular hypertension., is exclusively licensed worldwide to Bausch + Lomb, a Bausch Health Companies Inc. company, and commercialized in the U.S., Canada, Argentina and Mexico. VYZULTA has been also approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine.

- ZERVIATE®, indicated for the treatment of ocular itching associated with allergic conjunctivitis, is commercialized in the U.S. by our exclusive U.S. licensee Eyevance Pharmaceuticals or Eyevance, which was acquired by Santen Pharmaceutical Co., Ltd in September 2020. A Phase 3 clinical trial is currently being conducted in China by Ocumension Therapeutics, our exclusive Chinese partner for the development and commercialization of ZERVIATE in China. ZERVIATE is also exclusively licensed for development and commercialization in other territories.

Our lead product candidate, NCX 470, uses the same technology as VYZULTA, our commercialized product, by leveraging our proprietary expertise in generating novel patentable molecules, which we believe are new chemical entities (NCEs), that release NO. NO is a small signaling molecule that targets an intracellular enzyme, soluble guanylate cyclase (sGC). NO, naturally present in ocular tissues, plays a key role in the regulation of intraocular pressure, or IOP and can be linked with a pharmaceutical agent to potentially increase its effect on IOP lowering. Release of NO and the subsequent activation of sGC is one of the mechanisms that we believe leads to IOP lowering by Nicox's novel molecules. Adding NO to well-known molecules, such as prostaglandin analogs (PGAs), which is the most commonly prescribed class of IOP-lowering drugs, adds a potential second mechanism of action (MOA), and we believe allows certain of our products and product candidates to lower IOP further than the parent molecule alone. We believe that by designing our proprietary molecules with a dual MOA, we may be able to achieve greater IOP lowering compared to the parent compound alone.

Product candidates

NCX 470, discovered based on our proprietary NO-donating research platform, is our lead product candidate. NCX 470, which we believe is a NCE, is a novel NO-donating prostaglandin formulated as an ophthalmic solution, which is currently in late-stage clinical development for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Following a positive End-of-Phase 2 meeting with the U.S. FDA, the Company initiated the first Phase 3 clinical trial, Mont Blanc, in the U.S. on June 1st, 2020, evaluating NCX 470 for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The Mont Blanc trial is a multi-regional, double-masked, 3-month, parallel group trial evaluating the efficacy and safety of NCX 470

ophthalmic solution, 0.1% compared to latanoprost ophthalmic solution, 0.005% in patients with open-angle glaucoma or ocular hypertension. The 0.1% dose was selected through an initial adaptive design portion of the trial. The primary efficacy evaluation is based on time-matched IOP at 8 AM and 4 PM at Week 2, Week 6 and Month 3. The trial is expected to randomize approximately 670 patients at approximately 50 clinical sites, primarily in the U.S. and a small number of clinical sites in China. Top-line results from Mont Blanc trial are currently expected in H1 2022. On November 9th, 2020 Nicox initiated the second Phase 3 trial in the U.S., Denali, financed jointly and in equal parts by Nicox and Ocumension. Denali is a 3-month Phase 3 trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1% versus latanoprost ophthalmic solution, 0.005%, for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The Denali trial, which will also include a long-term safety extension, is expected to randomize 670 patients, at approximately 50 clinical sites in the U.S. and China, with a majority of patients to be recruited in the U.S. The Denali trial, together with the Mont Blanc trial, are designed to fulfill the regulatory requirements for Phase 3 safety and efficacy Phase trials to support NDA submissions in the U.S. and China. Top-line results from the Denali trial are currently expected in Q4 2022. In the U.S., multicenter, dose-response, Phase 2 clinical trial, Dolomites, NCX 470 ophthalmic solution 0.065% demonstrated non-inferiority and statistical superiority, based on the trial's pre-specified statistical analysis plan of diurnal mean IOP reduction at Day 28, to latanoprost ophthalmic solution, 0.005%, the U.S. market leader in prostaglandin analog prescriptions. The molecules in VYZULTA and NCX 470, discovered using this technology, are believed to lower IOP through a dual MOA, which combines NO donation, that activates sGC, with PGAs that activate Prostaglandin F, or FP, receptors, to increase the compounds' ability to lower IOP relative to the parent active compounds. 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 PGA and is the current market leader by sales value among all glaucoma therapies in the U.S. and EU, the two largest glaucoma markets worldwide. NCX 470's potential dual MOA is believed to lower IOP by increasing the outflow of fluid from the eye through the primary, or conventional outflow route via trabecular meshwork as well as through secondary, or unconventional outflow route via uveoscleral pathway. The primary outflow is believed to be increased by NO released from NCX 470 via activation of sGC and relaxation of trabecular meshwork while the secondary outflow pathway is believed to be increased by bimatoprost released from NCX 470 activation of FP receptors.

We are focusing our research efforts on ocular disorders in which NO is believed to play a major role in controlling IOP. Our research platform produced the NO-donating compounds, VYZULTA and NCX 470. VYZULTA demonstrated greater IOP lowering than the parent PGA compound in randomized clinical trials. This effect is believed to be due to the additional lowering in IOP from the NO-donating MOA. We are applying key learnings, based on Nicox's stand-alone NO-donors, to NO-donating moieties attached to other non-PGA therapeutic classes of compounds with the goal of enhancing the NO-mediated effects. NCX 1728 is the first in a new class of compounds in which NO-mediated effects are enhanced by concomitant phosphodiesterase-5 (PDE5) inhibition activity within the same molecule. PDE5 inhibition has been shown both to enhance the efficacy and the duration of NO-mediated effects. This class has the potential for development alone, as adjunctive therapy or in fixed-dose combinations with latanoprost or other PGAs for lowering IOP in patients with glaucoma or ocular hypertension.

In addition to our NO-donating product candidates in pre-clinical and clinical development, our pipeline includes a product candidate based on a novel and proprietary formulation of well-established molecule that has 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 a targeted topical treatment of the eyelids 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 well-established corticosteroid which has been marketed for more than 20 years for a number of non-ophthalmic 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. We believe that this is the first time that fluticasone propionate is being developed for an ophthalmic indication, and that NCX 4251 is the first product candidate developed as a targeted topical treatment of the eyelids for patients with acute exacerbations of blepharitis. Mississippi, a Phase 2b clinical trial of NCX 4251, evaluating once-daily dosed NCX 4251 0.1% versus placebo in patients with acute exacerbations of blepharitis was initiated in the U.S. on December 14th, 2020. The Mississippi trial is expected to randomize 200 patients at 5 to 10 clinical sites across

the U.S. The primary outcome measure is the proportion of patients achieving complete cure in eyelid redness, eyelid debris and eyelid discomfort, the hallmark signs and symptoms of blepharitis, at Day 15. Secondary outcome measures also include signs and symptoms of dry eye disease. Top-line results of the Mississippi trial are currently expected in Q4 2021. Should NCX 4251 meet the primary efficacy endpoint for blepharitis, the Mississippi trial could represent the first of two pivotal trials needed to support an NDA submission for the treatment of blepharitis in the U.S. Nicox completed the U.S. multicenter, dose escalating, first-in-human, 36-patient Danube Phase 2 clinical trial with NCX 4251 which evaluated its safety and tolerability in patients with acute exacerbations of blepharitis. In the Danube trial, NCX 4251 met the primary objective of selecting the dose for further development. The NCX 4251 0.1% once daily (QD) treatment was selected to advance into a larger Phase 2b clinical trial. In that trial, the selected dose of NCX 4251, 0.1%, also demonstrated promising efficacy against exploratory endpoints in reducing signs and symptoms of dry eye disease.

Products

Our lead commercial product, VYZULTA (latanoprostene bunod ophthalmic solution), 0.024%, represents the first FDA-approved drug developed based on our proprietary NO-donating research platform. In VYZULTA, an NO-donating group was linked to latanoprost, the active ingredient in XALATAN, a PGA, structurally related to prostaglandins. PGAs are in a class of molecules used in ophthalmology to lower IOP and are believed to do so by activating FP receptors located on the surface of cells. In the U.S., PGAs are the first line and the most commonly prescribed pharmacotherapy class for the lowering of IOP in glaucoma and ocular hypertensive patients. VYZULTA is the first PGA approved by the FDA for the reduction of IOP with one of its metabolites being NO. NO is believed to lower IOP by increasing the outflow of fluid from the eye via activation of sGC, a different mechanism from that of PGAs. Thus, VYZULTA is believed to possess a dual MOA in a single molecule. Prior to the FDA approval of VYZULTA, there were no other NO-donating products approved for the lowering of IOP in the U.S. VYZULTA is exclusively worldwide licensed to Bausch + Lomb, a Bausch Health Companies Inc. company, and is commercialized in the U.S., Canada, Argentina and Mexico. VYZULTA has been also approved in Colombia,, Hong Kong, South Korea, Taiwan and Ukraine.

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, a well-established oral antihistamine 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. ZERVIATE has been commercialized in the U.S. by Eyevance since March 2020. ZERVIATE has also been exclusively licensed for development and commercialization to Ocumension in the Chinese and majority of South East Asian Region markets, to Samil in South Korea, and to ITROM in Gulf and Arab markets. Ocumension initiated a Phase 3 clinical trial in China with ZERVIATE in December 2020. Subject to any additional data requested by the Chinese NMPA, this Phase 3 trial, in addition to the data package used by the FDA for ZERVIATE in the United States, is expected to be sufficient to support a Chinese NDA.

Ophthalmic Products Market

The current treatment landscape for open-angle glaucoma is dominated by two drug classes, topical PGAs and topical beta-blockers, with various combinations introduced over the past 20 years. Since PGAs began to replace topical beta-blockers as first line IOP-lowering agents in glaucoma, several have been approved and generic competition in the category is significant. In the U.S., PGAs have replaced beta-blockers as the first line therapy. Prior to the approval of VYZULTA, there had been no IOP-lowering drugs with new MOAs approved in U.S. and European Union since the launch of the first PGA more than twenty years ago. 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 ocular 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. While there are antimicrobial and antibiotic ointments and eye drops indicated for the treatment of blepharitis, among other conditions, we believe that there are no products solely and specifically indicated for the treatment of acute exacerbations of blepharitis. We believe that this creates a significant opportunity for future therapies specifically developed for 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 non-irritative shampoo solution.

