CHAPTER 5 OF NICOX'S 2019 DOCUMENT D'ENREGISTREMENT UNIVERSEL
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5 OVERVIEW OF NICOX'S ACTIVITIES

5.1 Main activities

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. Our lead products and product candidates leverage our proprietary expertise in generating novel patentable molecules, which we believe are new chemical entities, or NCEs, that release nitric oxide, or NO. NO is a small signaling molecule that targets an intracellular enzyme, soluble guanylate cyclase, or 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, or PGAs, which is the most commonly prescribed class of IOP-lowering drugs, adds a potential second mechanism of action, or 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. VYZULTA, based on our proprietary NO-donating research platform, has been approved by the U.S. Food and Drug Administration, or FDA, and is indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. VYZULTA, exclusively licensed worldwide to Bausch + Lomb, a Bausch Health Companies Inc. company, is commercialized in the U.S. and in Canada and has been approved in Mexico, Hong Kong and Argentina.

NCX 470, which is our lead proprietary clinical development stage product candidate, is also based on our proprietary NO-donating research platform. NCX 470 is a novel, second generation NO-donating bimatoprost analog which completed the U.S., multicenter, dose-response, 433-patient, safety and efficacy Dolomites Phase 2 clinical trial for IOP lowering in patients with open-angle glaucoma or ocular hypertension. In the Dolomites Phase 2 trial, NCX 470 0.065% demonstrated both statistical non-inferiority and superiority in IOP lowering, based on the trial's pre-specified statistical analysis plan of IOP reduction, to latanoprost 0.005%, the U.S. market leader in prostaglandin analog prescriptions. NCX 470 demonstrated an IOP lowering effect as reduction from baseline of 7.6 to 9.8 mmHg at 8 AM, 10 AM and 4 PM across the Week 1, 2 and 4 Visits, which we believe is the highest reduction seen in a glaucoma clinical trial with an eye drop. All doses were well tolerated with no drug-related serious adverse events. Based on head-to-head comparisons in preclinical studies, which are publicly available in a peer-reviewed scientific journal, NCX 470 has demonstrated IOP lowering of up to 3.5 mmHg more than bimatoprost. Based on these results, we believe 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. We believe that NCX 470 would be a significant, clinically meaningful improvement over the current standard of care with the potential to become the leading first-line therapy for glaucoma. Following a positive End-of-Phase 2 meeting with the U.S. FDA, the Company expects to start the first Phase 3 clinical trial of NCX 470 (the Mont Blanc trial) by the end of Q2 2020, with top-line results expected in Q3 2021. The Mont Blanc trial will be initiated with 0.065% and 0.1% doses of NCX 470, with one dose being selected during the trial through an adaptive design. NCX 470 has been exclusively licensed to Ocumension Therapeutics, or Ocumension, for development and commercialization in mainland China, Hong Kong, Macau and Taiwan, or the Chinese market.

NCX 4251, our second, proprietary product candidate at an advanced clinical development stage, is developed for the treatment of acute exacerbations of blepharitis. Based on fluticasone, which is an FDA approved corticosteroid with well established efficacy and safety, NCX 4251 is designed to be applied directly to the eyelid margin, the location where the blepharitis disease and its related inflammation originates. 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 in development as a targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis, a common eye condition characterized by eyelid inflammation. With this novel route of delivery, we believe NCX 4251 has the potential to minimize ocular adverse events often seen with steroid eye drops. NCX 4251 completed the U.S. multicenter, dose escalating, first-in-human, 36-patient Phase 2 clinical trial (the Danube trial) evaluating its safety and tolerability in patients with acute exacerbations of blepharitis. 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, subject to the outcome of a meeting with the FDA scheduled in Q1 2020 and the necessary financial resources being secured. The selected dose NCX 4251 0.1% also demonstrated promising efficacy in reducing signs and symptoms of dry eye disease. NCX 4251 for blepharitis has been exclusively licensed to Ocumension for development and commercialization in mainland China, Hong Kong, Macau and Taiwan, or the Chinese market.

ZERVIATE™, previously AC-170, our second FDA-approved product, is indicated for the treatment of ocular itching associated with allergic conjunctivitis and has been exclusively licensed in the U.S. to Eyevance Pharmaceuticals LLC, or Eyevance. The commercial launch in the U.S. is planned by Eyevance in the first half of 2020. ZERVIATE has also been exclusively licensed for development and commercialization to Ocumension in the Chinese market and to Samil Pharmaceutical Co. Ltd, or Samil, in South Korea.

Our pipeline also includes the clinical development stage product candidate NCX 4280, previously AC-120, exclusively worldwide licensed to Ora, Inc., or Ora, which targets eyelid swelling or morning ocular congestion, as well as research programs focused on NO-donating phosphodiesterase-5, or PDE5, inhibitors that combine NO-release with other MOAs to potentially lower IOP.

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, second generation NO-donating bimatoprost formulated as an ophthalmic solution, which is currently in clinical development for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. NCX 470 completed the U.S., multicenter, dose-response, Dolomites Phase 2 clinical trial demonstrating non-inferiority and statistical superiority, based on the trial's pre-specified statistical analysis plan of IOP reduction, to latanoprost 0.005%, the U.S. market leader in prostaglandin analog prescriptions. Molecules from the first generation (VYZULTA) and second generation (NCX 470) 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. Following a positive End-of-Phase 2 meeting with the U.S. FDA, the Company expects to start the first Phase 3 clinical trial of NCX 470 (the Mont Blanc trial) by the end of Q2 2020, with top-line results expected in Q3 2021. The Mont Blanc trial will be initiated with 0.065% and 0.1% doses of NCX 470, with one dose being selected during the trial through an adaptive design.

Current in-house research on novel NO-donating PDE5 inhibitors (fully Nicox-owned) target new horizons in glaucoma research where NO is linked to pharmacologically active molecules using different, non-PGA, MOAs. Our research platform produced first and second generation NO-donating compounds, VYZULTA and NCX 470 respectively, that demonstrated greater IOP lowering than the parent PGA compounds, in clinical trials and preclinical studies, which is believed to be due to the additional lowering in IOP from the NO-donating MOA. We are therefore actively conducting research on NO-donating compounds from different non-PGA pharmacological classes where we add NO donation to another MOA and thus potentially increase their IOP lowering activity.

