EDISON

Nicox

Initiation of coverage

Focus on sight

Pharma & biotech

Nicox develops drugs for eye diseases, with lead candidate NCX-470 in Phase III trials targeting the topical treatment of glaucoma by utilising and expanding on an already-established dual IOP-lowering mechanistic approach. Top-line data from Mont Blanc, the first of two Phase III studies, are expected in H122, and we expect a 2024 launch and sales of over €450m in 2030 in the US and major markets. Nicox is well funded through the Mont Blanc inflection point and we derive an rNPV valuation of €304m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/18	4.7	(18.6)	(0.63)	0.0	N/A	N/A
12/19	8.3	(16.0)	(0.40)	0.0	N/A	N/A
12/20e	10.4	(10.1)	(0.29)	0.0	N/A	N/A
12/21e	10.0	(16.7)	(0.45)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

NCX-470 takes aim at first-line glaucoma therapy

NCX-470 is based on the company's proprietary nitric oxide (NO) donating platform, which combines an NO-donating molecule with an analogue of established prostaglandin F2α (PGA) drug bimatoprost, thereby providing an additional mechanism for the drug to reduce intraocular pressure (IOP). NCX-470 0.065% has shown 1.4mmHg additional IOP lowering compared to latanoprost (the mostly commonly prescribed glaucoma drug in the US) in the Phase II study. The Phase III programme is testing a higher 0.1% concentration of NCX-470 and may even provide further IOP reduction, potentially positioning NCX-470, if approved, as the most potent single-agent glaucoma drug on the market in terms of IOP lowering efficacy.

Additional ophthalmic assets add value

NCX-4251 started Phase IIb studies in Q420 for the treatment of acute exacerbations of blepharitis, an indication with no specific FDA-approved product to date. Nicox also obtains recurring revenue from two out-licensed commercial-stage assets, Vyzulta (latanoprostene bunod) and Zerviate (topical cetirizine), where it obtains royalty rates no lower than mid-single digits. Vyzulta, Nicox's first NO-donating PGA drug, is approved for the treatment of glaucoma and licensee Bausch + Lomb (B+L) reported US$13m in net sales (up 30% y-o-y) in Q320. Zerviate is a topical antihistamine drug based on a commonly prescribed oral drug, and was launched by Eyevance (now owned by Santen) in 2020.

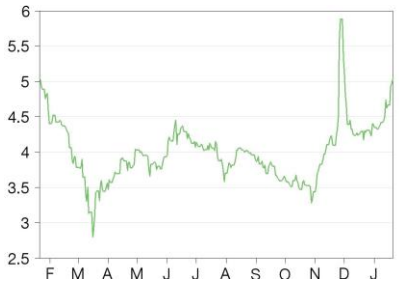
Valuation: rNPV of €304m

Our Nicox valuation applies a risk-adjusted net present value (nNPV) model with a 12.5% cost of capital and includes the prospects for NCX-470, NCX-4251, and the Vyzulta and Zerviate royalties. We obtain an rNPV of €303.7m. After including €29.4m in end-FY20 net cash, we obtain an equity valuation of €333.1m or €8.99/share. We model that Nicox's funds on hand should last into H222 and that it will raise €40m between 2022 and 2024 before launching NCX-470 in 2024.

21 January 2021

Price	**€5.00**
Market cap	**€185m**
	$1.23/€
Net cash (€m) at 31 December 2020	29.4
Shares in issue	37.03m
Free float	98%
Code	COX
Primary exchange	Euronext
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	17.3	40.0	(1.0)
Rel to TA-100	14.9	22.5	6.0
52-week high/low		€5.88	€2.80

Business description

Based in France, Nicox develops therapeutics for the treatment of ocular conditions. Lead development candidate NCX-470 is in Phase III studies for the treatment of glaucoma. Nicox also receives licence revenue from its partners for its FDA-approved drugs Vyzulta and Zerviate.

Next events

Phase IIb NCX-4251 top-line results	Q421
Mont Blanc Phase III NCX-470 top-line results	H122

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Edison profile page

Investment summary

Company description: Bench strength in eye care assets

Based in France, Nicox is a pharmaceutical company with multiple therapeutics assets in the ophthalmic sector, with lead candidate NCX-470 in Phase III trials targeting the topical treatment of glaucoma by utilising and expanding on an already established dual IOP-lowering mechanistic approach based on applying a nitric oxide-donating molecule to a leading prostaglandin F2α analogue (PGA) drug. If approved, NCX-470 would be the first monotherapy drug to demonstrate statistical superiority in Phase III to an existing approved PGA drug. NCX-4251, in Phase IIb studies, is being developed as a potential first-in-class treatment for acute exacerbations of blepharitis. Nicox also has commercialised assets, Vyzulta (latanoprostene bunod) and Zerviate (cetirizine ophthalmic), already on the market and marketed via commercial partners, enabling the company to obtain recurring royalty income. Nicox intends to commercialise NCX-470 itself at least for the US market and we expect that the drug's potential market introduction in 2024 could help transition Nicox into a consistently profitable commercial ophthalmic drug company.

Exhibit 1: Nicox upcoming catalysts

Event	Timing
NCX-470 Mont Blanc and Denali enrolment updates	H121
NCX-4251 Phase IIb top-line results	Q421
NCX-470 Mont Blanc Phase III top-line results	H122
NCX-470 Denali Phase III top-line results	Q422

Source: Edison Investment Research

Valuation: Pipeline rNPV of €304 reflects upside

Our Nicox valuation applies a risk-adjusted net present value (nNPV) model with a 12.5% cost of capital. Our approach includes the prospects for NCX-470 (50% probability of success in the US and 35% in Europe), NCX-4251 (40% probability of success) and the Vyzulta and Zerviate royalties. Altogether, we obtain a pipeline rNPV of €303.7m. After adding estimated FY20 net cash of €29.4m (excluding lease liabilities), we obtain an equity valuation of €333.1m or €8.99 per share.

Financials: Funded into H222 by our estimates

In Q420, Nicox raised €15m in a private placement and recently reported gross cash of €47.8m at 31 December 2020 along with €18.4m in gross debt, resulting in a net cash position of €29.4m. We model R&D costs (net of tax credits) of €16.7m in 2021 and €17.4m in 2022, due primarily to the NCX-470 and NCX-4251 trials. We model that net licence revenue, primarily from Vyzulta, will reach €12m in FY23 and help offset Nicox's costs. We forecast operating cash burn rates (excluding interest costs) of €15.8m in 2021 and €17.7m in 2022. We estimate that Nicox's cash on hand should enable it to fund its operations into H222 and we model €40m in fundraising needs (modelled as illustrative debt) between 2022 and 2024.

Sensitivities: Development risks, competition, IP

In addition to the usual regulatory and development risks, Nicox's lead products will be positioned in highly competitive markets and hence robust marketing efforts will be key for optimal penetration. For NCX-470 in particular, competitiveness will depend on the level of incremental IOP reduction to be shown vs latanoprost in ongoing pivotal trials. For NCX-4251, the company will still need to demonstrate to stakeholders that it would be a superior product to many of the drugs used off-label. Nicox is also dependent on the commercial efforts of its partners for Vyzulta and Zerviate. If expenditures are higher than forecast and/or royalty revenue is below our expectations, Nicox may need to raise capital beyond our forecasts. While our model accounts for financing(s) as long-term debt, the company may need to issue equity instead, at pricing that may not be favourable for

current shareholders and could lead to significant dilution. Finally, the success of Nicox's products will depend on its ability to defend the IP assets surrounding them.