Worldwide, the sales of pharmaceutical ophthalmic treatments reached $21.9 billion in 2019 and have grown at an average rate of 6% annually since 2015, according to IQVIA Health Analytics. In the U.S. alone, ophthalmology sales reached $8.8 billion in 2019, growing also at an average rate of 6% annually since 2015. With respect to our markets of focus, worldwide sales of treatments targeting glaucoma were $6.6 billion, representing 30% of the $21.9 billion worldwide market for ophthalmic drugs and sales. In the U.S. treatments targeting glaucoma generated approximately $3.2 billion in the U.S.in 2019, growing at an average annual rate of 6% since 2015 and representing 37% of the $8.8 billion total ophthalmic drug sales in the U.S. for 2019. While there are no approved treatments solely indicated for blepharitis, we estimate that the market potential for the treatment of acute exacerbations of blepharitis in the U.S. alone could be more than $700 million annually, and expect it to reach over $1 billion by 2024. Additionally, prescription topical treatments for ocular allergies generate approximately $400 million annually in the U.S., not including 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 in the U.S. for VYZULTA (through 2025), ZERVIATE (through 2032) and our product candidates NCX 470 (composition of matter protection in the U.S. until 2029 and formulation patent until 2039), and NCX 4251 (through 2033). 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 30, 2020, we had 34 employees, including personnel supporting our development operations in the U.S. and France, and research and nonclinical development operations in Italy. Our headquarters is located in Sophia-Antipolis, Valbonne, France, and we have been listed on Euronext Paris (COX.PA) since 1999.

5.1.2 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 novel 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 validated by VYZULTA and further demonstrated by the results of the NCX 470 Dolomites Phase 2 clinical trial;

- Our products commercialized in the U.S., VYZULTA (which is also commercialized in certain other territories outside of the U.S.) and ZERVIATE, both of which may potentially be able to obtain marketing approval in other countries where the data submitted to FDA are sufficient, or new data can be generated, for such approval;

- Our ability to identify and effectively advance additional product candidates, such as NCX 1728, both through our internal research and development 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 enter into successful partnerships with leading biopharmaceutical companies, as demonstrated by our worldwide exclusive licensing agreement with Bausch + Lomb for VYZULTA, to enter into regional collaboration agreements as demonstrated by the exclusive licensee agreements with Ocumension and to enter into commercialization partnerships, as demonstrated by our exclusive licensing agreement with Eyevance and as well by the development and commercialization agreements with Ocumension, Samil and ITROM;

- 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., Parion Sciences, Inc. and ISTA Pharmaceuticals, Inc.

5.1.3 Our Strategy

Our goal is to become a fully integrated ophthalmology pharmaceutical company focused on the discovery, development and commercialization of novel therapeutics for eye diseases with inadequately met need or unmet medical needs.

Key elements of our strategy include:

- ***Rapidly advance our product candidates through clinical development to approvals in the U.S.*** Our pipeline includes NCX 470 for glaucoma and NCX 4251 for blepharitis. We plan to develop and commercialize our product candidates internally in key markets including the U.S. and to keep the rights for Europe for potential future partnerships or for direct marketing;

- ***Optimize development through partnerships.*** We are seeking to optimize development and commercialization of our product candidates outside of the U.S. through regional collaborations where we can leverage the resources of a partner, such as our partnerships with Ocumension on NCX 470 in the Chinese, Korea and South East Asian markets and NCX 4251 in the Chinese market. In certain instances, we may partner a program for exclusive development;

- ***Advance the development of our product candidates.*** Nicox plans to advance the development of NCX 1728, the first development candidate selected from a new class of NO-mediated IOP-lowering agents. The Company also evaluates in-licensing or acquisition opportunities for additional ophthalmic product candidates or products.

- ***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 all 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. where it has been marketed since March 2020. We also entered into exclusive development and commercialization license agreements with Ocumension for the Chinese market in March 2019, expanding the rights to the majority of South East Asian markets in March 2020, with Samil in South Korea in December 2019 and also with ITROM in Gulf and Arab markets in August 2020. Similar to VYZULTA, we believe this strategy will allow us to efficiently use our internal resources while

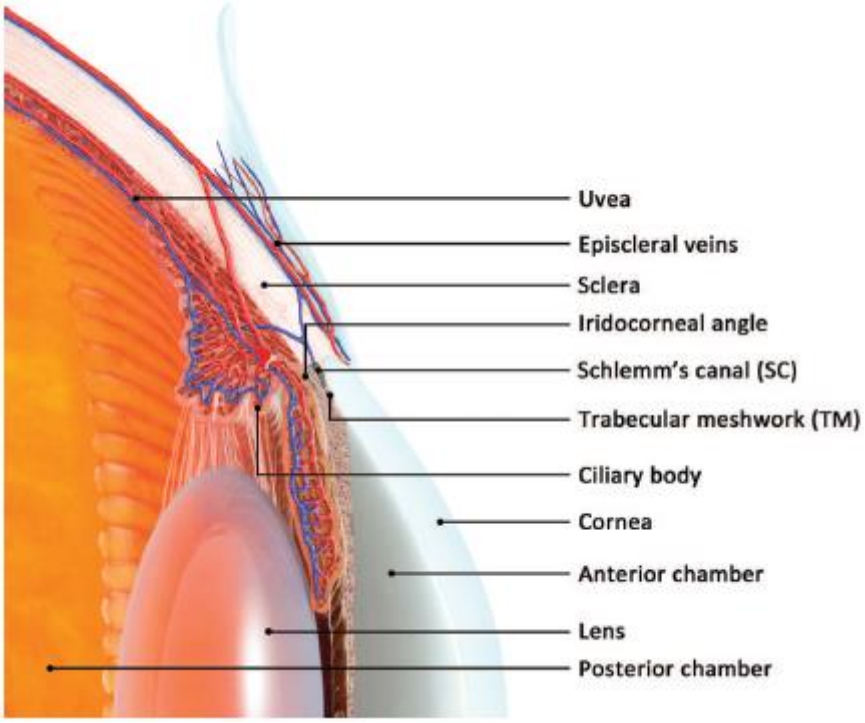
providing significant financial benefit. We are currently seeking partners capable of pursuing approval for and marketing ZERVIATE in other countries outside the U.S.

5.1.4 Description of the Eye

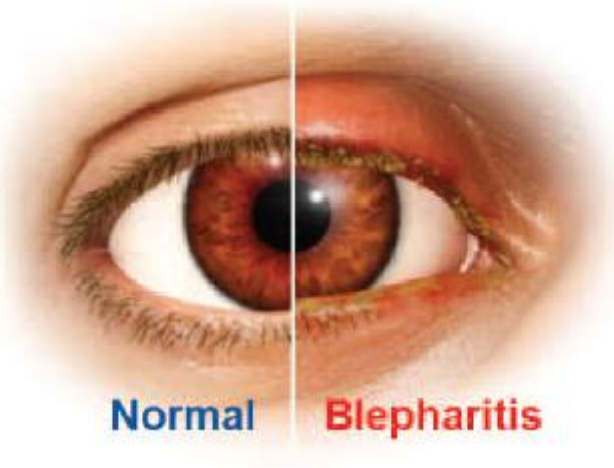
The eye is a fibrous globe that maintains its spherical geometry by being filled with a fluid called aqueous humor on the front side of the eye adjacent to cornea (also called the anterior segment) and a gel called vitreous humor on the back side of the eye adjacent to retina (also called the posterior segment). Both the front of the eye and the back of the eye are at the proper pressure to maintain the eye's shape and thus maintain an unobstructed and optically clear path for the light through the cornea and the lens to the retina. To maintain the pressure on the front of the eye, and therefore its shape, the aqueous humor is constantly produced inside the front compartment of 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 often resulting in glaucoma.

Blepharitis is a condition in which the margins of the eyelids become painful, 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 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. Both forms of blepharitis are associated with significant inflammation of the eyelid.

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



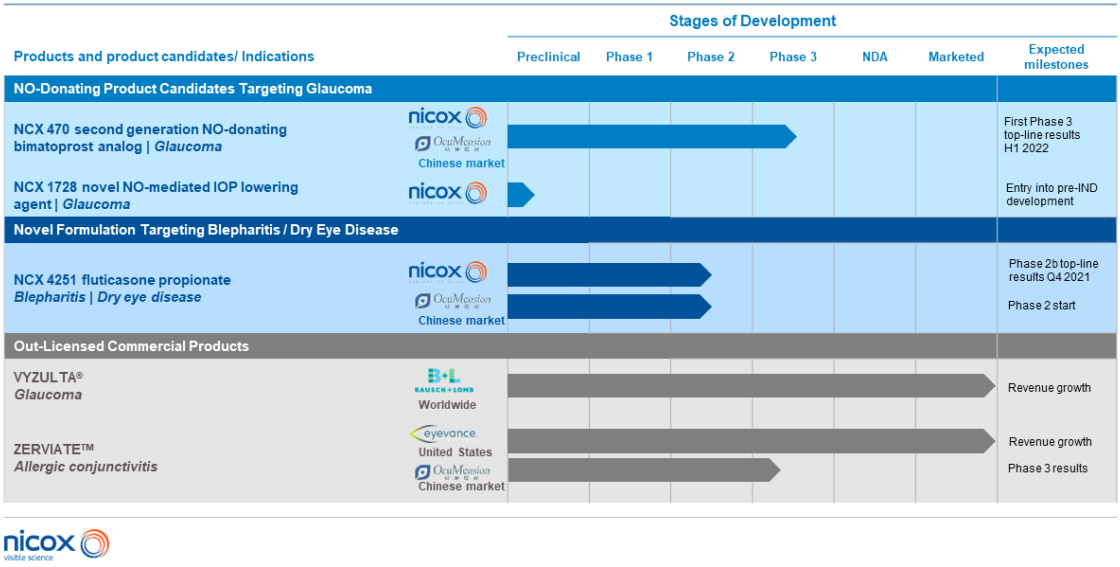
The picture below shows the inflammation (redness and swelling) of the eyelid associated with blepharitis.



5.1.5 Our Pipeline

We believe that our pipeline is strong in glaucoma and broadly across eye diseases of the anterior segment (i.e. the front of the eye), with two products commercialized, one product candidate in Phase 3 clinical development and another one in Phase 2b as well as one program in early-stage development. The future development of the Company depends on the outcome of the development activities of the Company and its ability to finance them.

The following table summarizes key information about our approved and commercialized products, and product candidates in preclinical and clinical development:



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Overview

Our product candidate pipeline features clinical and early development stage assets with a potential to offer novel treatments in various eye conditions. Those targeting the lowering of IOP in patients with open-angle glaucoma or ocular hypertension are from our proprietary NO-donating research platform. We are also developing a novel and proprietary formulation of a well-established molecule that has previously been used in other indications and therapeutic areas.

In addition, we have two commercialized products; VYZULTA, commercialized in the U.S., Canada, Argentina and Mexico, and which is also approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine, by our exclusive worldwide licensee, Bausch + Lomb, and, ZERVIATE, commercialized in the U.S. since March 2020 by our exclusive U.S. partner Eyevance.