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

NCX 4251, our novel patented ophthalmic suspension of fluticasone propionate nanocrystals, is being developed as a targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis, a common eye condition characterized by eyelid inflammation. Fluticasone propionate, the active ingredient in NCX 4251, is a well-established corticosteroid which has been marketed for more than 20 years for a number of extra 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 eyelid margin for patients with acute exacerbations of blepharitis, a common eye condition characterized by eyelid inflammation. NCX 4251 completed the U.S. multicenter, dose escalating, first-in-human, 36-patient Danube Phase 2 clinical trial which evaluated its safety and tolerability in patients with acute exacerbations of blepharitis. In the Danube Phase 2 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, subject to the outcome of a meeting with the FDA scheduled in Q1 2020 and the necessary financial resources being secured. The selected dose of NCX 4251, 0.1%, also demonstrated promising efficacy in reducing signs and symptoms of dry eye disease.

NCX 4280 is an ophthalmic solution that targets eyelid swelling or morning eye congestion. Eyelid swelling or morning eye congestion is a common complaint of aging individuals and is a condition with a range of different underlying causes. In an exploratory Phase 2 clinical program, one formulation of NCX 4280 led to a reduction in morning eyelid swelling with results that showed statistical significance in a change from pre-dose baseline (no placebo or active comparator was used in this trial). NCX 4280 demonstrated acceptable tolerability, with no treatment-related adverse effects and evidence of systemic treatment-related adverse events. The follow-on trial did not meet its primary efficacy endpoint of improvement in eyelid swelling scores. Pursuant to the exclusive licensing agreement, the development of NCX 4280 is being advanced by Ora in order to continue the program and ultimately identify a development and commercial partner. Ora plans to advance NCX 4280 to further build the Phase 2 package and refine the clinical-regulatory pathway to guide the design of potential Phase 3 clinical trials. We expect the next stage of development will be a further Phase 2 clinical trial. NCX 4280 is expected to be an OTC product.

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, also known by the brand name XALATAN, a PGA, which is a chemical entity 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 prostaglandin analog approved by the FDA for the reduction of IOP with one of its metabolites being NO. NO further is believed to lower IOP by increasing the outflow of fluid from the eye by a different mechanism from PGAs via activation of sGC. 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. and Canada .VYZULTA has been also approved in Mexico, Hong Kong and Argentina.

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. The commercial launch of ZERVIATE in the U.S. is planned by Eyevance in the first half of 2020. ZERVIATE has also been exclusively licensed for development and commercialization to Ocumension in the Chinese market and to Samil in South Korea.

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 in 1996, 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 drugs with new MOAs approved in U.S. and European Union for the lowering of IOP 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 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 soap solution.

Worldwide, the sales of pharmaceutical ophthalmic treatments reached $19.9 billion in 2018 and have grown at a rate of 4% annually since 2014, according to IQVIA Health Analytics. In 2018, worldwide sales of treatments targeting glaucoma were $5.4 billion representing 27% of the $19.9 billion worldwide market for ophthalmic drugs. In the U.S. alone, ophthalmology sales reached $8.7 billion in 2018, growing at an average rate of 5% annually since 2014. With respect to our markets of focus, worldwide sales of treatments targeting glaucoma were $5.4 billion representing 27% of the $19.9 billion worldwide market for ophthalmic drugs and sales in the U.S.generated approximately $2.8 billion in the U.S.in 2018, growing at an annual rate of 8% since 2014 and representing 32% of the $8.7 billion total ophthalmic drug sales in the U.S. for 2018. While there are no approved treatments solely indicated for blepharitis, we estimate that the market potential for 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. and do not include substantial sales of non-prescription and over-the-counter products used to alleviate symptoms of ocular allergies.

Our intellectual property portfolio consists of patents and pending patent applications related to composition of matter, pharmaceutical compositions and methods of use for our product candidates. We have patent protection in the U.S. for VYZULTA (through 2025), ZERVIATE (through 2032) and our product candidates NCX 470 (through 2029 and formulation patent through 2039), NCX 4280 (through 2030) 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 31, 2019, we had 35 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 portfolio of products approved for commercialization in the U.S., VYZULTA and ZERVIATE, both of which may potentially be able to obtain marketing approval in other countries where the FDA submitted data are sufficient, or new data can be generated, for such approval;

- Our ability to identify and effectively advance additional product candidates, 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 attract leading biopharmaceutical companies into successful partnerships with Nicox, as demonstrated by our worldwide exclusive partnership agreement with Bausch + Lomb for VYZULTA;

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

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

- ***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 on NCX 470 and NCX 4251 with Ocumension in the Chinese market. In certain instances, as we have done with NCX 4280 with Ora, we may partner a program for exclusive development;

- ***Expand our product candidate pipeline through internal research efforts and possible in-licensing activities or acquisitions of additional ophthalmic product candidates or products.*** We plan to maintain and expand our internal research efforts focused on enhancing our pipeline of novel ophthalmic assets based on NO releasewhich are NO-donating PDE5 inhibitors as well as evaluating additional in-licensing or acquisition opportunities for additional ophthalmic candidates;

- ***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;

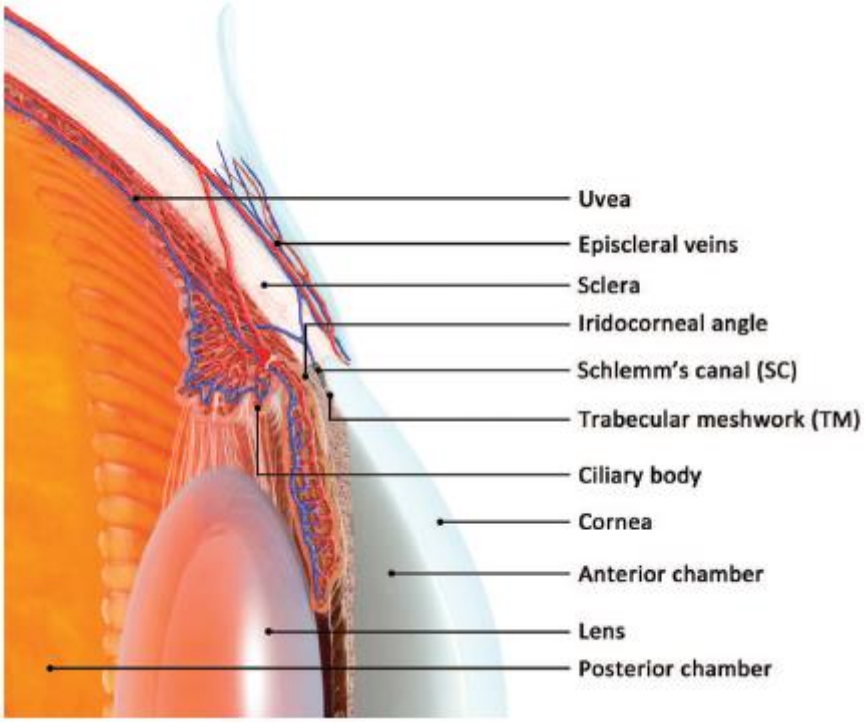
- ***Maximize the value of ZERVIATE through partnering.*** In September 2017, we entered into an exclusive licensing agreement with Eyevance for the commercialization of ZERVIATE in the U.S. We also entered into exclusive development and commercialization agreements with Ocumension for the Chinese market in March 2019 and with Samil in South Korea in December 2019. 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