A multi-asset ophthalmic drug company

Headquartered in Sophia Antipolis, France, Nicox is a pharmaceutical company with 34 employees (December 2020) specialising in developing drugs for the therapeutic eye care sector, with lead product candidate NCX-470 in Phase III trials targeting the topical treatment of glaucoma by utilising and expanding on an already established dual IOP-lowering mechanistic approach. Nicox also has a Phase IIb candidate, NCX-4251, being developed as a potential first-in-class treatment for acute exacerbations of blepharitis, a common chronic inflammation of the eyelids. Both assets are partnered with Ocumension for the Chinese market and Nicox maintains rights for the more lucrative North American, European and Japan/Australasia markets. Nicox also has commercialised assets, Vyzulta (latanoprostene bunod) and Zerviate (cetirizine ophthalmic), already launched and marketed via commercial partners, enabling it to obtain meaningful recurring royalty income, which will provide a funding source for its development activities. We anticipate that the potential market introduction of NCX-470 in 2024 could help transition Nicox into a consistently profitable commercial ophthalmic drug company.

NCX-470 for glaucoma

Nicox's lead drug candidate is NCX-470, a topical eyedrop intended as a first-line treatment to reduce intraocular pressure (IOP) in glaucoma. NCX-470 is a second clinical-stage compound based on the company's proprietary NO-donating platform that combines an NO-donating molecule with an established prostaglandin F2α (PGA) drug which, as explained below, provides an additional mechanism for the drug to reduce IOP. The technology has already been applied successfully in a first commercial glaucoma drug, Vyzulta, out-licensed to and commercialised (Q320 sales of $13m) by B+L, a subsidiary of Bausch Health Companies (BHC: TSX). Glaucoma is a series of ocular disorders characterised by optic nerve damage that results in a progressive and irreversible visual field loss. Glaucoma is often, but not always, caused by an elevated level of IOP, and persistent elevated IOP (ocular hypertension, OHTN) can damage the retinal ganglion cells (RGCs)[1] travelling through the optic nerve. Progressive damage of the RGCs leads to progressive irreversible vision loss. IOP results from the dynamic between the production and outflow of fluid (aqueous humour, AH) in the anterior chamber (AC) of the eye. Normally, the primary drainage path (80–90%) for AH is through trabecular meshwork (TM) and into the Schlemm's canal (SC), and the alternate drainage path (10–20%) is referred to as uveoscleral pathway.[2] The predominant treatment approach for glaucoma is to lower IOP. Neuroprotective treatment approaches (whereby the proposed treatment would aim to reduce the propensity for RGC injury) have generally not been successful in reducing progression in large-scale randomized clinical trials (RCTs). The US National Eye Institute (NIH) estimates the US glaucoma prevalence at 2.7 million people. Over 120,000 Americans go blind each year from glaucoma, comprising 9% to 12% of all blindness cases.

[1] Light is focused on photoreceptors located on the retina, then the visual information is relayed electrically through retinal bipolar, horizontal and amacrine cells, before being transmitted to retinal ganglion cells, which travel through the optic nerve prior to reaching further downstream visual processing areas (ie optic chiasm, lateral geniculate nuclei and visual cortex of the brain).

[2] Uveoscleral outflow refers to drainage of AH from the AC through a less structured pathway (ie not involving distinctive tubes and channels as with TM/SC) across the iris and anterior face of the ciliary muscle before existing through the sclera.

Glaucoma is the second leading cause of blindness (after age-related macular degeneration) in North America and Western Europe in patients over age 50.[3]

Current treatments for glaucoma

The first-line treatment for glaucoma, particularly open-angle glaucoma (OAG),[4] involves the chronic (often lifelong) usage of topical eye drop medications to lower IOP. We estimate that up to 80% of OAG patients use topical eye drop therapy as their only treatment. While many active drug molecules used in glaucoma therapy are now generic, GlobalData estimated the topical glaucoma drug market at $2.6bn in 2016 across seven major markets (including the US and Japan) and projected that it would grow to $3.8bn in 2026. Topical glaucoma treatments fall within several treatment/mechanism of action (MoA) classes, as shown below.

Exhibit 2: Commonly prescribed topical medication classes for glaucoma

Drug class	Examples	Mechanism of action	Typical IOP reduction	Typical dosing
Prostaglandin F2α analogue (PGA)	latanoprost (Xalatan), travoprost (Travatan Z), bimatoprost (Lumigan), tafluprost (Zioptan)	Increase outflow of AH through the uveoscleral tract	25-35%	Once daily
Nitric oxide (NO) donating PGA	latanoprostene bunod (Vyzulta)	Combines PGA mechanism with NO release, which further lowers IOP by increasing AH outflow through TM muscle relaxation	30-40%	Once daily
β-adrenergic receptor antagonist (β-blocker)	timolol (Timoptic), levobunolol, betaxolol, carteolol	Decrease AH production	20-30%	Once or twice daily
Carbonic-anhydrase inhibitors (CAI)	dorzolamide (Trusopt), brinzolamide (Azopt)	Decrease AH production	20-25%	Twice daily
α2-adrenergic receptor agonist	brimonidine (Alphagan), apraclonidine (Iopidine)	Decrease AH production, and increase outflow through uveoscleral tract	20-25%	Twice daily or thrice daily
rho-kinase (ROCK) inhibitor	netarsudil (Rhopressa)	Lowers IOP by relaxing TM (improving outflow), and also inhibits norepinephrine transporter (NET) thereby decreasing AH production	20-25%	Once daily

Source: Edison Investment Research

Starting with the FDA approval of latanoprost (0.005% concentration) in 1996, PGA drugs have become the most commonly used first-line glaucoma treatment, owing to their more effective reduction of IOP compared to nearly all other treatment classes (they work by reducing AH outflow through the uveoscleral tract), convenient dosing schedule (once daily), and relatively benign adverse event profile (iris darkening and growth of eyelashes are the most common side effects, along with eye redness or hyperaemia; unlike some other glaucoma drug classes, topical PGA drugs are very unlikely to cause systemic side effects). PGAs command c 50% of the topical glaucoma market in the US, and US PGA sales reflect about $1.5bn in gross yearly sales.

In late 2017, Vyzulta, which is a modified form of latanoprost designed to donate nitric oxide (NO), gained FDA approval. On instillation, Vyzulta is broken down into the active latanoprost acid and butanediol mononitrate, which is further broken down into NO and an inactive metabolite. Vyzulta provides latanoprost's PGA lowering MoA, but the donation of NO can also further reduce IOP by relaxing the TM muscle and thereby increasing AH outflow through the TM/SC pathway. As explained below, Vyzulta was first developed by Nicox and then partnered with B+L.

NCX-470 is a potentially improved NO-donating PGA

NCX-470 is a novel second NO-donating candidate which, instead of incorporating latanoprost (as in Vyzulta) as the base PGA molecule, is derived from an analogue of bimatoprost, and releases that molecule and NO when instilled into the eye. Bimatoprost is a second-generation PGA

[3] Flaxman SR, Bourne RRA, Resnikoff S et al. *Lancet Glob Health*. 2017 Dec;5(12):e1221-e1234. doi: 10.1016/S2214-109X(17)30393-5 www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30393-5/fulltext.