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 believed to be elicited locally at the tissue level via NO activation of the intracellular enzyme sGC expressed within ocular tissues. 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, or cGMP. The cellular machinery, that synthesizes 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 sequestration of intracellular calcium, 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 primary or conventional outflow pathway (i.e., via the trabecular meshwork, Schlemm's canal, aqueous veins, and episcleral veins). All of the foregoing events are thought to lead to lowering of IOP. The effect of NO in the sGC signaling cascade may be further increased or prolonged by sGC stimulators, which interact synergistically with NO to increase the production of cGMP. Additionally, the effect of NO on IOP lowering may be further increased and/or prolonged by PDE5 inhibitors, which inhibit the degradation of cyclic guanosine monophosphate (cGMP), a key intracellular messenger that is produced as a result of stimulation by NO. 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. An NO-donating moiety can be linked to other pharmaceutical agents to improve IOP-lowering efficacy, as is the case with our lead clinical development candidate NCX 470, a novel NO-donating prostaglandin analog, and our commercialized product with the same mechanism of action, VYZULTA. Release of NO and the subsequent activation of sGC is one of the mechanisms that is believed to lead to IOP-lowering by our novel molecules. We believe that by designing our proprietary molecules with a dual MOA, we may be able to achieve increased 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. NCX 470, a novel NO-donating prostaglandin analog, has demonstrated statistical superiority to latanoprost, based on pre-specified statistical analysis plan of IOP reduction, in the Dolomites Phase 2 trial. We believe that NCX 470 has the potential to become the first approved non-combination product with statistical superiority to a prostaglandin analog. We also believe that NCX 470 has the potential to lower IOP more than bimatoprost, an FDA-approved PGA that is the current U.S. market leader by sales marketed under the brand LUMIGAN. The results from the Dolomites Phase 2 trial on NCX 470 together with 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 and ongoing research activities

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, which we believe are NCEs, that release NO, our research center has conducted lead generation and lead evaluation in preclinical studies in ophthalmology, creating a significant patent portfolio.

We are focusing our research efforts on ocular disorders where NO is believed to play a major role in controlling IOP. Our research platform produced the NO-donating compounds, VYZULTA and NCX 470. VYZULTA has demonstrated greater IOP lowering than the parent PGA compound in randomized clinical trials. This effect is believed to be due to the additional lowering in IOP from the NO-donating moiety. 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 with the goal of enhancing the NO-mediated effects. NCX 1728 is the first in a new class of compounds where NO-mediated effects are enhanced by concomitant phosphodiesterase-5 (PDE5) inhibition activity within the same molecule. PDE5 inhibition has been shown both to enhance the efficacy and the duration of nitric oxide-mediated effects. This class has the potential for development alone, as adjunctive therapy or in fixed-dose combinations with latanoprost or other PGAs for lowering IOP in patients with glaucoma or ocular hypertension.

Mechanism of action of NO and NO-donating prostaglandin analogs

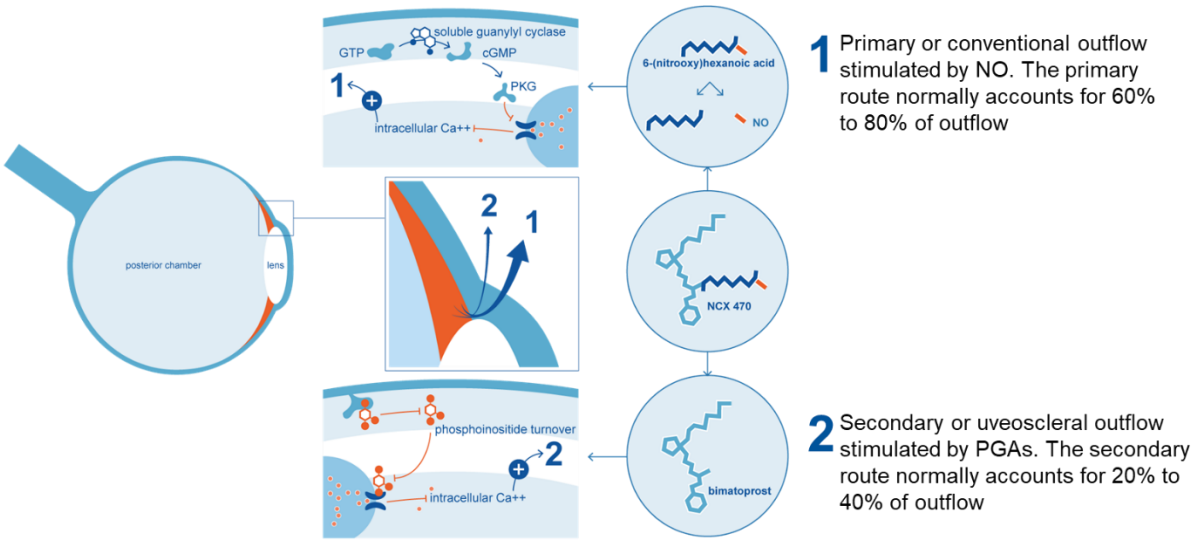
Evidence suggests that PGAs, which are indicated for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension, have a MOA which works via prostaglandin FP receptor activation with a primarily positive impact on the activity of certain enzymes, resulting in a widening of the interstitial 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 primary or conventional pathway is decreased in glaucoma. PGAs may have only a small impact on this pathway.

Because the primary or conventional 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 primary or conventional 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 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 supported by results of a Phase 2 clinical trial of latanoprostene bunod versus latanoprost conducted in glaucoma and ocular hypertension patients.

As mentioned above, NCX 470 is a novel NO-donating prostaglandin analog that we believe has the potential to become the first non-combination product with statistical superiority to a PGA (latanoprost) and to lower IOP more than bimatoprost, an FDA-approved PGA that is the current U.S. market leader by sales marketed under the brand LUMIGAN. Both NCX 470 and VYZULTA are designed to lower IOP 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, bimatoprost acid and latanoprost acid, 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 is believed to interact 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 is thought to trigger signals leading to a decrease in cell contractility and volume and, thus, allowing an enhancement of the conventional outflow pathway.

The picture below shows the MOAs of NO-donating PGAs: The trabecular meshwork outflow, also known as the primary or conventional outflow pathway, which is NO sensitive and the uveoscleral outflow, the secondary or non-conventional outflow pathway that is prostaglandin sensitive.



Glaucoma Overview

Glaucoma is a group of ocular diseases in which the optic nerve is injured, leading to irreversible, permanent 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 permanent blindness worldwide. Glaucoma is frequently linked to high IOP (generally approximately above 22 mmHg) 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.

High IOP usually does not 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, normotensive glaucoma patients, 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 in which 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 2019, worldwide sales of treatments targeting glaucoma were $6.6 billion representing 30% of the $21.9 billion worldwide market for ophthalmic drugs. In the U.S., sales of treatments targeting glaucoma totaled $3.2 billion in 2019 (approximately 36 million prescriptions) or 37% of the $8.8 billion U.S. market for ophthalmic drugs. Of the U.S. sales of treatments targeting glaucoma, $1.5 billion, or nearly 50%, were sales of prostaglandin analogs, of which almost 90% were branded products led by LUMIGAN and TRAVATAN Z. Over 70% of the prostaglandin analog prescriptions are for generic latanoprost. Prostaglandin analogs are currently used as the first line pharmacotherapy in the U.S. standard of care.

While not derived from head-to-head trials, the table below provides a summary of the U.S. FDA labeling information for the currently used first-line pharmacotherapies.

Summary of the U.S. FDA Labeling Information for the Currently Approved First-line Pharmacotherapies for the Treatment of Glaucoma Patients with Ocular Hypertension.

	XALATAN(1) (latanoprost 0.005%)	**LUMIGAN(1) (bimatoprost 0.01%)**	**TRAVATAN Z(1) (travoprost 0.004%)**	**VYZULTA(2) (latanoprostene bunod 0.024%)**	**ROCKLATAN(1) (latanoprost 0.005% and netarsudil 0.02%)**
IOP reduction.....	6 to 8 mmHg	Up to 7.5 mmHg (7 to 8 mmHg for 0.03% bimatoprost)	7 to 8 mmHg	Up to 7 to 9 mmHg	6.8 to 9.2 mmHg 1 to 3 mmHg greater than latanoprost or netarsudil (1.58 mmHg greater than latanoprost 0.005% at 3 months)(3)
Patient mean baseline IOP	24 to 25 mmHg	23.5 mmHg (26 mmHg for 0.03% bimatoprost)	25 to 27 mmHg	26.7 mmHg	23.6 mmHg(4)
Adverse reactions	Foreign body sensation 13%; punctate keratitis 10%; stinging 9%; conjunctival hyperemia 8%	Conjunctival hyperemia 31% (45% for 0.03% bimatoprost)	Conjunctival hyperemia 30% to 50%	Conjunctival hyperemia 6%; eye irritation 4%; eye pain 3%; instillation site pain 2%	Conjunctival hyperemia 59%; instillation site pain 20%; corneal verticillata 15%; conjunctival hemorrhage 11%

(1) Indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

(2) Indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

(3) See Section 14, Clinical Studies, Figure 1 and 2 of ROCKLATAN package insert for diurnal IOP at Day 90 for ROCKLATAN vs. Latanoprost including both Mercury-1 and Mercury-2 IOP values (1.5; 1.7; 1.3; 1.5;2.0; and 1.5 mmHg).

(4) See Section 14, Clinical Studies, Figure 1 and 2 of ROCKLATAN package insert for baseline IOP for ROCKLATAN including both Mercury-1 and Mercury-2 IOP values (24.8; 23.7; 22.6; 24.7; 23.3; 22.4 mmHg).

For patients whose glaucoma is not well-controlled on a single PGA eye drop, adjunctive therapies are added on the top of PGAs as second, third and fourth eye drops. The adjunctive therapies include beta blockers, alpha agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, or their fixed dose combinations. The total sales of adjunctive therapies accounted for approximately $1.7 billion of the $3.2 billion U.S. sales of treatments targeting glaucoma in 2019. 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 2018, around 36 million prescriptions were written in the U.S. annually for glaucoma drugs.

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 NO-donating PGA in development for the lowering of IOP in patients with open-angle glaucoma and ocular hypertension. NCX 470 has been evaluated in the Dolomites safety and efficacy Phase 2 clinical trial and is currently in two Phase 3 trials, Mont Blanc and Denali. 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 by sales in the class of PGAs, 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.

Whilst no head-to-head trials have been carried out, we believe that, through the contribution of NO, NCX 470 has the potential for greater IOP lowering activity than bimatoprost.

In December 2018 we entered into an exclusive licensing agreement with Ocumension for the development and commercialization of NCX 470 in the Chinese market. In March 2020 Ocumension's exclusive rights were extended to Korea and South East Asian markets.

Top line Results of the Dolomites Phase 2 NCX 470 Clinical Trial

We completed the randomized, double-masked, dose-response Dolomites Phase 2 trial to determine a concentration of NCX 470 for lowering IOP in patients with open-angle glaucoma or ocular hypertension to advance into further clinical development. The trial enrolled 433 patients across 25 sites in the U.S. Patients were randomized to receive either NCX 470 (0.021%, 0.042% or 0.065%) or latanoprost ophthalmic solution, 0.005% once a day in the evening for 28 days.