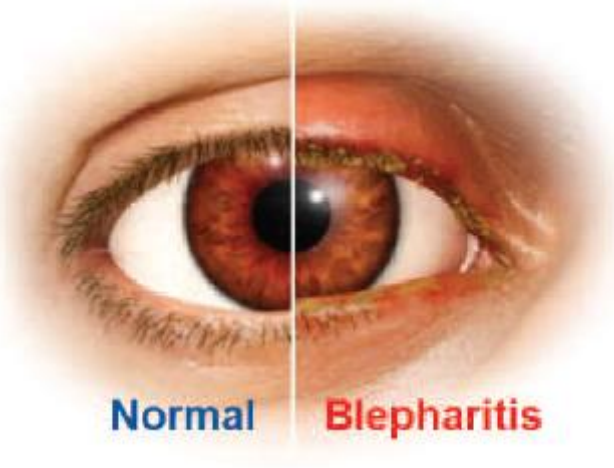
The eye is a fibrous globe that maintains its spherical geometry by being filled with a fluid called aqueous humor on the front side of the eye adjacent to cornea (also called the anterior segment) and a gel called vitreous humor on the back side of the eye adjacent to retina (also called the posterior 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 or near hair follicles) and scalp dandruff. Posterior blepharitis affects the inner edge of the eyelids, the moist part which makes contact with the tear film of the eye, and is most commonly caused by problems with certain eyelid oil glands, or meibomian glands. Acne, rosacea and scalp dandruff can also cause posterior blepharitis. 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.



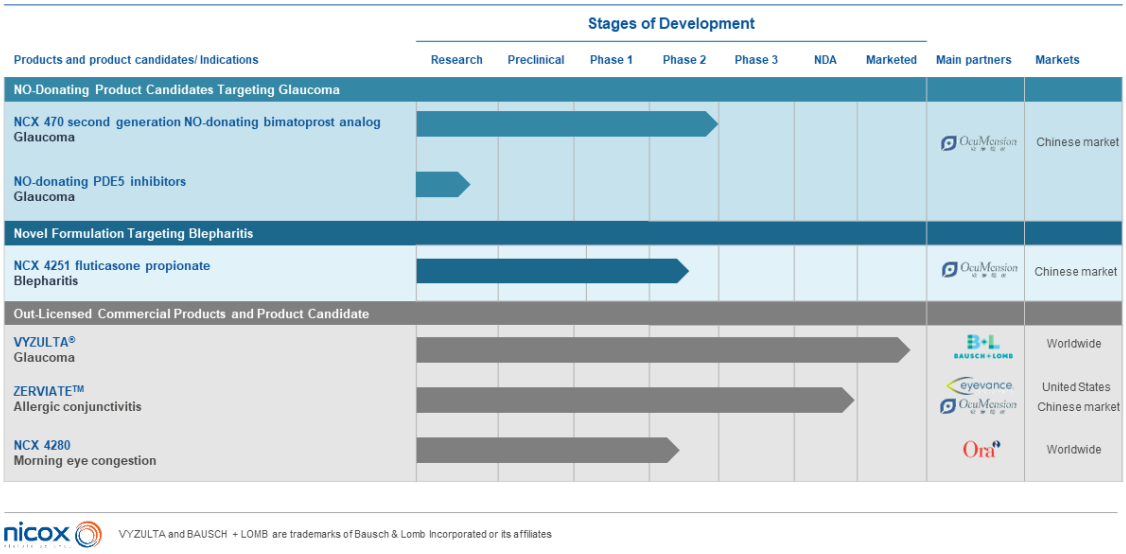
The picture below shows the inflammation (redness and swelling) of the eyelid associated with blepharitis.



5.1.5 Our Pipeline

Our ophthalmic pipeline features two products approved for commercialization by the FDA and product candidates in various stages of clinical development and research. 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 approved, two products in Phase 2 clinical development, and one program in research. 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 products, research and product candidate clinical development programs:



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Overview

Our product candidate pipeline features both clinical and research stage assets with a potential to offer novel treatments in various eye conditions. Those targeting the lowering of IOP in open-angle glaucoma and ocular hypertension are from our proprietary NO-donating research platform. We are also developing novel and proprietary formulations of well-established molecules that have previously been used in other indications and therapeutic areas. In addition, we have two products approved for commercialization by the FDA; VYZULTA commercialized in the U.S. and Canada by global exclusive partner Bausch + Lomb and approved in Mexico, Hong Kong and Argentina, and ZERVIATE whose commercial launch in the U.S. is planned by U.S. partner Eyevance in the first half of 2020.

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 intracellular enzyme sGC located 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 may be further increased or prolonged by PDE5 inhibitors, which inhibit phosphodiesterase type-5, an enzyme that degrades the second messenger, cGMP produced by sGC following its 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 and can be linked with another pharmaceutical agent. 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 is a novel, second generation NO-donating bimatoprost analog that has demonstrated statistical superiority to latanoprost, based on the trial's pre-specified statistical analysis plan of IOP reduction, in the Dolomites Phase 2 trial and which we believe also has the potential to become the first non-combination product with statistical superiority to a prostaglandin analog. We also believe 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 actively conducting research on NO-donating compounds of different chemical and pharmacological classes from those previously evaluated, in order to add NO donation to existing MOAs and thus potentially increase the overall IOP lowering potentials of the resulting new molecular entities. These new therapeutic agents are NO-donating PDE5 inhibitors. Data presented at the 2019 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO 2019), on the first lead molecule from the NO-donating PDE5 inhibitor program, NCX 1741, showed a statistically significant improvement vs. vehicle in lowering of IOP from baseline, averaged over all the time points at 24 hours, in a non-human primate model of ocular hypertension. We also have a second lead molecule from this program, NCX 1770. We expect to be able to announce an IND-track candidate from the NO-donating PDE5 inhibitor program in 2020.