[4] Approximately 75% of glaucomas are open-angle glaucoma (OAG) and the remaining 25% are closed-angle glaucoma (CAG), where IOP is sharply increased secondary to mechanical obstruction of the AC drainage angle. CAG is often treated with a laser iridotomy procedure, but many CAG patients will also require additional chronic IOP-lowering therapy.

marketed as Lumigan 0.01% by AbbVie (Allergan), and currently the best-selling branded glaucoma drug in the US in terms of revenue (although generic latanoprost accounts for the majority of US prescriptions). Bimatoprost is considered the most effective currently approved base PGA molecule for glaucoma, with meta-studies[5] suggesting incremental IOP reductions in the range of c 0.5mmHg to c 1.2mm Hg compared to latanoprost or travoprost, albeit with a higher incidence of hyperaemia. Furthermore, given that the NCX-470 formulation in current trials has a higher drug concentration (0.1%) than Vyzulta (0.024%), it will also provide a higher effective NO dose release per eye drop, which could potentially augment the therapeutic effect. Hence NCX-470 could potentially provide higher IOP lowering effect than Vyzulta.

Preclinical studies in monkeys with ocular hypertension and in normotensive dogs showed that compared to bimatoprost 0.03%, NCX-470 (at 0.042%) reduced IOP by an additional c 3mmHg and 2mmHg, respectively, at 18 hours post-dosing.[6]

NCX-470 was studied in a 433-patient US multi-centre 28-day Phase II trial (Dolomites) where different NCX-470 dose concentrations were compared with latanoprost 0.005%. Top-line results were reported in Q419, showing that the highest tested concentration (0.065%) demonstrated both statistical non-inferiority and superiority in IOP lowering to the latanoprost arm at day 28. The IOP lowering effect of NCX-470 (at 0.065%) from baseline was 7.6–9.8mmHg vs 6.3–8.8mmHg for latanoprost. Statistical superiority was met with NCX-470 (at 0.065%) being up to 1.4mmHg superior (in IOP lowering efficacy) to latanoprost at day 28 ($p<0.025$). All doses were well tolerated, with no drug-related serious adverse events. If comparable results are confirmed in Phase III trials, NCX-470 could potentially become the first non-combination glaucoma drug product in pivotal studies with statistical superiority to a standalone PGA drug.

NCX-470 Now in Phase III trials

In mid-2020, Nicox started the first Phase III studies for NCX-470, the Mont Blanc multi-site study (with around 50 US sites), which is intended to enrol 670 patients in total where OAG or OHTN subjects will take NCX-470 or latanoprost once daily in both eyes for three months. The study was planned to include an adaptive design, where the adaptive phase consists of two NCX-470 arms (0.065% or 0.1%), and latanoprost 0.005%. In September 2020, following completion of the adaptive phase, a 0.1% NCX-470 dose was selected, such that for the remaining portion of the trial, patients would be randomized to receive either NCX-470 at 0.1% or latanoprost 0.005% for three months, and there would be a head-to-head safety and efficacy evaluation between these two arms. The primary endpoint is the mean IOP reduction from a time-matched baseline at 8am and 4pm time points at weeks two and six and month three visits. The chosen NCX-470 concentration (0.1%) is higher than the 0.065% used in the Dolomites study and hence it is likely that the incremental IOP reduction to latanoprost 0.005% that can be shown could be higher than the 1.4mm shown in the Dolomites study. IOP reduction is the most widely accepted measure of a glaucoma treatment's efficacy in decelerating disease progression.

As part of the Mont Blanc trial, a small number of sites in China will be included. Top-line data for the entire Mont Blanc study are expected in H122. The second Phase III study in glaucoma, Denali, started in Q420. The Denali trial will be equally funded by Nicox and Ocumension (Nicox's commercial partner for the Chinese market) and will also evaluate NCX-470 ophthalmic solution, 0.1%, versus latanoprost 0.005%. It will include clinical sites in both the US and China, with the majority of the patients to be recruited in the US. The Denali and Mont Blanc trials are designed collectively to fulfil the regulatory requirements to support New Drug Application (NDA) filings in the US and China.

[5] Aptel F, Cucherat M, Denis P (2008). *J Glaucoma* 17: 667–673. www.ncbi.nlm.nih.gov/pubmed/19092464.

[6] Impagnatiello F, Toris CB, Batugo M et al. *Invest Ophthalmol Vis Sci*. 2015 Oct;56(11):6558-64. doi: 10.1167/iovs.15-17190. PMID: 26457541.

Ocumension partnership for China, Korea and South-East Asia

In late 2018, Nicox entered into an exclusive licence agreement with Ocumension Therapeutics to out-license NCX-470 commercial rights for the regions comprising mainland China, Hong Kong, Macau and Taiwan. Ocumension is responsible for costs involved in commercialising NCX-470 in those territories, including funding the required trial components. Nicox received a €3m upfront payment and will be entitled to tiered royalties of between 6% and 12% on net sales by Ocumension in the covered regions. In March 2020, the two parties amended their agreement such that Ocumension immediately paid Nicox €15m (in place of up to €36.25m in milestones from the original agreement), gained additional rights to NCX-470 for Korea and South-East Asia and agreed to pay 50% of the costs of the Denali study.

Market considerations for glaucoma therapeutics

Fortune Business Insights[7] estimated the glaucoma therapeutics market at $6.6bn worldwide in 2019, growing at a CAGR of 6.1% through 2027. Market Scope estimated the US market, after all discounts and rebates, at over $2bn in 2019,[8] and Nicox[9] and others[10] have estimated total US prescriptions for glaucoma medications (TRx) at more than 35 million annually.

Glaucoma treatment algorithms

OAG patients are usually initially treated with ocular hypotensive drugs in the first line and eye care practitioners (ECPs) examine how effective the IOP reduction is (percentage reduction vs pre-treatment) and, more importantly, whether there is disease progression as shown through 1) changes at the RGC level over time (as observed through OCT, optical coherence tomography), or 2) change in visual function as measured through automated visual field testing. If a single-agent IOP reducing drug is not sufficiently effective, often ECPs will aim to use a combination drug that incorporates the mechanisms of action of more than one drug class. Combination therapy may provide stronger IOP reduction than single-agent drugs but also raise the risk of AEs.

Exhibit 3: Glaucoma combination drug therapy examples

Drug class combinations	Examples	Typical dosing
PGA/β-blocker	travoprost/timolol (DuoTrav); latanoprost/timolol (Xalacom) bimatoprost/timolol (Ganfort)	Once daily
α2-agonist//β-blocker	brimonidine/timolol (Combigan)	Twice daily
CAI/β-blocker	dorzolamide/timolol (Cosopt); brinzolamide/timolol (Azarga)	Twice daily
CAI/α2-agonist	brinzolamide/brimonidine (Simbrinza)	Twice daily
ROCK inhibitor/PGA	netarsudil/latanoprost (Rocklatan)	Once daily

Source: Edison Investment Research

If glaucoma continues to progress in such cases, ECPs look towards more complex medical procedures to better control IOP such as laser trabeculoplasty (LT), minimally invasive glaucoma surgeries (MIGS), glaucoma drainage implants (GDIs) or filtration surgery. Even if LT or surgical intervention is performed, most patients continue topical therapy. One further consideration with glaucoma drug treatment is compliance, as many patients may not effectively and consistently administer topical eye drops at the required frequency/dosage. Extended-release glaucoma

7 Fortune Business Insights. 9 September 2020. www.globenewswire.com/news-release/2020/09/09/2090664/0/en/Glaucoma-Therapeutics-Market-to-Reach-USD-11-05-Billion-at-6-1-CAGR-by-2027-Rising-Research-on-Prostaglandin-Analogs-says-Fortune-Business-Insights.html

8 Market Scope. www.market-scope.com/pages/news/3476/glaucoma-drugs-continue-to-battle-for-market-share. Accessed 24 December 2020.

9 Nicox annual information form. www.nicox.com/assets/files/EN_Chapter-5-URD-2019-Overview-of-the-activities-_F1.pdf. Accessed 24 December 2020.