All three doses of NCX 470 (0.021%, 0.042%, and 0.065%) met the pre-specified primary efficacy endpoint of non-inferiority to latanoprost for reduction from baseline in mean diurnal IOP at Day 28. In a pre-specified secondary efficacy analysis for reduction from baseline in mean diurnal IOP at Day 28, the mid and high doses of NCX 470 (0.042% and 0.065%) met the secondary efficacy endpoint of statistical superiority to latanoprost based on the trial's pre-specified statistical analysis plan. Specifically, IOP reduction from baseline in mean diurnal IOP at Day 28 was 7.8 mmHg for the 0.021% dose of NCX 470 (p-value for NCX 470 vs. latanoprost not statistically significant); 8.2 mmHg for the 0.042% dose of NCX 470 (p-value for NCX 470 vs. latanoprost=0.0281); and 8.7 mmHg for the 0.065% dose of NCX 470 (p-value for NCX 470 vs. latanoprost=0.0009). The dose-dependent IOP reduction from baseline in mean diurnal IOP at Day 28 showed improved IOP lowering with each incremental concentration of NCX 470 tested, thus creating the potential for additional IOP lowering with a higher concentration of NCX 470.

In additional pre-specified secondary efficacy analysis for reduction from baseline in mean diurnal IOP, NCX 470 (0.065%) met the secondary efficacy endpoint of statistical superiority to latanoprost at Day 7 (p=0.004) and Day 14 (p=0.0174), in addition to Day 28 (p=0.0009; described above). In pre-specified secondary efficacy analyses, the 0.065% dose of NCX 470 showed statistical superiority in IOP lowering as a reduction from baseline at all three time points (8 AM, 10 AM and 4 PM IOPs) on Day 28 compared with latanoprost, with the difference reaching up to 1.4 mmHg (p=0.0214 at 8 AM, p=0.0008 at 10 AM, and p=0.0015 at 4 PM). The IOP lowering effect as reduction from baseline at the three time points (8 AM, 10 AM and 4 PM IOPs) across Day 7, Day 14 and Day 28 ranged from 7.6 to 9.8 mmHg for the 0.065% concentration of NCX 470 compared with 6.3 to 8.8 mmHg for latanoprost. Additionally, at Day 28, 44% of patients dosed with NCX 470 (0.065%) had a 1 mmHg or greater mean diurnal IOP reduction from baseline compared with the mean of 7.4 mmHg for the latanoprost group (p-value not significant); 37% of patients had 2 mmHg or greater reduction (p-value not significant); 27% had a 3 mmHg or greater reduction (p=0.0175); 16% had a 4 mmHg or greater reduction (p=0.0822); and 12% had a 5 mmHg or greater reduction (p=0.0150); compared with the mean for the latanoprost group. Furthermore, greater proportion of patients dosed with NCX 470 (0.065%) achieved a mean diurnal IOP reduction at Day 28 of 40% or greater (p=0.0287), 35% or greater (p=0.0393), 30% or greater (p-value not statistically significant), 25% or greater (p=0.0479) and 20% or greater (p=0.0115), compared with those dosed with latanoprost.

NCX 470 was well tolerated when dosed once daily for 28 days in patients with open-angle glaucoma or ocular hypertension. Only three out of the 433 patients in the trial discontinued due to an adverse event. The majority of adverse events in the trial were mild. The most frequently reported adverse event was conjunctival hyperemia, the majority of which were mild, in 16.8% of patients who dosed with the 0.065% dose of NCX 470 compared with 6.5% of patients who dosed with latanoprost. Notably, adverse events for conjunctival hyperemia plateaued at the 0.042% concentration, for which it was reported for 22.2% of patients. There were no treatment-related serious adverse events, and no evidence of treatment-related systemic side effects.

Mont Blanc and Denali Phase 3 Clinical trials

Nicox successfully completed an End-of-Phase 2 meeting with the U.S. Food and Drug Administration (FDA) and agreed on the design for the NCX 470 Phase 3 program, as well as nonclinical and CMC plans

supporting submission of a New Drug Application (NDA) in the U.S. On June 1st, 2020 Nicox initiated in the U.S. the first Phase 3 clinical trial, Mont Blanc, evaluating NCX 470 for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Mont Blanc is a multi-regional, double-masked, 3-month, parallel group trial evaluating the efficacy and safety of NCX 470 ophthalmic solution, 0.1% compared to latanoprost ophthalmic solution, 0.005% in patients with open-angle glaucoma or ocular hypertension. The 0.1% dose was selected through an initial adaptive portion of the trial. The primary efficacy evaluation of the Mont Blanc trial is based on time-matched IOP at 8 AM and 4 PM at Week 2, Week 6 and Month 3. The Mont Blanc trial is expected to randomize approximately 670 patients at approximately 50 clinical sites, in the U.S. and at a small number of clinical sites in China. Top-line results from Mont Blanc trial are currently expected in H1 2022.

On November 9th, 2020 Nicox initiated the second Phase 3 trial in the U.S., Denali, financed jointly and in equal parts by Nicox and Ocumension. Denali is a 3-month Phase 3 trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1% versus latanoprost ophthalmic solution, 0.005%, for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The Denali trial, which will also include a long-term safety extension, is expected to randomize approximately 670 patients, at approximately 50 clinical sites in the U.S. and China, with a majority to be recruited in the U.S. The Denali trial, together with the Mont Blanc trial, are designed to fulfill the regulatory requirements to support NDA submissions in the U.S. and China. Top-line results from the Denali trial are currently expected in Q4 2022.

NCX 470 Market Research

In order to understand the potential clinical adoption of NCX 470 for glaucoma and to assess its reimbursement and revenue potential, an independent third party market research agency with extensive experience in the ophthalmology market assessment conducted an initial primary market research trial in the U.S. in the first half of 2019. The market research was comprised of 40 interviews with U.S. ophthalmology key opinion leaders, high volume prescribers including ophthalmologists and optometrists, and third party payers.

Multiple target product profiles of NCX 470 were tested with differentiation from each other by increasing superiority in IOP reduction compared to latanoprost 0.005%, based on a hypothetical statistically significant outcome in a head-to-head Phase 3 clinical trial. The varying levels of efficacy in the three target product profiles tested were chosen based on the current U.S. FDA-approved therapies. Specifically, statistical superiority to latanoprost similar to VYZULTA's published Phase 2 VOYAGER trial was selected for the first profile but with a superior U.S. FDA label based on head-to-head Phase 3 trials vs. PGA for NCX 470, a statistical superiority to latanoprost similar to the published ROCKLATAN Phase 3 Mercury-1 clinical trial at Month 3 but with improved safety and tolerability vs ROCKLATAN was selected for the second profile and finally an ~2 mmHg or better statistical superiority to latanoprost was selected for the third profile. For all three profiles, the safety and tolerability were identical and based on existing PGAs.

Based on our market research, we concluded that there was an opportunity for an impactful product with any of the three profiles tested and that the market potential increased with the size of the improved reduction in IOP. More specifically, the results indicated that the VYZULTA-based product profile had peak U.S. net revenue potential of $230 million (25% market share of the U.S. first-line therapy branded market); the Mercury-1 ROCKLATAN-based product potential but with improved safety and tolerability to ROCKLATAN had peak U.S. net revenue potential of $310 million (35% market share of the U.S. first-line therapy branded market); and the profile based on ~2 mmHg superiority to latanoprost had peak U.S. net revenue potential of $540 million (60% market share of the U.S. first-line therapy branded market). The above forecasts include estimations about the future growth of the market and assume an appropriate level of reimbursement is available.

NCX 470 preclinical studies

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, with up to 3.5 mmHg greater lowering of IOP with NCX 470 as compared with bimatoprost 0.03% in a non-human primate preclinical model 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.

NCX 4251

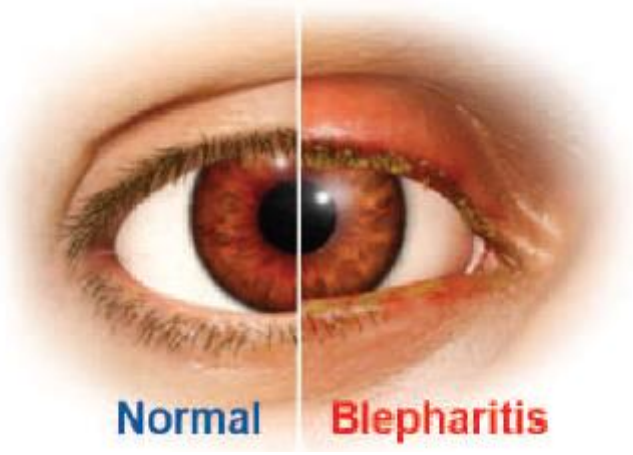
Our second product candidate in clinical development, which leverages an established molecule, is NCX 4251, a novel patented ophthalmic suspension of fluticasone propionate nanocrystals which is being developed as a targeted topical treatment of the eyelids for patients with acute exacerbations of blepharitis. Nicox has completed one Phase 2 trial, Danube with NCX 4251, and is currently in a larger Phase 2b trial, Mississippi, initiated in the U.S. on December 14, 2020 with top-line results currently expected in Q4 2021. We believe that this is the first time that fluticasone propionate is being developed for an ophthalmic indication, and that NCX 4251 is the first product candidate developed as a targeted topical treatment of the eyelids in patients with acute exacerbations of blepharitis. Thus we believe that NCX 4251 may be able to achieve first-in-class status as a treatment for this indication. Blepharitis is a common eye condition characterized by eyelid inflammation. NCX 4251 is being developed for application via an applicator to the eyelids, applied directly to the site where the disease originates and thereby minimizing potential exposure of the drug through the cornea which can lead to the damaging side effects such as IOP increase found with current topical steroids.

In July 2019, we entered into an exclusive license agreement with Ocumension for the development and commercialization of NCX 4251 for blepharitis in the Chinese market.

Blepharitis Overview

Blepharitis is a condition in which the margins of the eyelids become painful, 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 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. Both forms of blepharitis are associated with significant inflammation of the eyelid.

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. There is not a definitive 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 blepharitis disease.

There is currently no FDA-approved prescription product solely indicated for blepharitis, which limits our ability to estimate prevalence and market size. There are, however, antimicrobial and antibiotic products, such as ointments and eye drops, indicated for the treatment of blepharitis, as well as other conditions. Treatment options also include lid scrubs, topical ophthalmic steroids, topical ophthalmic antibiotics and topical ophthalmic antibiotic/steroid combinations. We estimate that the market for treatment of acute exacerbations of blepharitis in the U.S. alone may be more than $700 million, rising to over $1 billion by 2024. Surveys reveal that ophthalmologists and optometrists 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 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.