Mechanism of action of NO and NO-donating prostaglandin analogs

Evidence suggests that prostaglandin analogs, which are indicated for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension, have a MOA 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. Prostaglandin analogs may have only a small impact on this pathway.

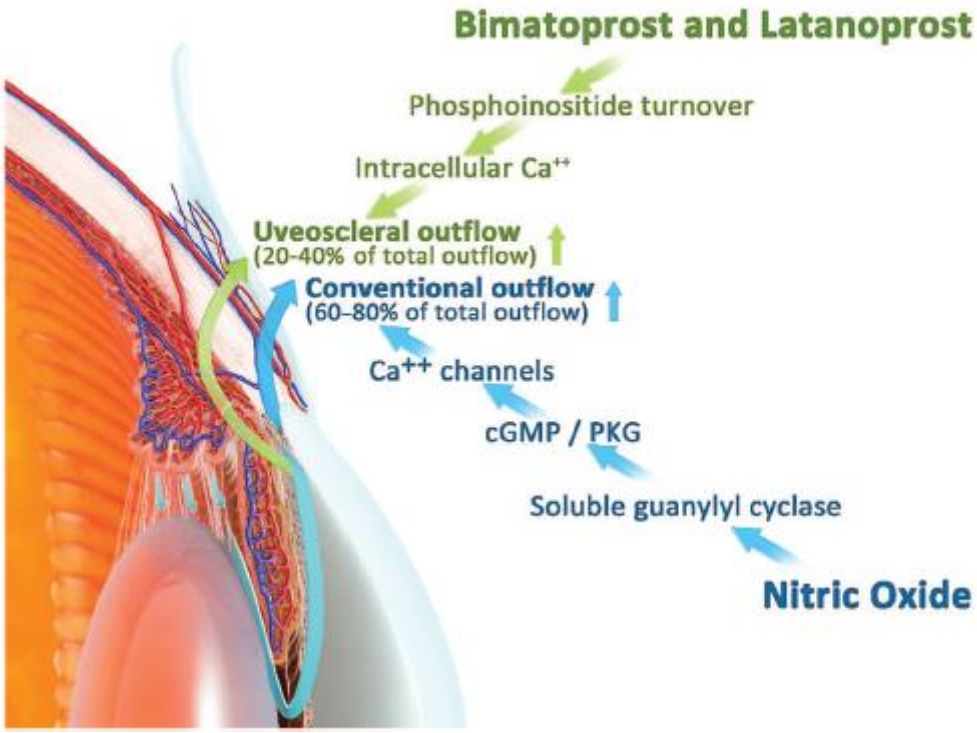
Because the primary or conventional pathway is known to be NO-sensitive, we sought to create a compound that would both release a prostaglandin analog to target the uveoscleral and secondary pathway by activating FP receptors and, at the same time, release NO to stimulate sGC to target the primary or 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 picture below shows the uveoscleral outflow, the secondary or non conventional outflow pathway that is prostaglandin sensitive, and the trabecular meshwork outflow, also known as the primary or conventional outflow pathway, which is NO-sensitive.

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, second generation NO-donating bimatoprost analog that we believe has the potential to become the first non-combination product with statistical superiority to a prostaglandin analog 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 in two different ways, or via two MOAs. Upon administration to the eye, NCX 470 and VYZULTA are transformed by certain enzymes present in the eye into the prostaglandin analogs, latanoprost acid and bimatoprost 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 figure below illustrates these MOAs:



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 does not usually cause any symptoms, except in cases of acute angle closure where the IOP may rise to three or four times that of normal IOP, but can lead to optic nerve damage and vision loss if left untreated. Optic nerve damage and vision loss can also occur in patients with normal IOP, 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 where the patient's IOP is within normal ranges.

IOP lowering is associated with a decreased risk in progression to open-angle glaucoma in subjects with ocular hypertension, as well as progression of visual field loss in patients with open-angle glaucoma; every mmHg of IOP-lowering results in a risk reduction in open-angle glaucoma progression of approximately 10% to 20%. Patients with open-angle glaucoma who attain target IOP-lowering have a lower risk of disease progression and vision loss.

In 2018, worldwide sales of treatments targeting glaucoma were $5.4 billion representing 27% of the $19.9 billion worldwide market for ophthalmic drugs. In the U.S., sales of treatments targeting glaucoma totaled $2.8 billion in 2018 (35.4 million prescriptions) or 32% of the $8.7 billion U.S. market for ophthalmic drugs. Of the U.S. sales of treatments targeting glaucoma, $1.4 billion, or approximately 50%, were sales of prostaglandin analogs, of which more than 85% were the branded products 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 prostaglandin analog eye drop, adjunctive therapies are added on the top of prostaglandin analogs 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 $1.4 billion of the $2.8 billion U.S. sales of treatments targeting glaucoma in 2018. 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, 35.4 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 second generation NO-donating bimatoprost analog in development for the lowering of IOP in patients with open-angle glaucoma and ocular hypertension. NCX 470 has completed the Dolomites safety and efficacy Phase 2 clinical trial. NCX 470 is designed to release both bimatoprost and NO following instillation into the eye. Bimatoprost, marketed under the brand name LUMIGAN by Allergan, Inc., is the leading product in the class of 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. Additionally, the highest NCX 470 concentration studied in the completed Dolomites Phase 2 trial delivered up to 2.4 times more nitric oxide compared to VYZULTA. We believe that, through the addition 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.

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 v. 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 which, subject to FDA agreement, may be tested in future clinical trials.

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=0.0242 at 8 AM, p=0.0013 at 10 AM, and p=0.0016 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 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.

Future 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. The Mont Blanc trial, the first Phase 3 clinical trial of NCX 470, is expected to start by the end of Q2 2020, with top-line results expected in Q3 2021. The Mont Blanc trial will be initiated with 0.065% and 0.1% doses of NCX 470, with one dose being selected during the trial through an adaptive design. Additional details of the trial design will be disclosed following the initiation of the trial.