10 Emerald Bioscience Investor Presentation. Available at https://ir.emeraldbio.life/. Accessed 24 December 2020.

implants such as Durysta (bimatoprost implant by Allergan/AbbVie, approved by the FDA in H120) or Glaukos's iDose (in Phase III) may gain significant traction in patients with compliance concerns.

Since PGA drugs hit the market, only one new drug class has subsequently been approved to treat the condition,[11] rho kinase (ROCK) inhibitors, with the only molecule on the US market being netarsurdil (Rhopressa from Aerie Pharmaceuticals), launched in Q218. Aerie reported that combined US Rhopressa and Rocklatan (netarsudil/latanoprost, launched in 2019) sales were $58.5m in 9M20. Rhopressa is generally viewed as having a milder effect on IOP than PGA drugs, of up to 5mmHg vs baseline, compared to 6–8mmHg from latanoprost. One potential benefit of ROCK inhibitors could be neuroprotection[12] (potentially by improving optic nerve and retinal blood flow), although further studies will likely be needed to support this theory. Like PGA drugs, Rhopressa has a very safe systemic AE profile and, unlike PGA drugs, it does not raise the risk of iris pigmentation or modify the length of the eyelashes. However, in pre-approval trials, conjunctival hyperaemia was shown in 53% of patients, and c 20% of patients had corneal verticillata (corneal deposits that did not affect vision function and resolved on discontinuation of treatment).[13]

Competitive landscape considerations for NCX-470

Following Xalatan (latanoprost 0.005%) approval, two competing PGA products were approved in 2001, namely bimatoprost (Lumigan) and travoprost (Travatan, now Travatan Z). Xalatan went off patent in 2011 and generic latanoprost accounts for about 74%[14] of US PGA prescriptions, compared to 13% for Lumigan and 11% for Travatan Z, whereas Lumigan leads by value. Net US Lumigan sales (after all discounts) were reported by Allergan at $269m in 2019, and its international sales including Ganfort (bimatoprost/timolol combination) were $361m (both were down 8% y-o-y).

Among current US approved products, we perceive the most direct competitors to NCX-470 as Lumigan, Vyzulta and Rocklatan. One further competitive advantage vs Vyzulta could arise from the registration trial endpoints chosen for NCX-470. Nearly every PGA-based glaucoma drug that has been commercialised in recent years, including Vyzulta, has had its Phase III registration trials compare efficacy against a β-blocker drug for the primary endpoint. NCX-470 is being measured against latanoprost, a PGA, and if successful, could potentially be more easily marketable as having a stronger therapeutic effect (compared to a conventional base PGA) than Vyzulta. Rocklatan has shown statistical superiority to latanoprost in Phase III studies, and EvaluatePharma's consensus forecast is for c $360m in peak global sales in 2026. However, it is a combination drug (and thus has the AE profiles of both constituent molecules) and hence, as with Rhopressa, can lead to hyperaemia (59% incidence in registration trials)[15] and corneal verticillata. This is in addition to the AE associated with a PGA drug, which may limit Rocklatan's uptake.

Emerging pipeline considerations

NCX-470 may need to compete with other topical agents in the pipeline. We provide a selected list of some of the later-stage product candidates below (to our knowledge, none of these have yet shown statistical superiority in IOP-lowering efficacy to an approved PGA drug). Some of these (eg K-232, PHP-201) are targeting Asian markets first and/or may not be initial competitors for the US or Europe. In the pipeline, we believe Santen's DE-117, already launched in Japan and currently in US Phase III studies, could be an interesting entrant. DE-117 targets prostanoid receptor EP2 (unlike current approved PGA drugs, which target receptor FP) and, as a result, may also improve outflow through the conventional (TM/SC) pathway, in addition to the uveoscleral pathway, and may have a reduced likelihood for PGA-related AEs. Razuprotafib recently reported positive top-line

[11] Vyzulta's FDA approval in 2017 made it the first single-molecule glaucoma drug (and PGA drug) to release nitric oxide (NO) to increase outflow and thereby exert a new dual mechanism of action.

[12] Abbhi V, Piplani P. *Curr Med Chem*. 2020;27(14):2222-2256. PMID: 30378487.

[13] Rhopressa Prescribing Information.

[14] MIDAS TRx data provided by Nicox.

[15] Rocklatan Prescribing Information.

Phase II data with a twice-daily regimen, although the once-daily regimen did not show a significant incremental IOP benefit versus latanoprost plus placebo. Cenegermin (recombinant human nerve growth factor), already approved for neurotrophic keratitis, represents a unique treatment approach given that it directly aims for neuroprotection (rather than IOP control), but remains at a very early stage.

Exhibit 4: Selected emerging potentially competing topical drug treatments for glaucoma

Product	Company	Stage or Status	Description	Notes
Omidenepag isopropyl (DE-117)	Santen	Phase III (US); launched in Japan in 2018	Selective agonist for prostanoid receptor EP2 vs current approved PGA drugs which act on a FP receptor. DE-117 is believed to increase the pathway of AH drainage through the conventional (TM/SC) and uveoscleral outflow pathways, whereas current PGAs are believed to only increase the uveoscleral pathway	Phase III studies (NCT03691649 and NCT03691662) started in Q418 and will each enrol c 430 patients with glaucoma or OHT across 70 US sites. Their objectives are to assess whether DE-117 is non-inferior to timolol at reducing IOP after 3 months. Prior Phase III study in Japan (NCT02623738) found that DE-117 was non-inferior to latanoprost (n=189). Due to the drug's selective activation of EP2, it may avoid some of the AE of current PGAs, including abnormal eyelash growth.
Sepetaprost (DE-126)	Santen/Ono Pharmaceuticals	Phase IIb	Prostaglandin with a novel mode of action that is both an FP- and EP- receptor dual agonist	Phase IIb (NCT03216902) dose-ranging (n=241) study found 0.002% concentration (n=44) arm had 7mmHg reduction in IOP vs baseline (29% drop) vs 6.8mmHg (26% drop) for latanoprost comparator arm; 0.002% DE-126 arm was well-tolerated with lower AE than latanoprost arm
K-232 (ripasudil/ brimonidine)	Kowa	Phase III (Japan)	Ripasudil is ROCK inhibitor (lowers IOP by relaxing TM); brimonidine is an α2-receptor agonist	Ripasudil (standalone) approved in Japan in 2014; Phase III studies of K-232 started in early 2020
Bamosiran (SYL040012)	Sylentis (Grupo Zeltia)	Phase II	Topical RNAi-based therapy that blocks production of the β2-adrenergic receptors	180-pt Phase II (NCT02250612) showed non-inferiority vs twice-daily timolol in patients with baseline IOP over 25mmHg, but did not show non-inferiority in total study population
Razuprotafib (AKB-9778)	Aerpio Pharmaceuticals	Phase II	Inhibitor of vascular endothelial protein tyrosine phosphatase (VE-PTP), resulting in activation of Tie2 (tyrosine kinase receptor 2), which is projected to restore SC vasculature and improve AH outflow	Phase II (NCT04405245; n=194) top-line results showed that the change from baseline at day 28 in diurnal mean IOP in eyes treated with razuprotafib twice-daily plus latanoprost showed a statistically significant improvement in IOP reduction (mean difference of 0.92mmHg) compared to those treated with latanoprost plus placebo
H-1337	D.Western Therapeutics Institute	Phase II	Multikinase inhibitor that inhibits various protein kinases, including leucine-rich repeat kinase (LRRK) and Rho, and is thought to stimulate AH drainage via TM/SC	87-pt US Phase II study (NCT03452033) completed in 2018 and showed 4.7mm incremental reduction in IOP vs baseline compared to placebo at 28 days; Company is seeking out-licensing options
PHP-201	pH Pharma	Phase IIb (pre-Phase III)	ROCK inhibitor (lowers IOP by relaxing TM)	Phase IIb trial in patients with normotensive glaucoma showed superior reduction in IOP vs placebo; company plans to conduct Phase III trials in Korea, China and Japan
Cenegermin (rhNGF)	Dompe	Phase I/II	Recombinant human nerve growth factor (rhNGF) designed to support RGC survival (rather than control IOP)	Lower dose formulation (Oxervate) has already been approved for treatment of neurotrophic keratitis; Awaiting published results of 60-pt Phase Ib/II study (NCT02855450)