Top-line results of the Danube Phase 2 clinical trial

In December 2019 we completed the U.S. multi-center, randomized, double-masked, placebo-controlled, first-in-man administration, dose-escalation, 14-day Phase 2 clinical trial, Danube, aimed to evaluate the safety and tolerability of NCX 4251 compared to placebo in patients with acute exacerbations of blepharitis. The trial enrolled 36 patients in clinical sites across the U.S. The Danube Phase 2 trial met the primary objective of selecting the dose of NCX 4251 for further development.

NCX 4251 0.1% once daily (QD) treatment was selected to advance into a larger Phase 2 clinical trial.

The selected dose also demonstrated promising efficacy against exploratory endpoints in the study in reducing the signs and symptoms of dry eye disease.

Danube Phase 2 clinical trial summary

All patients in the once daily (n=10 for NCX 4251 and n=5 for placebo) and twice daily (n=10 for NCX 4251 and n=11 for placebo) cohorts successfully completed the 14-day dosing period followed by a 14-day safety evaluation period.

Both once daily (QD) and twice daily (BID) NCX 4251 0.1% were well tolerated. There were no serious adverse events, no treatment related systemic adverse events, and no adverse events of intraocular pressure (IOP) elevation, the most common side effect of topical ophthalmic steroids.

Although the study was not powered for efficacy, in the prospectively defined pooled analysis of QD and BID dosing of NCX 4251 0.1%, there was a statistically significant reduction in the composite score of eyelid redness, eyelid debris and eyelid discomfort at the Day 14 study endpoint ($n = 20$ for NCX 4251 0.1% and $n = 16$ for placebo with $p = 0.047$ for study eyes and $p = 0.025$ for the combined study eyes and contralateral eyes). Twenty percent of patients on QD dosing of NCX 4251 achieved complete cure, compared to 0% in patients treated with placebo. Due to the small sample size, these results were not statistically significant. Complete cure is defined as a score of zero in eyelid redness, eyelid debris and eyelid discomfort, also referred to as a Composite Score of zero.

Exploratory analyses of signs and symptoms of dry eye disease, including symptom evaluation using visual analog scale and sign evaluation based on corneal and conjunctival fluorescein staining, revealed encouraging reduction from pre-study baselines.

Mississippi Phase 2b clinical trial

Nicox is conducting the Mississippi Phase 2b clinical trial, a 200 patient trial initiated on December 14, 2020 in the U.S., evaluating once-daily dosed NCX 4251 0.1% versus placebo in patients with acute exacerbations of blepharitis. The primary outcome measure is the proportion of patients achieving complete cure in eyelid redness, eyelid debris and eyelid discomfort, the hallmark signs and symptoms of blepharitis, at Day 15. Top-line results of the Mississippi trial are currently expected in Q4 2021. Should NCX 4251 meet the primary efficacy endpoint for blepharitis, the Mississippi trial could represent the first of two pivotal trials needed to support an NDA for the treatment of blepharitis in the U.S. The Mississippi trial is also designed to assess the impact of NCX 4251 on dry eye signs and symptoms, paving the way for a potential future standalone Phase 3 program in this indication.

NCX 1728 - First in a new class of NO-mediated intraocular pressure lowering agents.

We are focusing our research efforts on ocular disorders where NO is believed to play a major role in controlling IOP. Our research platform produced the NO-donating compounds, VYZULTA and NCX 470. VYZULTA demonstrated greater IOP lowering than the parent PGA compound in randomized clinical trials. This effect is believed to be 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 with the goal of enhancing the NO-mediated effects. NCX 1728 is the first in a new class of compounds where NO-mediated effects are enhanced by concomitant phosphodiesterase-5 (PDE5) inhibition activity within the same molecule. PDE5 inhibition has been shown both to enhance the efficacy and the duration of nitric oxide-mediated effects. This class has the potential for development alone, as adjunctive therapy or in fixed-dose combinations with latanoprost or other PGAs for lowering IOP in patients with glaucoma or ocular hypertension. NCX 1741, an analog of Nicox's development candidate NCX 1728, demonstrated a reduction of IOP to a similar extent to travoprost, with faster onset of activity. Travoprost is a PGA, a class of molecules which are considered standard of care for IOP lowering in humans.

Our Out-Licensed Commercial Products

VYZULTA—Our Lead Commercial Product

Overview

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024% is a PGA with one of its metabolites being NO. At the time of its approval, VYZULTA was the first eye drop approved in twenty years with a novel approach to reduce IOP. VYZULTA was approved by the 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 which is commercialized in the U.S., Canada, Argentina and Mexico and has been also approved in Colombia, Hong Kong, South Korea, Taiwan, Ukraine.

VYZULTA has demonstrated greater IOP lowering at many of the trial's timepoints 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 one Phase 2 clinical trial, and two Phase 3 clinical trials, respectively.

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

- **Increased IOP Lowering**— In the Phase 3 clinical trials, VYZULTA dosed once daily demonstrated statistically significantly 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. Additionally, in the open-label safety extensions for both Phase 3 trials, VYZULTA demonstrated sustained IOP lowering effect without any loss of efficacy over 12 months (12-month duration of treatment in first Phase 3 trial and 6-month duration of treatment in

the second Phase 3 trial). 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. VYZULTA, the 0.024% dose (N=83), 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% VYZULTA dose reaching greater than 1 mmHg (statistical significance: $p<0.01$).

- **Novel Dual Mechanism of Action**—VYZULTA is the first PGA 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 potential distinct MOAs that are mediated by a prostaglandin and NO.

- **Established 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. The most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%).

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.

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. which is commercialized there since March 2020. In March 2019 we entered into an exclusive licensing agreement with Ocumension for the development and commercialization of ZERVIATE in the Chinese market. The exclusive rights were expanded to the majority of South East Asian markets in March 2020. Ocumension initiated a Phase 3 clinical trial on ZERVIATE in China in December 2020.Subject to any additional data requested by the Chinese NMPA, this Phase 3 trial, in addition to the data package used by the FDA for ZERVIATE in the United States, is expected to be sufficient to support a Chinese NDA.

In December 2019 we entered into an exclusive licensing agreement with Samil for the development and commercialization of ZERVIATE in South Korea.

In August 2020 we entered into an exclusive licensing agreement with ITROM for the registration and commercialization of ZERVIATE in Gulf and Arab markets.

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 eight 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.

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.

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 $400 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.

Non-core partnered program

NAPROXCINOD

Naproxcinod is a Cyclooxygenase-Inhibiting Nitric Oxide-Donating, or CINOD, anti-inflammatory product candidate, which is partnered with Fera Pharmaceuticals in the U.S. Following results from *in vivo* primary pharmacodynamics study of naproxcinod in models of sickle-cell disease, Fera decided to focus its development on the treatment of painful vaso-occlusive crisis in sickle-cell disease. Fera filed an application with the FDA for an Orphan Drug Designation (ODD) for naproxcinod in sickle-cell disease, which was refused. In addition, Fera will evaluate naproxcinod as a potential adjuvant treatment for patients with COVID-19 infection. Subject to successful completion of the ongoing manufacturing of naproxcinod test material, Fera plans to initiate pre-clinical proof-of-concept studies in models of COVID-19 infection in early 2021.

We had previously 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. We do not plan to further develop naproxcinod for osteoarthritis.

5.2 Commercial, Industrial and financial contracts and Intellectual Property

5.2.1 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. Latanoprostene bunod is commercialized by Bausch + Lomb under the brand name VYZULTA in the U.S., Canada, Argentina and Mexico and approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine.

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 clinical trial completion in late 2011.

As a result of the FDA's approval of VYZULTA in November 2017, we received a $17.5 million milestone payment from Bausch + Lomb 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 U.S. 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 U.S.

Additionally, Bausch + Lomb had the option, pursuant to our agreement, to develop additional NO-donating compounds for the reduction of IOP 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 and a milestone payment $3.0 million in July 2019 resulting from the achievement by us of certain manufacturing and regulatory objectives. We are eligible to receive up to an additional $37.5 million in future

milestones 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 consideration related to certain manufacturing costs that resulted from a delay in the completion of certain manufacturing activities which could be up to $900,000, which will be directly deducted from royalty payments. Nicox may also pay to Eyevance $250,000 if certain additional manufacturing activities are undertaken by Eyevance.

Eyevance has the exclusive right to commercialize ZERVIATE in the U.S. where it has been marketed since March 2020. In February 2021, Eyevance has entered into a partnership with Hikma Pharmaceuticals for promoting ZERVIATE to U.S. healthcare professionals working outside the eyecare specialty, with all sales continuing to be booked by Eyevance, on which Nicox will receive royalties.

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, granting Fera exclusive rights to develop and commercialize naproxcinod in the United States. The agreement was amended in September 2018 and in December 2020. Fera will evaluate naproxcinod as a potential adjuvant treatment for patients with COVID-19 infection.

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.

ITROM Pharmaceutical Group

In August 2020 we entered into an exclusive license agreement with ITROM Pharmaceutical Group for the registration and commercialization of ZERVIATE for the treatment of ocular itching associated with allergic conjunctivitis in Gulf and Arab markets including the Kingdom of Saudi Arabia, the United Arab Emirates and Qatar. ITROM is a regional, Dubai-based, internationally recognized pharmaceutical marketing and distribution group of companies specializing in the introduction and representation of breakthrough ophthalmology products since 1999.

Under the terms of the agreement ITROM is granted exclusive rights to develop and commercialize ZERVIATE in Bahrain, Egypt, Iraq, Jordan, Kuwait, Libya, Oman, Qatar, the Kingdom of Saudi Arabia, the United Arab Emirates and Yemen. Nicox is eligible to receive 15% royalties on net sales of ZERVIATE in certain key countries, and 10% in other countries. Nicox will also receive a license fee on signature and may receive a future milestone payment upon product launch. ITROM will be responsible, at its own cost, for development and commercialization of ZERVIATE in the countries of the agreement. ZERVIATE is expected to require only the existing approved U.S. New Drug Application (NDA) package to support approval.

Ocumension Therapeutics

In December 2018 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, or the Chinese market. NCX 470 is currently in two Phase 3 trials, Mont Blanc and Denali, designed to fulfill the regulatory requirements for Phase 3 safety and efficacy trials to support NDA submissions of NCX 470 in the U.S. and China. All development activities are 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 Nicox was eligible to receive a further €2.5 million when we initiate a Phase 3 clinical trial with NCX 470 outside the territory of this agreement. and as well 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. However, the agreement was amended in March 2020. Ocumension paid Nicox €15 million (in replacement of the totality of the milestones in the original agreement), gained additional exclusive rights to NCX 470 for Korea and South East Asia and will pay 50% of the costs of the second glaucoma Phase 3 clinical trial of NCX 470, Denali. No future NCX 470 milestones will be due from Ocumension to Nicox. In the case that the Joint Trial would not take place, partial or limited refunds of this payment may be made and in certain situations the original milestones of the agreement would again apply. The tiered royalties of 6% to 12% of the original agreement remain unchanged and will apply to sales in the original and the additional territories.