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, a 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 three but with improved safety and tolerability vs ROCKLATAN was selected for the second profile, and ~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

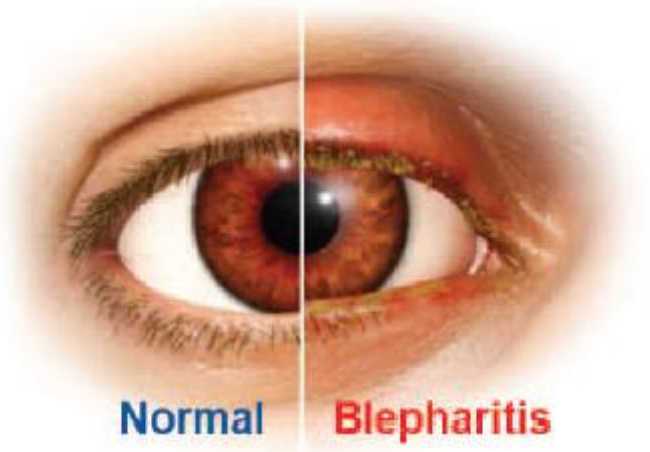
Another of our product candidates, which leverages an established molecule, is NCX 4251, a novel patented ophthalmic suspension of fluticasone propionate nanocrystals which is being developed as a targeted topical treatment of the eyelid margin for patients with acute exacerbations of blepharitis. We 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 eyelid margin for 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 eyelid applicator to the eyelid margin, applied directly to the site where the disease originates and thereby minimizing potential penetration of the drug through the cornea which can lead to the damaging side effects such as IOP increase found with current topical steroids.

In July 2019, we entered into an exclusive license agreement with Ocumension Therapeutics 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 or near hair follicles) and scalp dandruff. Posterior blepharitis affects the inner edge of the eyelids, the moist part which makes contact with the tear film of the eye, and is most commonly caused by problems with certain eyelid oil glands, or meibomian glands. Acne, rosacea and scalp dandruff can also cause posterior blepharitis. 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 man administration, dose-escalation, 14-day Phase 2 clinical trial (the Danube trial) 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 2b clinical trial, subject to the outcome of a meeting with the U.S. Food and Drug Administration (FDA) scheduled in Q1 2020 and the necessary financial resources being secured.

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 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 combined eyes and contralateral eyes).

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

Research programs

NO-donating phosphodiesterase 5 (PDE5) inhibitors

We are focusing our research efforts on ocular disorders where NO is believed to play a major role as a modulator, including glaucoma and ocular hypertension. Our research platform produced first and second generation NO-donating compounds, VYZULTA and NCX 470, that demonstrated greater IOP lowering than the parent PGA compounds, in clinical trials and preclinical studies respectively, which 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.

We are therefore actively researching NO-donating compounds of different, non-PGA chemical and pharmacological classes to add NO donation to another MOA and thus to potentially increase the overall IOP lowering activity of the resulting new therapeutic agent classes. Our research activities include, among others, a collaboration with Novaliq to investigate novel formulations that could potentially improve ocular comfort and enhance drug delivery performance with no antimicrobrial preservative for these NO-donating compounds. Some of these are new therapeutic agent classes directly targeting primary outflow by combining NO release with other pharmacological actions. These new therapeutic agent classes are NO-donating PDE5 inhibitors which have the potential to be developed alone or as an adjunctive therapy. For patients whose glaucoma is not well-controlled on a single prostaglandin analog eye drop, adjunctive therapies are added on the top of prostaglandin analogs 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.

Data from the NO-donating PDE5 inhibitor program were presented at ARVO 2019. The first lead molecule from the NO-donating PDE5 inhibitor program, NCX 1741, showed a statistically significant improvement vs. vehicle in lowering of IOP from baseline, averaged over all the time points at 24 hours, in a non-human primate model of ocular hypertension. We also have a second lead molecule, NCX 1770 from this program. We expect to be able to announce an IND-track candidate from the NO-donating PDE5 program in 2020.

The Company is no longer working on NO-donation combined with sGC activation and the collaboration with Cyclerion Therapeutics is being terminated.

Our Out-Licensed Commercial Products and Product Candidate

VYZULTA—Our Lead Commercial Product

Overview

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024% is a PGA with one of its metabolites being NO. VYZULTA is the first eye drop approved in the past twenty years with a novel approach to reduce 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. and Canada and has been also approved in Mexico, Hong Kong and Argentina.

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 a Phase 2 clinical trial and two Phase 3 clinical trials.

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 significant greater IOP lowering than twice-daily dosed timolol maleate ophthalmic solution 0.5% throughout the day at three months of treatment. Based on analysis of the pooled results of these trials, the IOP lowering from baseline was in the range of 7.5-9.1 mmHg across three months of treatment. 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 prostaglandin analog approved by the FDA for the lowering of IOP with one of its metabolites being NO and the only once-daily single-agent IOP-lowering product to provide activity through two 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. where a commercial launch is planned by Eyevance in the first half of 2020. In March 2019 we entered into an exclusive licensing agreement with Ocumension Therapeutics for the development and commercialization of ZERVIATE in the Chinese market. Ocumension is expected to have to conduct additional clinical trials for the regulatory approval of ZERVIATE in the Chinese market. In December 2019 we also entered into an exclusive licensing agreement with Samil for the development and commercialization of ZERVIATE in South Korea.

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.

NCX 4280

NCX 4280 is an ophthalmic solution that targets eyelid swelling or morning eye congestion. Eyelid swelling or morning eye congestion is a common complaint of aging individuals and is a condition with a range of underlying causes. In an exploratory Phase 2 clinical program, one formulation of NCX 4280 led to a reduction in morning eyelid swelling with results that showed statistical significance in a change from pre-dose baseline (no placebo or active comparator was used in this trial). NCX 4280 demonstrated acceptable tolerability, with no treatment related adverse effects and evidence of systemic treatment-related adverse events. The follow-on trial did not meet its primary efficacy endpoint of improvement in eyelid swelling scores. Pursuant to the exclusive licensing agreement, the development of NCX 4280 is being advanced by Ora in order to continue the program and ultimately identify a development and commercial partner. Ora plans to advance NCX 4280 to further build the Phase 2 package and refine the clinical-regulatory pathway to guide the design of potential Phase 3 clinical trials. We expect the next stage of development for NCX 4280 will be a further Phase 2 clinical trial. NCX 4280 is expected to be an OTC product.

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.