Source: Edison Investment Research

Commercial forecasts

The absolute level of IOP reduction (to be shown in the Phase III studies vs latanoprost) is an important factor for most ECPs, but when selecting a first-line drug, they may also look at the AE profile and emerging research on neuroprotection. Generic PGAs account for the large majority of US glaucoma drug prescriptions, suggesting that a large portion of ECPs may not perceive the incremental IOP-lowering ability of the newer (branded) drugs as being sufficiently material in terms of slowing glaucoma progression. These points all affirm our underlying view that a very robust sales and marketing effort will be critical for NCX-470 to gain substantial market share, as Nicox plans to commercialise NCX-470 itself for the US market. All said, we believe that if NCX-470 can show a c 1.5–2mmHg improvement vs latanoprost in the pivotal programme (and if the AE profile remains favourable), it can be very effectively positioned as a leading first-line glaucoma drug.

With NCX-470 in Phase III trials and employing a proven (NO-emitting molecule combined with approved base PGA molecule) therapeutic modality, we assign a 50% probability of success in the US (to be re-evaluated once the Mont Blanc results are released). We assume the Denali study will be completed in Q422 and that NCX-470 will be launched in the US in 2024 and also in China by

Ocumension. For Europe, we anticipate that an additional Phase III study will be needed, given our understanding that European regulators prefer a longer interval measure of efficacy (eg six months) and we model a separate Phase III study starting in late 2021 or H122, and a European launch in 2026. We also apply a lower 35% probability of success for Europe given our forecast need for a separate pivotal study. We model an initial gross (pre-discount) price of $220/bottle, comparable to Vyzulta's current price, and 50% net-to-gross. Our commercial forecasts are summarised below.

Exhibit 5: Financial forecasts for NCX-470

	2024e	2025e	2026e	2027e	2028e	2029e	2030e
US market							
Estimated number of glaucoma drop bottles dispensed per year (000s)	66,916	69,593	72,376	75,271	78,282	81,413	84,670
Market share for NCX-470 (%)	0.33	0.55	0.93	1.57	2.65	3.00	3.00
Estimated price per bottle ($), net of discounts/rebates	110.00	115.50	121.28	127.34	133.71	140.39	147.41
Net sales ($000)	23,947	44,194	81,559	150,515	277,772	342,891	374,437
Ex-US markets							
Net sales for Europe and regions not covered by Ocumension agreement (€000)	0	0	13,297	24,539	45,285	83,573	154,233
Net licence & royalty revenue from Ocumension for China (€000)	57	189	356	670	1,260	2,359	2,708
Assumed $/€ rate	1.23	1.23	1.23	1.23	1.23	1.23	1.23
Worldwide total NCX-470 related revenue (€000)	19,526	36,119	79,960	147,578	272,376	364,706	461,361

Source: Edison Investment Research

We assume that 55 million (as estimated by IQVIA) glaucoma drop bottles were dispensed in 2019[16] in the US and that this will grow at 4% pa. We estimate that at peak share, NCX-470 will account for 3% of such prescriptions, resulting in nearly $375m net US sales in 2030. NCX-470's primary US patent expires in 2029 (with up to five years of term extension) and its formulation patent expiring in 2039. We assume gradual erosion of sales after 2035. In China, there were an estimated 13 million people with glaucoma in 2015,[17] but there is less visibility on the market size, although Research and Markets estimated that latanoprost sales in 2017 were more than CNY40m (over $6m).[18] Santen recently estimated that the market size of the Chinese glaucoma market by value is around one-twelfth that of Japan, while China's population is roughly 12 times higher, suggesting much untapped potential. Our preliminary forecasts for revenue from Ocumension are conservative, but we may revisit our assumptions once the product approaches launch and as further details on the commercialisation strategy become available.

NCX-4251 for acute exacerbations of blepharitis

NCX-4251 is currently in Phase IIb trials for the treatment of acute exacerbations of blepharitis. Blepharitis is a chronic inflammation of the eyelids and contributes to dry eye disease (DED) and related discomfort. A survey of US optometrists and ophthalmologists reported that between 37% and 47% of their patients have the condition.[19] NCX-4251 is a proprietary ophthalmic suspension of fluticasone propionate nanocrystals designed to be directly applied to the eyelids using an applicator. Fluticasone propionate is an established approved corticosteroid drug and an inhaled formulation is sold in the US under the Flonase brand. Fluticasone has high affinity for the glucocorticoid receptor and was reported to have over 14x higher affinity than dexamethasone,[20] a commonly prescribed ophthalmic corticosteroid. The nanocrystal formulation is designed to provide a sustained release of drug into the eyelids. Corticosteroids have well-established use in eyecare

16 Note that TRx data cited above do not readily take into account refills and hence the number of glaucoma eye drop bottles (c 55m) dispensed in the US exceeds the IMS TRx data (c 35m).

17 Song P, Wang J, Bucan K, et al. *J Glob Health*. 2017 Dec;7(2):020705. doi: 10.7189/jogh.07.020705. www.ncbi.nlm.nih.gov/pmc/articles/PMC5737099/

18 Press release by Research & Markets on 24 July 2018.

19 Lemp et al. *Ocul Surf*. 2009 Apr;7(2 Suppl): S1-S14. doi: 10.1016/s1542-0124(12)70620-1.

20 Johnson M. *Allergy*. 1995;50(23 Suppl):11-4. doi: 10.1111/j.1398-9995.1995.tb02735.x. PMID: 7604948 Review

for inflammatory conditions, but prolonged use (eg more than three to four weeks) can lead to significant AE including lens opacities (cataract) and elevated IOP.

Blepharitis is associated with occasional flare-ups and NCX-4251 is being advanced specifically for such acute exacerbations, with a short 14-day treatment regimen intended to reduce the likelihood of corticosteroid-induced AE. In late 2019, the US Phase II Danube dose-ranging trial found that 14-day treatments with 0.1% NCX-4251 once-daily (n=10) and twice-daily (n=10) doses were well-tolerated and a pooled analysis showed statistically significant reductions in the composite score of eyelid redness, eyelid debris and eyelid discomfort at the day 14 study endpoint vs placebo (n=20 for NCX-4251 and n=16 for placebo).

The Mississippi Phase IIb trial started in late 2020 and may enroll up to 300 patients who will be randomized to take a 14-day course of once-daily NCX-4251 0.1% or placebo. The primary endpoint will be the proportion of subjects with complete cure (score 0 on a 0–3 scale) in each of the following: eyelid margin redness, eyelid debris, eyelid discomfort at day 15. While not statistically powered for efficacy, the Danube study showed that 20% of patients in the NCX-4251 once-daily arm had a complete cure score using the same efficacy endpoint vs 0% of the placebo arm. Nicox has confirmed with the FDA that if the primary endpoint is met, the Mississippi study could count as one of two pivotal trials required by the FDA for NDA submission. Mississippi results are expected in Q421 and, if successful, we expect the next pivotal study to commence shortly thereafter and lead to commercialisation in 2025. NCX-4251 is licensed to Ocumension Therapeutics for mainland China, Hong Kong, Macau and Taiwan, and Nicox retains NCX-4251 rights for the remaining regions including the US and Europe.