In March 2019 we entered into an exclusive license agreement with Ocumension for the development and commercialization of Nicox's product ZERVIATE for the treatment of allergic conjunctivitis for the Chinese market. All development activities will be overseen by a Joint Governance 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 ZERVIATE, at its own cost, in the agreed territory. Under the terms of the agreement, we are eligible to receive development and sales milestones of up €17 million together with royalties of between 5% and 9% on sales of ZERVIATE. The agreement was amended in March 2020 granting Ocumension additional exclusive rights of ZERVIATE in the majority of the Southeast Asian region. Other terms of the original agreement remain unchanged. ZERVIATE is currently in a Phase 3 clinical trial in China.

In June 2019, we entered into an exclusive license agreement with Ocumension for the development and commercialization of Nicox's product candidate, NCX 4251, for blepharitis in the Chinese market. Ocumension is responsible, at its own cost, for all development activities necessary for the approval of NCX 4251 in the territory, overseen by a Joint Development Committee comprising representatives of both companies. Ocumension received exclusive rights for the agreed territory to develop and commercialize NCX 4251 in blepharitis. Under the terms of the agreement, Nicox received an upfront payment of US$ 2.3 million and may potentially receive

development and sales milestones of up to US$ 11.3 million together with tiered royalties of between 5% and 10% on sales of NCX 4251.

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.

Samil Pharmaceutical

In December 2019 we entered into an exclusive license agreement with Samil Pharmaceutical Co., Ltd, or Samil, for the development and commercialization of ZERVIATE (cetirizine ophthalmic solution), 0.24% for the treatment of ocular itching associated with allergic conjunctivitis in South Korea. Samil is considered as one of the leading Korean companies specialized in the field of ophthalmic medicines including the research and development of drugs in the field of ophthalmology.

Samil will receive exclusive rights to develop and commercialize ZERVIATE in South Korea, where the market for allergic conjunctivitis was worth nearly €31 million for the 12 months to Q3 2019. Nicox is eligible to receive 10% royalties on net sales on ZERVIATE in South Korea and a milestone payment of 5% of net sales for each calendar year in which net sales exceed approximately US$900,000 (at current exchange rates). Nicox will also receive a license fee, and may receive approval and launch milestone payments which, together with the license fee, may total almost US$250,000. Samil will be responsible, at its cost, for development and commercialization of ZERVIATE in South Korea. ZERVIATE is expected to require only manufacturing transfer and associated pharmaceutical development to support approval in South Korea, in addition to the existing approved U.S. NDA package.

5.2.2 Other Partnerships

We have other 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.

5.2.3 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."

5.3 Patents

5.3.1 Industrial property protection policy

Intellectual property is of vital importance to the Company's businesses. Nicox takes all possible measures to protect intellectual property, including by obtaining and maintaining patent protection in different territories (particularly in the United States) for its products under development and other inventions important for its business. The Group must also use of trade secrets to protect and ensure the confidentiality of proprietary information to protect those aspects of its business operations that do not lend themselves to patent protection or considered by Nicox as not appropriate for patent protection. The Company must also have recourse to the filing of trademarks, copyrights and contractual obligations to establish and protect its intellectual property rights.

Nicox's activities are dependent on its intellectual property and as such are subject to risks linked to the uncertain protection offered by patents and other intellectual property rights. The position of pharmaceutical companies like Nicox with respect to patents is highly uncertain and involves extremely complex legal, scientific and factual circumstances. In addition, the protections sought in patent applications may be significantly reduced before the patent is issued and its scope may be reinterpreted after it is issued. For that reason, the possibility cannot be excluded that Nicox might not be successful in obtaining or maintaining a patent protection for one of its products under development. The Company cannot anticipate if the patent applications currently pending will result in the issuance of patents in all the targeted territories, or if the claims of the patents issued will offer sufficient protection against the competition. Any patent held by the Company may be challenged, circumvented or invalidated by third parties. The reader is invited to refer to section 3 "risk factors" of the universal registration document that describes the risk factors related to the uncertain protection provided by patents and other intellectual property rights.

The Group has a patent department within its Italian subsidiary Nicox Research Institute Srl. The Group's patent department regularly uses industrial property law firms in several countries around the world.

Nicox also relies on trade secret protection for its confidential and proprietary information. Even though the Group takes measures to protect its proprietary information and trade secrets, including through contractual provisions with its employees and consultants, third parties may develop independently information and proprietary techniques substantially equivalent or gain access to its trade secrets or disclose its technology. For those reasons, Nicox might not be able to effectively protect its trade secrets. The company's policy requires staff, consultants, external scientific staff and other consultants to sign confidentiality agreements at the start of their employment or relations as consultants with Nicox. The agreements thus concluded with employees also provide that all inventions designed by an employee in the course of his or her term of employment within the Company or based on the use of confidential information of the Company remain the exclusive property of Nicox.

5.3.2 Nature and coverage of patent families owned by the company

As of December 31, 2020, our patent portfolio included 322issued patents and 79 pending patent applications and 3 patent applications under the Patent Cooperation Treaty, or PCT. In the U.S., our patent portfolio includes 42 issued patents and 9 pending patent applications. We also have 17 patents granted by the European Patent Office, which have been validated in the principal European countries, and 7 pending European patent applications.

Latanoprostene bunod (the active ingredient of VYZULTA) is protected in the United States by four granted patents which expire in 2025. A patent term extension (PTE) application was filed in December 2017. If this Patent Term Extension (PTE) is accepted, it could provide additional protection until 2030.

In Europe, a patent covering latanoprostene bunod (the active ingredient of VYZULTA) was issued in February 2016 and validated in 36 countries of the EPC (European Patent Convention) and will provide protection until 2024. An application could be made for a Supplementary Protection Certificate (SPC) to extend the term of the patent to a maximum of 5 years.

On November 23, 2016, Teva Pharmaceutical Industries Ltd. filed a notice of opposition against the grant of the European patent covering latanoprostene bunod. On July 13, 2018, the Opposition Division rejected the

opposition and decided to maintain the patent as granted. On September 12, 2018, Teva Pharmaceutical Industries Ltd. filed an appeal against the decision of the Opposition Division. In March 2019, Nicox filed its statement of appeal. The date this appeal decision will be rendered is not known on this date.

In Japan, latanoprostene bunod (the active ingredient of VYZULTA) is protected by a patent which expires in 2024.

ZERVIATE is protected in the United States by four patents expiring in 2030 and 2032. In Europe a patent application is currently under examination. If issued, this patent will offer protection until 2030.

In Japan, ZERVIATE is covered by two patents expiring in March 2030.

NCX 4251 is protected in the United States and in Europe by patents which expire in 2033. In Europe.

In July 2020, Nicox filed a PCT application and national patent applications in the U.S., Europe (EPC), China, Japan, Taiwan and Argentina covering the process for the preparation of the NCX 4251 formulation under development and the NCX 4251 formulation as product; this patent family, if granted, will provide worldwide patent coverage until 2040.

NCX 4240 is protected in the United States, Japan and Mexico by granted patents covering the NCX 4240 eyedrop formulation and its therapeutic use for treating specific viral infections of the eye. In Canada the patent application is under review. These patents will provide protection until 2035.

NCX 470 is covered by a patents family which includes the granted patent US 8,101,658 expiring in 2029 and the European patent EP 2 274 279 which was validated in France, Germany, Italy, Spain and the United Kingdom. The product patent family also includes patents granted in Canada, Japan, China, Hong Kong, Argentina and India which are in force until 2029. Patent US 8,101,658 is eligible for a patent term extension which, if granted, may extend the expiration date for a period of up to five years.,

In July 2019, Nicox filed a PCT application and national patent applications in USA, Europe (EPC), China, Japan, Taiwan and Argentina covering the NCX 470 formulation under development. In 2020, the U.S., the European and the Japanese patents were granted extending patent coverage of the NCX 470 formulation to 2039.

In February 2019, Nicox filed a PCT application and other national patent applications covering an industrial process of synthesis of NCX 470. These patent applications, if granted, will provide worldwide patent coverage for NCX 470 until 2039 - 2040. In Europe a patent was granted in September 30th, 2020 and it was validated in 14 member States of the European Patent Convention (EPC).

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 United States, 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.

The length of the patent term extension is related to 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. In the future, if our products receive FDA approval or other regulatory authorities, 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 will agree with our assessment of whether such extensions should be granted and, if granted, the length of such extensions.

The following tables summarize the status of our current patent portfolio for Nicox products and key product candidates as of December 31, 2020. For each family of patents, a table shows the different members of the family in force, by country, with the maximum possible expiration date subject to regular payment of maintenance fees and the absence of questioning of the validity of the patent concerned.

VYZULTA (latanoprostene bunod)

Patent title: PROSTAGLANDIN DERIVATIVES

This patent family covers nitrooxy-derivatives of prostaglandin F2α analogues having improved pharmacological activity and enhanced tolerability and their use for the treatment of glaucoma and ocular hypertension.

Latanoprostene bunod, its use for the treatment of glaucoma and ocular hypertension and its pharmaceutical formulations are specifically disclosed and claimed.

Patent owner: Nicox SA

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted	Europe#	EP 1 704 141	27-Dec-2004	24-Feb-2016	27-Dec-2024
	United States	US 7,273,946^	05-Jan-2005	25-Sep-2007	03-Oct-2025
		US 7,629,345^	05-Jan-2005	08-Dec-2009	05-Jan-2025
		US 7,910,767^	05-Jan-2005	22-Mar-2011	05-Jan-2025
		US 8,058,467^	05-Jan-2005	15-Nov-2011	05-Jan-2025
	Japan	JP 3 984 283	27-Dec-2004	13-July-2007	27-Dec-2024
	39 other countries		Dec-2004 - Jan-2005	Aug-2006 - Feb-2016	Dec-2024 - 5-Jan-2025
Pending	Europe	EP3643702 A1	9-sep-2019	—	27-Dec-2024
	7 other countries		27-Dec-2004	—	27-Dec-2024

(*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(#) EP 1 704 141 was validated in 36 member States of the European Patent Convention (EPC). On November 23, 2016, TEVA Pharmaceutical Industries Ltd, or TEVA, filed a Notice of Opposition at the EPO. On July 13, 2018, the Opposition Division decided to reject the Opposition and to maintain the patent as granted. A notice of appeal against the decision of the Opposition Division was filed by TEVA Pharmaceutical Industries Ltd on September 12, 2018. On March 2019, Nicox filed a reply to the grounds of appeal. Appeal decision is still pending.

(^) U.S. 7,273,946, U.S. 7,629,345, U.S. 7,910,767 and U.S. 8,058,467 are listed in the Orange Book for VYZULTA.