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

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

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

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

Eyevance Pharmaceuticals

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

Under the agreement, Eyevance made a one-time non-refundable upfront payment to us of $6.0 million in 2017 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. This amount will become payable only when Nicox receives royalty payments from Eyevance and will be directly deducted from these 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. The commercial launch of ZERVIATE in the U.S. is planned by Eyevance in the first half of 2020.

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

Fera Pharmaceuticals

In November 2015, we entered into an exclusive license agreement with Fera Pharmaceuticals, or Fera, granting Fera exclusive rights to develop and commercialize naproxcinod in the United States. The agreement was amended in September 2018. Naproxcinod is a Cyclooxygenase-Inhibiting Nitric Oxide-Donating, or CINOD, anti-inflammatory product candidate. The development will focus on an undisclosed rare disease. Fera is conducting pre-clinical proof-of-concept studies on naproxcinod and may submit an application for an Orphan Drug Designation to the FDA. Fera believes that naproxcinod will be able to enter directly into a future clinical efficacy trial in patients.

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

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

Our product candidate naproxcinod is a non-steroidal anti-inflammatory drug, or NSAID, that is an NO-donating naproxen. The NO-donating MOA makes naproxcinod a CINOD, a class of drugs that are hoped to produce similar analgesic efficacy to traditional NSAIDs, but with an improved gastrointestinal and cardiovascular side effect profile. We 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.

Novaliq

In December 2018 we entered into a research collaboration with Novaliq GmbH for the development of novel topical ophthalmic formulations of our NO-donating PDE5 inhibitors based on Novaliq's water-free enabling EyeSol® technology, for lowering intraocular pressure (IOP). In this collaboration, Novaliq is developing and characterizing novel formulations for lead series of the NO-donating PDE5 inhibitor new chemical entities using its EyeSol® technology. If successful, we will be testing the novel topical ophthalmic formulations of NO-donating PDE5 inhibitors for IOP lowering activity in established preclinical models. Newly developed intellectual property from the collaboration will be jointly owned.

Ocumension Therapeutics

In December 2018 we entered into an exclusive license agreement with Ocumension 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. Ocumension is expected to have to conduct additional clinical trials for the regulatory approval of NCX 470 in the Chinese market. 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 will receive a further €2.5 million when we initiate a Phase 3 clinical trial with NCX 470 outside the territory of this agreement. Under this agreement, we are also eligible to receive up to an additional €14.5 million in milestones associated with Ocumension's progress with NCX 470, up to and including regulatory approval, and up to €16.25 million split over three separate sales milestones associated with potential sales in the territory of up to € 200 million, as well as tiered royalties from 6% to 12% on sales.

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 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 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.

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.

Ora

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

Under the terms of the exclusive worldwide license agreement, Ora will be responsible for all development activities and will fund this program through its investment arm with which products from clients and partners are incubated and advanced with the goal to help find a final development and commercial partner. Ora plans to continue the clinical development of NCX 4280 before sub-licensing this compound to a third party for future commercialization. We are eligible to receive a $10 million milestone payment from Ora upon approval of NCX 4280 by the FDA. We are also eligible to receive 12.5% of any proceeds received by Ora under a potential sub-license agreement. If Ora or its affiliates sell licensed products, we are eligible to receive a tiered royalty of 3% to 4% of net sales from such products. Upon Ora's submission to a drug approval agency in Germany, UK, France, Italy and Spain to market a licensed product, we have a right of first negotiation to exclusively commercialize and sell licensed products in that country. We have no additional financial obligations under this agreement.

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

Pfizer

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

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 Pharmaceutical 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.

VISUfarma

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

In September 2017, we amended the terms of the partnership agreement. Under the terms of the amended agreement, we agreed to amend the terms and conditions related to the €5 million potential milestone payments, which would have been made in a combination of ordinary shares and interest-bearing loan notes. As a result of the amended agreement, we received an additional €1.65 million in upfront consideration in a combination of ordinary shares and interest-bearing loan notes, making the total consideration for the assets equal to an aggregate of €22.65 million, increased from the €21 million initially. We are now eligible to receive a milestone payment of up to €3.35 million in a combination of ordinary shares and interest-bearing loan notes if certain business objectives are achieved by VISUfarma. We will also no longer be responsible for completing development and regulatory approval for NCX 4240 in Europe, but will retain rights to develop NCX 4240 in the U.S. and Japan. However, we currently have no such development plans, and there is no guarantee that this program will be developed further. Subsequently, we agreed with VISUfarma that we will no longer be responsible for completing development and regulatory approval for AzaSite in Europe. Finally, we made a one-time cash payment of € 479,000 to VISUfarma. As a minority shareholder, we have a right to occupy one seat on the board of directors of the new company, which we do not currently occupy and reserve the ability to exercise this right.

5.2.2 Other Strategic Partnerships

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

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

The Group's patent and patent application portfolio covers a number of products. The Group has granted patents on products covering a wide range of nitric oxide donating products and its main products in development. The Group has also filed patent applications for composition of matter covering a wide range of drugs classes, including non-steroidal anti-inflammatory drugs, prostaglandins, angiotensin inhibitors and nitric oxide donors.

As of December 31, 2019, our patent portfolio included 239 issued patents and 61 pending patent applications and 4 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 14 patents granted by the European Patent Office, or EPO, 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 a patent which expires in October 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.

Teva Pharmaceuticals filed a patent opposition on November 23, 2016 for the European patent covering latanoprostene bunod. On July 13, 2018, the Opposition Division of the European Patent Office rejected this patent opposition. On September 12, 2018, Teva Pharmaceuticals filed an appeal of this decision of the European Patent Office. 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 patent applications are currently under examination. If issued, these patents 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 by a parent patent which expires in 2033. In Europe, a patent application for NCX 4251 is currently under examination and would provide protection until 2033 if accepted.

In July 2019, Nicox filed an US provisional application covering a process for the preparation of the NCX 4251 formulation under development; the patent family deriving from this US provisional application, if granted, will provide worldwide patent coverage until 2039 -2040.

Nicox is the holder of patent applications in, Canada, Mexico and Japan covering NCX 4240, its composition of matter and therapeutic treatment and the patent applications at the national level are under review. These patents will provide protection until 2035.

The US patent was granted in March 2019, the patent expires in 2035.