Commercial considerations for NCX-4251

Blepharitis has been estimated to account for 700,000 visits to ECP offices in the US in 2014.[21] In the first line, blepharitis is generally managed with non-prescription supportive non-invasive therapies such as eyelid hygiene (lid scrubs), hot compresses (including the use of dedicated eye masks), omega-3 fatty acid supplementation, and ocular lubricants (for accompanying DED). Given the bacterial contribution to the disease in many cases, topical antibiotic products are also often prescribed (to be applied onto the lid margins) for acute cases such as erythromycin, azithromycin, tobramycin, or bacitracin.

For acute blepharitis episodes, NCX-4251 may need to compete with the existing approved topical corticosteroid or combination antibiotic/corticosteroid products which, while not specifically indicated for acute exacerbations, are frequently used ‘off-label’ for these events. Examples include prednisolone, dexamethasone, fluoromethalone and loteprednol. The combination drugs provide the additional benefit of antibacterial action (given that excess bacteria contributes to blepharitis) and examples include Tobradex (dexamethasone/tobramycin), Blephamide (prednisolone/ sulfacetamide) and Zylet (loteprednol/tobramycin).

Effectively, the task for Nicox would be to position NCX-4251 as a preferred alternative to the above corticosteroid or corticosteroid/antibiotic products for acute blepharitis. NCX-4251 is distinguished from most of these in that it is designed for specific placement onto the lid margins (allowing for targeted treatment) with a supplied applicator, whereas most existing corticosteroid-based products are generally instructed to be applied into the cul-de-sac (area between the lower lid and eyeball). This distinction may support its adoption although a future head-to-head study of NCX-4251 against an alternative corticosteroid-based product (not modeled in our forecasts) could be helpful for driving a shift in ECP prescribing behaviour and positioning NCX-4251 as the superior product. We forecast relatively modest US peak sales of $51m in 2030. As a comparison, we note that US Lotemax (branded loteprednol 0.5% by B+L) sales were reported[22] to have been c $90m by IQVIA in 2019, although we note this drug is used for a broader range of inflammatory conditions

[21] Pizarro et al. *International Journal of Development Research* Vol. 5, Issue, 07, pp. 5039-5043, July, 2015.

[22] Press release from Akorn dated 28 June 2019.

(including uveitis, post-operative inflammation, etc.). Given the Danube results and fluticasone's established efficacy in other areas, we assign a 40% probability of success (to be reviewed on completion of the Phase IIb study).

NCX-1728: A potential new IOP-lowering drug class

Nicox is also developing NCX-1728, a first compound in a new class of non-PGA related compounds with NO-mediated IOP lowering effects. Nicox reports that an NCX-1728 analogue reduced IOP in non-human primates compared to travoprost. NCX-1728's NO-mediated IOP lowering effects are also believed to be enhanced and prolonged by concomitant phosphodiesterase-5 (PDE5) inhibition. Nicox owns all rights to NCX-1728. Further optimisation of the NCX-1278 formulations will proceed prior to the formal commencement of pre-IND enabling studies. We will await further advancements before incorporating it into our valuation model.

Out-licensed commercial-stage products

Vyzulta

Vyzulta is the first NO-emitting PGA backbone drug and has been commercialised by B+L since late 2017. B+L entered into a worldwide licensing agreement with Nicox for the drug in 2010, making a $10m initial payment and a $10m milestone in 2012. Vyzulta is now commercialised in the US, Canada, Mexico and Argentina, and has been approved in Hong Kong, Taiwan, Colombia and the Ukraine. Nicox is entitled to tiered net royalties[23] of 6–12% on net sales and may also be entitled to up to $150m in future net milestone payments from B+L on Vyzulta sales. Vyzulta's US composition-of-matter patent is covered to 2025 and term extension is expected to maintain US market exclusivity until 2030. We model that the US market will account for over 80% of global Vyzulta sales and that peak global sales in 2030 will reach c $217m before declining due to generic competition; we forecast peak net royalties of c €17.5m to Nicox in 2030. We also model that Nicox will receive a $5m net milestone in 2023 (triggered on global yearly Vyzulta sales reaching $100m), leading Nicox to receive a total of €11.6m in net licence fees from B+L in that year. B+L reported that Q320 global Vyzulta sales were $13m, up 30% y-o-y. Altogether, we believe that B+L can effectively position Vyzulta as a leading PGA type drug given its dual mechanism of action and the fact that it has shown up to c 1.2mmHg superior IOP reduction vs latanoprost in the Phase II VOYAGER study. Once NCX-470 reaches the market, Vyzulta may lose some of its cachet and we expect its growth to decelerate but still remain positive (aided by ongoing growth in market size and average selling price) until 2030. The US glaucoma market has in the past shown that it can absorb multiple branded drugs from different providers with comparable mechanisms of action (eg Lumigan, Travatan and Xalatan co-existed for a decade).

Zerviate

Zerviate (cetirizine 0.24%) is an antihistamine drug approved by the FDA for the treatment of ocular itching associated with allergic conjunctivitis. Zerviate is licensed by Nicox in the US to Eyevance (acquired by Santen in September 2020) and was launched in the US in Q120. Zerviate is licensed to Ocumension in the Chinese market (a Phase III study in China started in Q420) and to Samil in South Korea. The ocular allergy market is very competitive, but what sets Zerviate apart is that it is the only topical US anti-allergy drug that is based on an existing approved oral product (oral cetirizine is marketed in the US under the Zyrtec brand by Johnson & Johnson), and this familiarity may potentially help its positioning with primary care providers or family physicians.

[23] Nicox recovered rights to latanoprostene bunod from Pfizer in 2009 and it must pay royalties to Pfizer proportionate to the product's net sales. After giving effect to these payments, the net royalty that Nicox receives on net Vyzulta sales is between 6 and 12% of net product sales. We model the payments to Pfizer as part of Nicox's cost of sales.

We see limited clinical advantage in Zerviate compared to the existing ocular allergy alternatives. The standard of care in mild-to-moderate ocular allergy are drugs that combine antihistamine properties with mast cell (MC) stabilisation, given there is a synergistic benefit in targeting both mechanisms. An allergic reaction occurs when the immune system identifies an allergen and produces immunoglobulin E (IgE) antibodies that bind to MCs, which in turn 'degranulate' and release chemical mediators such as histamine that result in local inflammation and symptoms. A strict MC stabiliser drug (examples include cromolyn, lodoxamide, nedocromil, pemirolast) helps interrupt this process but does not affect any mediators that have already been released and may not provide immediate relief. An antihistamine drug without significant MC inhibition properties like Zerviate will provide rapid itching relief, but may not prevent progression of the allergic cascade or inhibit the activity of other pro-inflammatory mediators (eg prostaglandins and leukotrienes). Nielsen et al. observed that cetirizine has no effect on MC activation.[24]

Several newer-class antihistamine molecules have both H1 blocker and MC stabilisation properties, and thus affect both axes and can generally provide more complete control of allergy symptoms. These are generally viewed as the first-line or mainstay treatments for ocular allergy and examples include olopatadine, alcaftadine, azelastine, bepotastine besilate, ketotifen and epinastine. Drugs in this combination activity class are either indicated for once-daily or twice-daily dosing (Zerviate is indicated for twice-daily dosing). Ketotifen has been available OTC since 2007, and in 2020 the FDA approved olopatadine for OTC sale at concentrations up to 0.7% (eg olopatadine 0.7% was formerly marketed as a once-daily prescription product). Alcon reports that olopatadine is the number one prescribed ocular allergy relief product, with over 40 million prescriptions since 2008.