In December 2017, Nicox filed requests for PTE for U.S. 7,273,946, U.S. 8,058,467 and U.S.7,629,345 at the USPTO.

ZERVIATE (cetirizine)

Patent title: OPHTHALMIC FORMULATIONS OF CETIRIZINE AND METHOD OF USE

This patent family covers topical ophthalmic formulations comprising cetirizine and its salts wherein cetirizine is present in an amount of 0.1% to 0.25% (w/v), and method for alleviating signs and symptoms of allergic conjunctivitis by topical administration of the ophthalmic formulations.

ZERVIATE, 0.24% cetirizine hydrochloride formulation and its use in the treatment of ocular itching associated with allergic conjunctivitis are specifically claimed.

Patent owner: Nicox Ophthalmics Inc.

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted	United States	US 9,254,286^	15-March-2010	9-Feb-2016	09-July-2032
		US 8,829,005^	21-May-2013	9-Sep-2014	15-March-2030
		US 9,750,684^	29-Dec-2015	05-Sept-2017	15-March-2030
		US 9,993,471^	29-Dec-2015	12-June-2018	15-March-2030
	Japan	JP 6033677	15-March-2010	04-Nov-2016	15-March-2030
		JP 6144393	12-Aug-2016	19-May-2017	15-March-2030
	other country	CA 2,755,679	15-March-2010	12-Sept-2017	15-March-2030
Pending	Europe	EP 2 408 453 A US	15-March-2010	—	15-March-2030
	United States	2020/0405711	11-Sept-2020	—	15-March-2030

(*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(^) U.S. 9,254,286, U.S. 8,829,005, U.S. 9,750,684 and U.S. 9,993,471 are listed in the Orange Book for ZERVIATE.

NCX 470 (NO-donating bimatoprost)

Patent title: NITRIC OXIDE DONATING PROSTAMIDES

This patent family covers nitrooxy-derivatives of bimatoprost and their use for treating glaucoma and ocular hypertension.

NCX 470 is specifically disclosed and claimed.

Patent owner: Nicox SA

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted	Europe#	EP 2 274 279	11-May-2009	31-July-2013	11-May-2029
	United States	US 8,101,658	11-May-2009	24-Jan-2012	11-May-2029
	Japan	JP 5 401 540	11-May-2009	01-Nov-2013	11-May-2029
	China	CN102099330	11-May-2009	30-Apr-2014	11-May-2029
	4 other countries		11-May-2009	2015 - 2019	11-May-2029

(*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(#) EP 2 274 279 was validated in five main European countries.

NCX 470 eyedrop formulation

Patent title: OPHTHALMIC COMPOSITIONS CONTAINING A NITRIC OXIDE RELEASING PROSTAMIDE

This patent family covers aqueous ophthalmic compositions in the form of solution containing NCX470 and macrogol 15 hydroxystearate as the only solubilizing agent, and a method for their preparation.

Patent owner: Nicox SA

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Active	PCT§	WO2020/011845	10-July-2019	NA	
Granted	Europe#	EP 3 583 788#	10-July-2019	28-Oct-2020	10-July-2039
	United States	US 10,688,073	10-July-2019	23-June-2020	10-July-2039
	Japan	JP 6672512	10-July-2019	6-March-2020	10-July-2039
Pending	Europe	EP20172140.4	29-Apr-2020	-	10-July-2039
	United States	US 2020/0206176	11-Mar-2020	-	10-July-2039
	China	CN201910622356.1	10-July-2019	-	10-July-2039
	China	CN 111249228A	4-Mar-2020		10-July-2039
	Japan	JP 2020-105201 A	4-Mar-2020	-	10-July-2039
	3 other countries		10-July-2019	-	10-July-2039

(*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(#) EP 3 583 788 will be validated in 42 member States of the European Patent Convention (EPC).

(§) PCT/ WO2020/011845 will enter the national phases in January 2021

In February 2019, Nicox filed a PCT application and national patent applications in Taiwan and Argentina covering an industrial process of synthesis of NCX 470. This patent family, if granted, will provide worldwide patent coverage until 2039. In Europe a patent was granted in September 30, 2020 and it was validated in 14 member States of the European Patent Convention (EPC)

NCX 4251 (Fluticasone propionate nanocrystals)

Patent title: PREPARATION OF HYDROPHOBIC THERAPEUTIC AGENTS, METHOD OF MANUFACTURE AND USE THEREOF

This patent family covers nanocrystals of Fluticasone propionate (Form A) wherein the nanocrystals have the c-axis crystallographic direction normal to the surfaces that define the thickness of the nanocrystals and an average particle size of 100 nm to 1000 nm.

This patent family also covers: nanosuspensions containing nanocrystals of Fluticasone propionate (Form A), methods for treating or alleviating symptoms of blepharitis, post-operative ocular inflammation, dry eye or eye allergy and the sonocrystallization process for preparing the Fluticasone propionate nanocrystals.

Patent owner: Nicox Ophthalmics Inc.

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted	United States	US 8,765,725	07-Jan-2013	01-July-2014	7-Jan-2033
	United States	US 10,174,071	26-July-2018	8-Jan-2019	6-May-2033
	Japan	JP 6285419	06-May-2013	09-Feb-2018	6-May-2033
	Japan	JP 6564891	01-Feb-2018	2-Aug-2019	6-May-2033
	Japan	JP 6752940	17-June-2019	21-Aug-2020	6-May-2033
	Europe	EP 2 847 207^	06-May-2013	27-March-2019	6-May-2033
	Europe	EP 3517541#	11-Feb-2019	15-July-2020	6-May-2033
	China	CN 107880091	23-Nov-2017	18-Dec-2020	6-May-2033
	7 other countries		06-May-2013	2018-2020	6-May-2033
Pending	Europe	EP 3 741 772 A1	29-May-2020	—	6-May-2033
	United States	US 2019/0169224	29-Nov-2018	—	6-May-2033
	6 other countries				

(*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(^) EP 2 847 207 was validated in 12 member States of the European Patent Convention (EPC)

(#) EP 3 517 541 was validated in 24 member States of the European Patent Convention (EPC)

NCX 4280 (formerly AC-120)

Patent title: METHOD FOR THE TREATMENT AND PREVENTION OF EYELID SWELLING

This patent family covers the use of a composition comprising oxymetazoline and glycerine for treating eyelid swelling.

This patent family also discloses topical pharmaceutical compositions comprising an osmotically active agent and a vasoconstrictor agent. The preferred osmotically active agent is glycerin and the vasoconstrictor agent is selected from oxymetazoline or naphazoline.

Patent owner: Nicox Ophthalmics Inc.

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted	United States	US 8,685,439	26-Apr-2007	01-Apr-2014	09-July-2030
Pending	United States	US 14/178,846	12-Feb-2014	—	26-Apr-2027
		US 15/366,559	01-Dec-2016	—	26-Apr-2027

(*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

Protection for other NO-donating compounds

Our novel NO-donating PDE5 inhibitors have potential patent protection in the United States, Europe and other main countries until 2039. Additional novel molecules combining NO-donation and other non-PGA MOAs compounds are protected in the United States, Europe and other main countries by patents and patent applications that provide patent protection until 2034.

5.4 Important events

5.4.1 Important events since January 1st, 2020

January 13, 2020: **Nicox's Partner Secures Approval of VYZULTA® in Mexico**

https://www.nicox.com/assets/files/EN_VYZULTA-Mexico-approval_20200113_F1.pdf

January 16, 2020: **Nicox's Partner Secures Additional Approvals of VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% in Hong Kong and Argentina**

https://www.nicox.com/assets/files/EN_VYZULTA-HK-and-Argentina-PR_20200116-F2.pdf

January 21, 2020: **Nicox Fourth Quarter 2019 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_Q4_2019_RESULTS_F_20200121.pdf

February 3, 2020: **Nicox Receives Formulation Patent Extending NCX 470 U.S. Patent Coverage to 2039**

https://www.nicox.com/assets/files/EN_NCX470_USFORMULATIONPATENTPR_20200203_F.pdf

March 5, 2020: **Nicox's Positive End-of-Phase 2 Meeting with the U.S. FDA Sets Stage for NCX 470 Phase 3 Program in Glaucoma**

https://www.nicox.com/assets/files/EN_NCX470_FDAEOP2_PR_20200305_-F1.pdf

March 6, 2020 **Nicox Announces 2019 Financial Results and 2020 Key Milestones**

https ://www.nicox.com/assets/files/EN_2019-YE-results_-20200306_F1.pdf

March 9, 2020 **Nicox's Partner Secures Additional Approval of VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% in Taiwan**

https://www.nicox.com/assets/files/EN_VYZULTA_TAIWAN_APPROVAL_PR_20200309_F.pdf

March 11, 2020 **Nicox Updates on ZERVIATE™ Progress in China and Expands the Countries of its Agreement with Ocumension Therapeutics**

https://www.nicox.com/assets/files/EN_OCUMENSION_ZERVIATE_AMENDMENT_20200311_F.pdf

March 11, 2020 **Nicox to Receive €15 Million and Half of the Cost of the Second NCX 470 Phase 3 Clinical Trial from Ocumension Therapeutics under Amended Agreement**

https://www.nicox.com/assets/files/EN_OCUMENSION_NCX470_JOINT_TRIAL_20200311_F.pdf

March 31, 2020 **Nicox Announces ZERVIATE™ Launch by Partner Eyevance Pharmaceuticals in the United States**

https://www.nicox.com/assets/files/EN_ZERVIATE-U.S.-LAUNCH-PR-_20200331_F1.pdf

April 2, 2020 **Nicox's Partner Fera Pharmaceuticals Files Application for Orphan Drug Designation for Naproxcinod in Sickle-Cell Disease**

https://www.nicox.com/assets/files/EN_Fera_SickleCell_PR_20200402_F.pdf

April 8, 2020 **Nicox Outlines Plans to Progress NCX 4251 into Phase 2b Trial Following Positive Meeting with FDA**

https://www.nicox.com/assets/files/EN_NCX-4251-FDA-MEETING_20200408_F.pdf

April 17, 2020 **Nicox First Quarter 2020 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_Q1-2020-results-_20200417_F.pdf

June 2, 2020 **Nicox Initiates First Phase 3 Trial of NCX 470 in Glaucoma**

https://www.nicox.com/assets/files/EN_NCX-470_Mont-Blanc-FPFV_PR_F.pdf

July 10, 2020 **Nicox Strengthens Cash Position With Divestment of its VISUfarma Shareholding**

https://www.nicox.com/assets/files/EN_VISUFARMA_STAKE_SALE_PR_20200710_F-.pdf

July 10, 2020 **Nicox Partner Ocumension Completes Successful Hong Kong IPO at an approximately US$1,090 Million Valuation**

https://www.nicox.com/assets/files/EN_OCUMENSION_POST-IPO_PR_20200710_F1.pdf

July 15, 2020 **Nicox Reports on Enrollment Progress in Mont Blanc Phase 3 Clinical Trial in Glaucoma**

https://www.nicox.com/assets/files/EN_NCX-470-Phase-3-enrollment-PR-_20200715.pdf