NCX 470 is covered by a family of product patents which includes patent US 8 101 658 expiring in 2029 and European patent EP 2 274 279 which will cover France, Germany, Italy, Spain and the United Kingdom. The product patent family also includes equivalent patents delivered in Canada, Japan, China, Hong Kong, Argentina and India which will remain in force until 2029. Patent US 8 101 658 is eligible for a patent term extension which, if granted, may extend the initial expiration date for a period of up to five years, it being specified that this extension may not exceed 14 years after the product marketing authorization date.

In 2019, Nicox filed a PCT application and national patent applications in USA, EU (EPC), CN, JP, TW and AR covering the NCX 470 formulation under development. Nicox received a formulation patent extending NCX 470 U.S. patent coverage to 2039. In addition Nicox filed a PCT application and other patent applications covering the industrial process of synthesis of NCX 470. These patent families, if granted, will provide worldwide patent coverage for NCX 470 until 2039 - 2040.

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, 2019. 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		EP			
	Europe#	1 704 141	27-Dec-2004	24-Feb-2016	27-Dec-2024
		US			
	United States	7,273,946^	05-Jan-2005	25-Sep-2007	03-Oct-2025
		US			
		7,449,469	05-Jan-2005	11-Nov-2008	05-Jan-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 - 05-Jan-2025
Pending.....		EP			
	Europe	191962383	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 with the maintenance of the patent as granted. A notice of appeal against the decision of the Opposition Division was filed by TEVA on September 12, 2018. On March 2019, Nicox filed a reply to the grounds of appeal filed by TEVA. 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 6 033 677	15-March-2010	04-Nov-2016	15-March-2030
		JP 6 144 393	12-Aug-2016	19-mai-2017	15-March-2030
		JP 6 449 202	12-Aug-2016	14-dec-2018	15-March-2030
	other country	CA 2 755 679	15-March-2010	12-Sept-2017	15-March-2030
Pending	Europe	EP 2 408 453	15-March-2010	—	15-March-2030
	United States	US 16/001,679	06-June-2018	—	15-March-2030
	Japan	JP 2018-118671	22-June-2018		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		EP			
	Europe#	2 274 279	11-May-2009	31-July-2013	11-May-2029
		US			
	United States	8,101,658	11-May-2009	24-Jan-2012	11-May-2029
		JP			
	Japan	5 401 540	11-May-2009	01-Nov-2013	11-May-2029
	5 other countries		11-May-2009	Apr 2014 - Feb 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.

In 2018, Nicox filed two European patent applications covering, respectively, the industrial process of synthesis of NCX 470 and the NCX 470 formulation under development; the patent families claiming priority of the above applications, if granted, will provide worldwide patent coverage until 2039.

In 2019, Nicox filed a PCT application and national patent applications in the U.S., EU (EPC), China, Japan, Taiwan and Argentina claiming the priority of the above mentioned European patent application covering the NCX 470 formulation under development, and a PCT application and national patent applications in Taiwan and Argentina claiming the priority of the above mentioned European patent application covering the industrial process of synthesis of NCX 470. These two patent families, if granted, will provide worldwide patent coverage for the NCX 470 formulation and its method of synthesis until 2039.

In August 2019, Nicox filed two European patent applications covering improvements of the current industrial process of synthesis of NCX 470; the patent families deriving from these EPC applications, if granted, will provide further patent coverage until 2039-2040.

NCX 4251 (Fluticasone propionate nanocrystals)

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

This patent family covers nanoplates of Fluticasone propionate Form I (Form A) wherein the nanoplates have the c-axis crystallographic direction normal to the surfaces that define the thickness of the nanoplates.

This patent family also covers methods for treating or alleviating symptoms of blepharitis, post-operative ocular inflammation, dry eye or eye allergy and the method for preparing the Fluticasone propionate nanoplates.

Patent owner: Nicox Ophthalmics Inc.

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted		US			
	United States	8,765,725	07-Jan-2013	01-July-2014	7-Jan-2033
		US			
	United States	10,174,071	26-July-2018	8-Jan-2019	06-May-2033
	Japan	JP 6285419	06-May-2013	09-Feb-2018	06-May-2033
	Japan	JP 6564891	01-Feb-2018	21-Aug-2019	06-May-2033
		EP			
	Europe	2 847 207^	06-May-2013	27-March-2019	06-May-2033
	5 other countries		06-May-2013	Aug-2016 - Aug-2018	06-May-2033
Pending		EP			
	Europe	19156409.5	11-Feb-2019	—	06-May-2033
		US			
	United States	16/203,324	29-Nov-2018	—	06-May-2033
		JP 2018-			
	Japan	016232	06-May-2013	—	06-May-2033

(*) 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)

In July 2019, Nicox filed a U.S. provisional application covering a process for the preparation of ophthalmic nanosuspensions containing Fluticasone propionate nanocrystals. The U.S. provisional application also includes claims directed to NCX 4251 formulation under development. The patent family deriving from this U.S. provisional application, if granted, will provide worldwide patent coverage until 2039-2040.

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 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, 2019

January 4, 2019: **VYZULTA Approved in Canada by Nicox's Partner**

https://www.nicox.com/assets/files/EN-VYZULTA-Canada-PR_-2019-01-04_2_Fa.pdf

January 8, 2019: **Nicox Reaches 50% Enrollment Threshold in U.S. Phase 2 Study with NCX 470 Ahead of Schedule**

https://www.nicox.com/assets/files/EN-NCX-470-enrollment-PR_20190108.pdf

January 17, 2019: **Nicox Fourth Quarter 2018 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN-_Q4-2018-PR-_20190117_-F2.pdf

January 25, 2019: **Nicox extends cash runway beyond 2020 with bond financing from Kreos Capital of up to €20 million**

https://www.nicox.com/assets/files/EN-_Kreos-PR_201901.pdf

January 28, 2019: **Nicox Establishes High-Profile Glaucoma Clinical Advisory Board**

https://www.nicox.com/assets/files/EN_Nicox-GAB-PR-_20190128-_F.pdf

January 29, 2019: **Nicox Announces U.S. FDA Acceptance of Investigational New Drug Application for NCX 4251 Phase 2 Trial in Blepharitis**

https://www.nicox.com/assets/files/EN_NCX4251_IND_PR_20190129.pdf

March 6, 2019: **Nicox Announces 2018 Financial Results and 2019Milestones**

https://www.nicox.com/assets/files/EN_FY_2018_PR_20190306_F1-1.pdf

March 15, 2019: **Nicox signs agreement for ZERVIATETM in China for up to €17 million in milestone payments plus royalties**

https://www.nicox.com/assets/files/EN_Ocumension_ZERVIATE_PR_20190315_F.pdf

March 18, 2019: **Nicox Poster Presentation at AGS 2019 Annual Meeting Discloses Preclinical Data for NCX 4251, a Novel Blepharitis Therapy**

https://www.nicox.com/assets/files/EN_-AGS-NCX-4251-poster-presentation_20190318.pdf