For severe acute allergy episodes with significant redness and inflammation, or for more complex ocular hypersensitivity conditions such as atopic or vernal conjunctivitis, corticosteroids such as loteprednol etabonate are often prescribed. We do not expect Zerviate to become a market-leading anti-allergy product but anticipate that Eyevance, especially under Santen leadership, will have sufficient resources to effectively promote it and this, as well as family physicians' familiarity with cetirizine, should allow the product to generate US peak sales of $41m in 2030, or c 2.5% of ophthalmic anti-allergy prescriptions.

Valuation

Our Nicox valuation applies a risk-adjusted net present value (nNPV) model with a 12.5% cost of capital. For NCX-470, the lead asset, we separate the contributions for the US, Europe and the Ocumension arrangement. We apply a 50% probability of success for the US and China and a lower probability (35%) for Europe as an additional clinical trial beyond the Denali and Mont Blanc studies may be needed (and hence we model market launch in Europe in 2026 vs 2024 in the US and China). As Vyzulta and Zerviate are already on the market, we apply a 100% probability of success assumption and, given our expectation for continued Vyzulta growth (in line with trends recently reported by B+L), it is the second largest contributor to our rNPV valuation, after NCX-470.

[24] Nielsen PN, Skov PS, Poulsen LK et al. *Clin Exp Allergy*, 31 (2001), pp. 1378-1384

Exhibit 6: Nicox rNPV assumptions

Product contribution	Indication	Stage	NPV (€m)	Probability of success	rNPV (€m)	rNPV/ share (€)	Launch year	Peak sales (€m) in 2030
NCX-470 (net of R&D and SG&A costs) in US market	Glaucoma	Phase III ongoing	387.1	50%	186.8	5.05	2024	304
NCX-470 (net of R&D and SG&A costs) in Europe and unpartnered regions	Glaucoma	Phase III	177.0	35%	57.4	1.55	2026	154
NCX-470 licence fees from Ocumension (China and other)	Glaucoma	Phase III ongoing	8.6	50%	4.2	0.11	2024	2.7*
NCX-4251 (net of R&D and SG&A costs) sales and licence fees/royalties	Acute blepharitis	Phase IIb ongoing	52.5	40%	18.4	0.50	2025	49.9
Vyzulta royalties from B+L	Glaucoma	Commercial	84.6	100%	84.6	2.28	2017	17.5*
Zerviate royalties from Eyevance and others	Allergic conjunctivitis	Commercial	18.4	100%	18.4	0.50	2020	4.7*
Corporate costs			(66.0)	100%	(66.0)	(1.78)		
Total			662.1		303.7	8.20		
Net cash (end FY20e) excluding lease liabilities			29.4		29.4	0.79		
Total equity value			691.6		333.1	8.99		
FD shares outstanding (000) (31 December 2020)			37,030					

Source: Edison Investment Research. Note: *Reflects net licence and royalties received by Nicox rather than commercial sales by licensee.

Altogether, we obtain a pipeline rNPV of €303.7m. After adding FY20 net cash of €29.4m (excluding lease liabilities), we obtain an equity valuation of €333.1m or €8.99 per share.

Sensitivities

Development and regulatory risk: if safety concerns emerge with NCX-470 or NCX-4251, affecting their approvability, this could significantly affect our valuation.

Commercial and competition risk: the markets for Nicox's products and candidates are very competitive, and success will depend largely on the marketing and commercialisation efforts undertaken to differentiate them from available alternatives. NCX-470's competitiveness will largely depend on the level of incremental IOP reduction that it shows vs latanoprost in Phase III. For NCX-4251, Nicox will need to demonstrate that its benefits are sufficient to displace the use of off-label alternatives.

Partnership risk: Nicox is dependent on the commercialisation efforts of B+L, Eyevance and Ocumension for most of its partnered revenue. Nicox may also decide to license NCX-470 or NCX-4251 in markets outside the US and, if so, it would be dependent on the commercial efforts and partnership terms of such potential agreements.

Financing risk: we expect that Nicox will need to raise additional capital before commercialising NCX-470 and model €40m financings between 2022 and year-end 2024. If expenditures are higher than forecast and/or if royalty revenue is below our expectations, it many need to raise further capital. While our model accounts for the financing(s) as long-term debt, the company may need to issue equity instead, at pricing that may not be favourable for current shareholders and could lead to significant dilution.

Intellectual property risk: the success of Nicox's products will depend on its ability to defend the IP assets surrounding them. Assuming five years of patent term extension post expiry, we anticipate the patents or intellectual property surrounding NCX-470, NCX-4251, Vyzulta and Zerviate would provide US market protection through at least 2034, 2038, 2030, and 2035, respectively. Comparable protections exist for Europe.

Financials

On 30 June 2020, Nicox reported €40.4m in gross cash and €5.0m as securities held for sale of European speciality pharma company VISUfarma (for which €5m proceeds were received in July). The company had €17.7m in short- and long-term debt, resulting in a net cash position of €27.8m (or €26.4m IFRS 16 net cash after including €1.4m in lease liabilities). In December 2020, it raised €15m in a private placement and on 20 January it provided a Q420 update where it highlighted its year-end gross cash position of €47.8m along with €18.4m in gross debt, resulting in a net cash position of €29.4m.

In 2019, the company had an operating cash burn rate (excluding net interest income) of €17.7m and in H120 it had positive operating cash flow of €6.0m, largely due to the revision of the Ocumension NCX-470 agreement in March 2020 (discussed above). Given this revision to their agreement, Nicox initially recorded €14m of the €15m upfront received from Ocumension in H120 as deferred revenue. In H220, it recorded €5.5m in licence payments from this upfront payment. In total for FY20, Nicox recognised €6.5m in licence payments from Ocumension and €2.4m in net royalties, which we estimate are predominantly derived from Vyzulta net sales and calculated after royalty obligations to Pfizer (which we model as part of cost of sales). This represents €8.9m in FY20 gross profit, or 'net revenue' as reported by Nicox. Gross FY20 revenue (ie prior to the consideration of royalties to Pfizer) has not yet been reported. The company plans to report audited FY20 results in March, which we expect to show the FY20 gross revenue amount, and which may differ from the €8.9m net revenue reported. We expect that net royalty payments should increase in forthcoming years, but this will be offset by a slower rate of recognition for the remaining portion (€8.5m) of the €15m Ocumension upfront.

We model that royalty revenue, primarily from Vyzulta, will help offset the company's G&A and R&D costs in the coming years. Altogether, we model operating cash burn rates (excluding interest costs) of €15.8m in 2021 and €17.7m in 2022. Nicox has guided that it expects its current funds on hand will enable it to operate beyond the conclusion of the Mont Blanc study readout (expected in H122). We estimate these funds should allow Nicox to maintain operations into H222, although depending on licence revenues (particularly from Vyzulta), the runway could potentially stretch even further. We model a €10m fund-raise in 2022, followed by an additional €10m in 2023 and €20m in 2024 (all fund raisings modelled as illustrative debt). Following NCX-470 launch in 2024, we do not expect Nicox will require additional capital as its royalty streams plus NCX-470 sales should enable it to start achieving consistent positive operating income starting in FY25.