July 17, 2020 **Nicox Second Quarter 2020 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_Q2_2020_results-_PR_20200717_F1.pdf

July 31, 2020 **Nicox Receives €5 Million Upon Closing of VISUfarma Divestment**

https://www.nicox.com/assets/files/EN_CLOSING_SALE_VISUFARMA_STAKE_PR_F.pdf

August 5, 2020 **Nicox: Implementation of a liquidity contract with Kepler Cheuvreux**

https://www.nicox.com/assets/files/EN_Kepler-liquidity-contract-2020-PR_20200805_F.pdf

August 5, 2020 **Nicox Negotiating €2 million Non-Dilutive Loans Guaranteed by the French State**

https://www.nicox.com/assets/files/EN_PGE-confirmation-PR-August-5-F.pdf

August 12, 2020 **Nicox Partners ZERVIATE™ in the Gulf and Arab Markets**

https://www.nicox.com/assets/files/EN_ZERVIATE_ITROM_LICENSE_AUGUST2020_PR_F.pdf

September 2, 2020 **Nicox Completes Enrollment of the Adaptive Design Cohort of NCX 470 Mont Blanc Phase 3 Glaucoma Trial**

https://www.nicox.com/assets/files/EN_NCX-470-Ph3_adaptive-cohort_20200902_F.pdf

September 10, 2020 **Nicox First Half 2020 Financial Results and Business Update**

https://www.nicox.com/assets/files/EN_H1-2020results_20200910_F2_F.pdf

September 18, 2020 **Nicox Announces Senior Management Change**
https://www.nicox.com/assets/files/EN_TNDepartureSept2020_PR_20200918_F.pdf

September 22, 2020 **Nicox's ZERVIATE™ Receives IND Approval in China**

https://www.nicox.com/assets/files/EN_ZERVIATEChineseINDapproval_20200922_F.pdf

September 23, 2020 **Nicox Selects 0.1% NCX 470 Dose in Adaptive Stage of Mont Blanc Phase 3 Glaucoma Trial**

https://www.nicox.com/assets/files/EN_NCX470_AdapativeDesignDoseSelection_PR_20200923_F.pdf

September 24, 2020 **Bausch Health Announces VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, is now approved in seven countries**

https://www.nicox.com/assets/files/EN_VYZULTA-Approved-in-Seven-Countries_20200924_F1.pdf

October 13, 2020 **Nicox Announces Plans for NCX 4251 Phase 2 Trial in Blepharitis**

https://www.nicox.com/assets/files/EN_NCX4251Phase2TrialDesign_PR_20201013_F.pdf

October 20, 2020 Nicox Announces Third Quarter 2020 Business Update and Financial Highlights

https://www.nicox.com/assets/files/EN_Q3ResultsOctober2020_PR_20201020_F.pdf

October 23, 2020 **Nicox Selects Development Candidate in a New Class of NO-mediated Intraocular Pressure (IOP)**

https://www.nicox.com/assets/files/EN_NCX-1728-selection-PR_20201023_F..pdf

Lowering Agents

October 26, 2020 **Nicox's NCX 470 Receives Approval by Chinese Authorities for Local Start of Mont Blanc Phase 3 Trial**

https://www.nicox.com/assets/files/EN_NCX470Chinese-IND-Approval-PR_20201026_F.pdf

October 29, 2020 **Nicox Granted New Patent for NCX 470, Extending Exclusivity in Europe to 2039**
https://www.nicox.com/assets/files/EN_NCX-470-EUFormulation-Patent-Approval-PR_20201029_F1-1.pdf

November 10, 2020 **Nicox Initiates Second Phase 3 Trial of NCX 470 in Glaucoma**

https://www.nicox.com/assets/files/EN_NCX470-Denali-Phase-3-Start-PR_20201110_F.pdf

November 23,2020 **Nicox's Licensee Bausch + Lomb Launches VYZULTA® in Argentina**

https://www.nicox.com/assets/files/EN_VYZULTA-Argentina-Launch_20201123_F.pdf

November 25, 2020 **Nicox Analyst Coverage Initiated by Kepler Cheuvreux**

https://www.nicox.com/assets/files/EN_Kepler-coverage-initiation_VF.pdf

December 11, 2021 **Nicox's Partner Fera Pharmaceuticals to Investigate Naproxcinod as Potential Covid-19 Adjuvant Treatment**

https://www.nicox.com/assets/files/EN_FeraNaproxcinodCOVID_PR_F.pdf

December 15, 2021 **Nicox Initiates Phase 2b Trial of NCX 4251, a Potential First-in-Class Treatment for Blepharitis**

https://www.nicox.com/assets/files/EN_NCX4251-Mississippi-Phase-2b-Start_PR_20201215_F.pdf

December 22, 2021 **Nicox's Licensee Bausch + Lomb Secures Approval of VYZULTA® in Colombia**

https://www.nicox.com/assets/files/EN_VYZULTA-approval-Colombia_20201222_F.pdf

December 30, 2021 **Nicox's Partner Ocumension Therapeutics Initiates ZERVIATE Phase 3 Clinical Trial in China**

https://www.nicox.com/assets/files/EN_OcumensionZerviateChinaPhase3Trial_20201230_PR.pdf

January 5, 2021 **Nicox Highlights Successful 2020 Development Progress and Clinical Milestones for 2021**

https://www.nicox.com/assets/files/EN_Update-PR_20200105_F.pdf

January 6, 2021 **Nicox's Licensee Bausch + Lomb Launches VYZULTA® in Mexico**

https://www.nicox.com/assets/files/EN_VYZULTA-Launch-Mexico-PR_20210206_F.pdf

January 20, 2021 **Nicox Provides Fourth Quarter 2020 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_Q4-2020-Results-PR_20210120_F1.pdf

January 22, 2021 **Nicox Analyst Coverage Initiated by Edison Investment Research**

https://www.nicox.com/assets/files/EN_Edison-Nicox-Initiation-PR_20210122_F1.pdf

January 29, 2021 **Nicox Amends Bond Financing Agreement with Kreos to Provide Financial Flexibility in 2021**

https://www.nicox.com/assets/files/EN_Kreos-Amendment-PR_20210129_F.pdf

February 9, 2021 BAUSCH HEALTH ANNOUNCES VYZULTA® (LATANOPROSTENE BUNOD OPHTHALMIC SOLUTION), 0.024%, IS NOW APPROVED IN SOUTH KOREA

https://www.nicox.com/assets/files/EN_-Joint-PR_VYZULTA-approval-South-Korea_20210209_-F2.pdf

February 15, 2021 Nicox's U.S. Licensee Eyevance Expands U.S. Promotion of ZERVIATE® In Agreement with Hikma

https://www.nicox.com/assets/files/EN_ZERVIATEEyevanceNonOphthaCoPromote_PR_20210215_F.pdf

February 23, 2021 Nicox Announces the Publication in Leading Scientific Journal of Pre-Clinical Efficacy Results on a New Class of Non-PGA NO-donating IOP-Lowering Compounds

https://www.nicox.com/assets/files/EN_NCX1741-JOPT-PR_20210223_F.pdf

5.5 Competition

5.5.1 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 biodegradable 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.

5.5.2 Reduction of IOP in patients with glaucoma and ocular hypertension

Prostaglandin analogs are used as first line IOP lowering therapy and account for more than 50% of prescriptions for IOP lowering drugs in the U.S., where the leading branded product by sales is LUMIGAN (bimatoprost ophthalmic solution) 0.03% from Allergan, the other leading branded product is TRAVATAN Z (travoprost ophthalmic solution) 0.004% from Novartis, and the leading generic product is latanoprost. Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%, a fixed dose combination of netarsudil and latanoprost, was also approved and launched in the U.S. by Aerie Pharmaceuticals, or Aerie, in 2019. It was also approved in Europe in January 2021, under the brand name Roclanda. XELPROS (latanoprost ophthalmic emulsion) 0.005% was recently approved for IOP lowering in patients with open-angle glaucoma or ocular hypertension and was launched in the U.S. by a subsidiary of Sun Pharmaceutical Industries Ltd in 2019. Allergan, Inc., an Abbvie company, launched Durysta, a bimatoprost extended release biodegradable for IOP lowering, in the U.S.in 2020.The other products in the market, currently used mostly as adjunct therapies added on the top of PGAs, are alpha agonists, beta blockers and carbonic anhydrase inhibitors, most of which are available as generic as well as branded forms. Another adjunct therapy, Rhopressa (netarsudil ophthalmic solution) 0.02%, a Rho kinase inhibitor, was approved and launched in the U.S.by Aerie in 2018, and was approved under the brand name Rhokiinsa in Europe in 2019.

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 (excluding generics of existing, approved products):

- *Glaukos* is conducting Phase 3 clinical development of the 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.* has conducted Phase 3 clinical development of OTX-TP, a sustained release travoprost punctal plug formulation that is aimed at lowering IOP, which did not meet its primary endpoint. Other clinical studies are ongoing.

- *Santen* is developing DE117, an EP2 agonist for the lowering of IOP. It has been launched in Japan under the brand name EYBELIS and an NDA filing in the U.S. was planned for 2020.

5.5.3 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, together with generic olopatadine products. Olopatadine is now also available as a non-prescription drug in the U.S. The list below sets out the principal programs in Phase 3 (excluding generics of existing, approved products):

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

- *Faes Pharma*, has completed a Phase 3 clinical trial in the U.S. with bilastine for allergic conjunctivitis.

- *Ocular Therapeutix, Inc.* is developing Dextenza, a dexamethasone insert. It has completed a Phase 3 clinical trial for allergic conjunctivitis and an NDA submission was made in December 2020.

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. There are also antibiotic and antimicrobial products, such as ointments and eye drops, indicated for the treatment of blepharitis, along with other conditions. The list below sets out the principal programs in Phase 3 (excluding generics of existing, approved products):

- *Sun Pharma* is developing ISV-305, dexamethasone in DuraSite® 2, targeting the treatment of blepharitis, which has completed a Phase 3 clinical trial.

- *Tarsus Pharmaceuticals* is developing TP-03 for demodex blepharitis, currently in a Phase 2b/3 clinical trial.

5.5.4 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:

- *AntiRadical Technologies* is developing caged NO molecules for the treatment of life threatening disruption of blood flow.

- *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 NO 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.

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

- *Vast Therapeutics* is developing controlled and local delivery of NO via macromolecules for treatment of severe respiratory infections in patients with cystic fibrosis.

- *Zylo Therapeutics* is developing transdermal drug delivery systems including NO.

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.