March 19, 2019: **Nicox Initiates Phase 2 Trial of NCX 4251 in Blepharitis**

https://www.nicox.com/assets/files/EN_NCX4251_Phase2-start_March-2019_F.pdf

April 18, 2019: **Nicox First Quarter 2019 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_2019Q1Results_20190418cy22.pdf

May 3, 2019: **Nicox Presents First Data on Promising New Class of Nitric Oxide (NO)-Donating Compounds for Glaucoma at the ARVO 2019 Annual Meeting**

https://www.nicox.com/assets/files/EN_NOPDE5_ARVO_PR_052019_FINAL.pdf

May 6, 2019: **Dr. Thomas Walters Presents Update on Nicox's NCX 470 Phase 2 Clinical Study in Podium Presentation at ASCRS 2019**

https://www.nicox.com/assets/files/EN_NCX470_ASCRS_2019_PR_FINAL2.pdf

July 2, 2019: **Nicox signs agreement for NCX 4251 in China with Ocumension Therapeutics for up to €12 million in milestones plus royalties**

https://www.nicox.com/assets/files/EN_Ocumension-deal-NCX-4251_PR_July-2.2019.pdf

July 9, 2019: **Nicox Receives $3 Million Milestone Payment from Eyevance for ZERVIATE™ in the U.S.**

https://www.nicox.com/assets/files/EN_ZERVIATE_MANUFACTURING_MILESTONE_PR_July-9.-2019.pdf

July 16, 2019: **Nicox Announces Completion of Enrollment in NCX 470 Phase 2 Clinical Study with Top-Line Results on Track for Early 4Q 2019**

https://www.nicox.com/assets/files/EN_NCX470_ENROLLEMENT_COMPLETION_PR_16July.pdf

July 17, 2019: **Nicox: Second Quarter 2019 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_Q2_2019_Results_PR_Final_1a_clean_July17.2019.pdf

September 17, 2019: **Nicox: First Half 2019 Financial Results and Business Update**

https://www.nicox.com/assets/files/EN_H12019_Results_PR_20190917.pdf

September 27, 2019: **Nicox Completes Enrolment of NCX 4251 Phase 2 Trial with Top-Line Results on Track for Q4 2019**

https://www.nicox.com/assets/files/EN_NCX4251_CompleteRecruitment_20190927_F.pdf

October 2, 2019: **Top Line Results from Glaucoma Dolomites Phase 2 Trial Show Nicox's NCX 470 Meets Primary Endpoint and Demonstrates Statistical Superiority vs Latanoprost**

https://www.nicox.com/assets/files/EN_NCX470_Phase2_Results_20191002.pdf

October 10, 2019: **Nicox Amends Bond Financing Agreement with Kreos and Draws Down Additional €4 Million**

https://www.nicox.com/assets/files/EN_KreosAmendment2_PR_20191010.pdf

October 16, 2019: **Nicox: Third Quarter 2019 Business Update and Financial Highlights**

https://www.nicox.com/assets/files/EN_Q3_2019_ResultsPR_20191016.pdf

October 22, 2019: **Nicox Reports Positive Results of Secondary Analyses from Phase 2 Trial Further Highlighting Potential of NCX 470 in Glaucoma**

https://www.nicox.com/assets/files/EN_NCX-470-Additional-Results_20191022_Final-1.pdf

November 18, 2019: **Nicox Raises €12.5 Million to Advance NCX 470 into Phase 3 in Glaucoma**

https://www.nicox.com/assets/files/EN_PIPE-2019_20191118-.pdf

December 6, 2019: **Nicox signs agreement for ZERVIATE™ in South Korea**

https://www.nicox.com/assets/files/EN_ZERVIATE-SOUTH-KOREA-AGREEMENT-PR_-F_-20191206.pdf

December 17 2019: **Nicox Draws Down Last Tranche from Bond Financing Agreement with Kreos Capital to Support Key Development Programs**

https://www.nicox.com/assets/files/EN_KREOS_DRAWDOWN_F_20191217.pdf

December 19, 2019: **Nicox's NCX 4251 Meets Primary Endpoint in Phase 2 Blepharitis Trial and Shows Promising Efficacy in Dry Eye Disease**

https://www.nicox.com/assets/files/EN_NCX-4251Danube-Ph.2-results_20191219.pdf

5.4.2 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

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. A New Drug Application has been filed in Europe for Roclanda (the name of Rocklatan in Europe). 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. 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. A MAA has been filed in Europe for Rhopressa.

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

- *Allergan, Inc*. has filed an NDA for bimatoprost extended release, a biodegradable intraocular insert consisting of bimatoprost and a biodegradable polymer matrix for IOP lowering, in the United States.

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

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

- *Ocular Therapeutix, Inc.* 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.

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

- *Senju* has conducted Phase 3 clinical development of SJP0125 which is now pending approval in Japan.

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. Olopadine is now also a non-prescription drug available in the U.S. The list below sets out the principal programs in Phase 3 or above (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 is currently in Phase 3 clinical trials for allergic conjunctivitis.

Blepharitis

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

- *Sun Pharma* is developing ISV-305, dexamethasone in DuraSite® 2, targeting the treatment of blepharitis, which is currently in a Phase 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 nitric oxide 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 nitric oxide for application in wound care, dermatology, critical care, respiratory and transdermal drug delivery
- *Kowa Pharmaceutical Europe Co. Ltd.* markets HYPADIL Kowa Ophthalmic Solution 0.25% in Japan for the treatment of glaucoma and intraocular hypertension. The active ingredient of this drug is nipradilol, an alpha- and beta-adrenergic blocker with NO-releasing action.
- *Mallinckrodt PLC* markets INOmax in the United States, a gaseous NO product for the treatment of persistent pulmonary hypertension of the newborn.
- *Novan Therapeutics* is developing NO donors for the treatment of acne, viral infections, onychomycosis and inflammatory skin disease. Their most advanced program is in Phase 3.
- *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 nitric oxide.

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