Exhibit 7: Financial summary

€'000s	2018	2019	2020e	2021e	2022e	2023e	2024e
31-December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS							
Revenue	4,717	8,260	10,431	9,964	11,689	18,140	33,115
Cost of Sales	(690)	(1,405)	(1,531)	(1,819)	(2,290)	(4,622)	(8,815)
Gross Profit	4,027	6,855	8,900	8,145	9,399	13,519	24,300
General & Administrative	(9,506)	(7,666)	(6,946)	(7,207)	(7,521)	(10,915)	(28,847)
Net Research & Development	(15,491)	(16,883)	(11,461)	(16,700)	(17,350)	(12,350)	(7,350)
Amortisation of intangible assets	0	(659)	(1,290)	(1,273)	(1,251)	(1,228)	(1,206)
Operating profit before exceptionals	(20,970)	(18,353)	(10,797)	(17,036)	(16,723)	(10,975)	(13,104)
EBITDA	(20,718)	(17,366)	(9,048)	(15,334)	(15,069)	(9,367)	(11,466)
Depreciation & other	(252)	(328)	(459)	(428)	(403)	(380)	(432)
Operating Profit (before amort. and except.)	(20,970)	(17,694)	(9,507)	(15,762)	(15,472)	(9,746)	(11,898)
Exceptionals including asset impairment	302	(6,115)	(7,312)	0	0	0	0
Other	0	0	0	0	0	0	0
Operating Profit	(20,668)	(23,809)	(16,819)	(15,762)	(15,472)	(9,746)	(11,898)
Net Interest	2,390	1,690	(559)	(898)	(1,179)	(2,146)	(3,060)
Profit Before Tax (norm)	(18,580)	(16,004)	(10,066)	(16,660)	(16,651)	(11,892)	(14,958)
Profit Before Tax (FRS 3)	(18,278)	(22,778)	(18,668)	(17,933)	(17,901)	(13,120)	(16,164)
Tax	(113)	3,856	(26)	0	0	0	0
Profit After Tax and minority interests (norm)	(18,693)	(12,148)	(10,092)	(16,660)	(16,651)	(11,892)	(14,958)
Profit After Tax and minority interests (FRS 3)	(18,391)	(18,922)	(18,694)	(17,933)	(17,901)	(13,120)	(16,164)
Average Number of Shares Outstanding (m)	29.6	30.3	35.2	37.2	37.4	37.6	37.9
EPS - normalised (€)	(0.63)	(0.40)	(0.29)	(0.45)	(0.44)	(0.32)	(0.39)
EPS - normalised and fully diluted (€)	(0.63)	(0.40)	(0.29)	(0.45)	(0.44)	(0.32)	(0.39)
EPS - (IFRS) (€)	(0.62)	(0.62)	(0.53)	(0.48)	(0.48)	(0.35)	(0.43)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET							
Fixed Assets	112,498	110,660	98,498	97,149	95,816	94,662	93,852
Intangible Assets	71,397	72,120	71,063	69,790	68,539	67,311	66,105
Tangible Assets	25,628	27,517	27,365	27,289	27,207	27,281	27,677
Investments in long-term financial assets	15,473	11,023	70	70	70	70	70
Current Assets	26,092	32,146	54,117	36,327	27,623	27,574	31,193
Short-term investments	0	0	0	0	0	0	0
Cash	22,059	28,102	47,761	30,729	21,577	18,608	20,588
Other	4,033	4,044	6,357	5,598	6,046	8,967	10,605
Current Liabilities	(8,069)	(9,828)	(9,172)	(10,530)	(10,941)	(13,385)	(11,365)
Creditors	(8,069)	(7,751)	(5,202)	(6,560)	(6,971)	(9,415)	(7,395)
Short term borrowings	0	(2,077)	(3,970)	(3,970)	(3,970)	(3,970)	(3,970)
Long Term Liabilities	(16,868)	(23,681)	(37,474)	(33,974)	(40,474)	(48,974)	(68,974)
Long term borrowings	0	(9,045)	(14,430)	(14,430)	(24,430)	(34,430)	(54,430)
Other long term liabilities	(16,868)	(14,636)	(23,044)	(19,544)	(16,044)	(14,544)	(14,544)
Net Assets	113,653	109,297	105,970	88,972	72,024	59,877	44,706
CASH FLOW							
Operating Cash Flow	(21,533)	(17,741)	(6,021)	(15,782)	(17,652)	(10,370)	(14,132)
Net Interest	2,390	1,690	(559)	(898)	(1,179)	(2,146)	(3,060)
Tax	0	0	0	0	0	0	0
Capex	(268)	(95)	(239)	(353)	(321)	(454)	(828)
Acquisitions/disposals	0	0	0	0	0	0	0
Financing	0	11,290	14,250	0	0	0	0
Dividends	0	0	0	0	0	0	0
Net Cash Flow	(19,411)	(4,856)	7,431	(17,032)	(19,152)	(12,969)	(18,019)
Opening net debt/(cash)	0	(37,532)	(28,003)	(29,431)	(12,399)	6,753	19,722
HP finance leases initiated	0	0	0	0	0	0	0
Other	56,943	(4,673)	(6,003)	0	0	0	0
Closing net debt/(cash)	(37,532)	(28,003)	(29,431)	(12,399)	6,753	19,722	37,742
Lease debt	na	1,527	1,365	1,365	1,365	1,365	1,365
Closing net debt/(cash) inclusive of IFRS 16 lease debt	(37,532)	(26,476)	(28,066)	(11,034)	8,118	21,087	39,107

Source: Company reports, Edison Investment Research

Contact details	Revenue by geography
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Management team

Chairman and Chief executive officer: Michele Garufi	Executive Vice-President and Chief Business Officer: Gavin Spencer
Mr Garufi has significant experience in business development, licensing and international marketing in the European pharmaceutical industry. Prior to founding Nicox in 1996, he was VP of the international division and director of licensing at Recordati Italy and MD of its Spanish subsidiary. He previously served as director of the international division at Italfarmaco (1988–92), assistant to the general manager at Poli Chimica (1984–88), assistant to the president at Medea Research (1983) and technical director of one of the Italian subsidiaries of the Lipha Group (1978–82). He is a member of the board of directors of Novaera and of LaMed Pharma. He has previously served on the board of directors of Novuspharma, Novexel, Lica, Scharper, Delife and Relivia, VISUfarma (Iris TopCo) and OncoBioTek. Mr Garufi graduated with honours in pharmaceutical chemistry from the University of Milan and earned a pharmacist's degree in 1989.	Dr Spencer has been with Nicox since 2005. Prior to joining Nicox, he served as senior manager, new technology and product innovation at Novartis Consumer Health, where he had responsibilities in the identification, evaluation and development of new technologies. Dr Spencer began his career at Boots Healthcare International. He has more than 25 years of management and operational experience in the life sciences industry across many strategic roles. He was key in building and managing Nicox's partnerships, including closing deals with Pfizer in 2006, B+L in 2010 and the transaction with VISUfarma. Dr Spencer holds a BSc in chemistry with first-class honours and a PhD in chemistry from the University of Aberdeen.
Vice President and Interim Head of R&D: José Boyer	**Vice President, Finance: Sandrine Gestin**
José L Boyer, PhD, has been interim head of R&D at Nicox since October 2020. He has more than 30 years' experience in academic research and drug development in the pharmaceutical industry including senior leadership roles in ophthalmology development at Parion Biosciences and Inspire Pharmaceuticals.	Ms Gestin joined Nicox in 1999 and has held several positions at the company, including director of accounting and financial controller and, more recently, VP of finance. Before joining Nicox, she worked for 10 years at IBM France, where she was responsible for the consolidation of overseas subsidiaries. Ms Gestin has a master's degree in accounting and finance (Maîtrise des Sciences et Techniques Comptables et Financières) from the Institut d'Administration des Entreprises, Nice.

Principal shareholders	(%)
HBM	7.1
OrbiMed	3.5

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