EDISON

Nicox

Company outlook

Eye health portfolio targets large markets

Pharma and biotech

Nicox's lead candidate NCX-470 continues to advance in the Mont Blanc Phase III trial targeting the topical treatment of glaucoma, having recently reached 98% enrolment. While Mont Blanc data are still expected in Q123, the company has recently pushed back the forecast completion timeline for Denali, the second Phase III trial, and we have thus postponed our NCX-470 launch expectation into H226 (from H225). Nicox's decision to advance NCX-4251 into dry eye disease (DED) significantly boosts the commercial prospects of this proprietary corticosteroid formulation, as over 30 million people in the United States experience DED. We derive a risk-adjusted NPV (rNPV) valuation of €298m, up from €294m previously.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/20	14.4	(10.2)	(0.30)	0.0	N/A	N/A
12/21	8.6	(15.5)	(0.32)	0.0	N/A	N/A
12/22e	5.3	(18.7)	(0.43)	0.0	N/A	N/A
12/23e	7.0	(19.8)	(0.44)	0.0	N/A	N/A

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

Potential first-line glaucoma therapy

NCX-470 is based on Nicox's proprietary nitric oxide (NO) donating platform, which combines an NO-donating molecule with an analogue of established prostaglandin F2α (PGA) drug bimatoprost. NCX-470 0.065% has shown 1.4 mmHg additional lowering of intraocular pressure (IOP) compared to PGA latanoprost in its Phase II study. The Phase III trials are testing a higher 0.1% drug concentration, which may provide further IOP reduction. If approved, NCX-470 could become the most potent single-agent commercial glaucoma drug in terms of IOP lowering efficacy.

Additional ophthalmic assets can drive further value

NCX-4251, originally studied for acute blepharitis, recently showed potentially promising data for DED in the Mississippi Phase IIb study, and Nicox is exploring how to best advance its development into DED. We now believe NCX-4251 could generate over $400m in peak US sales given the larger scope we estimate for the DED opportunity compared to blepharitis. Nicox also obtains recurring royalty revenue from two out-licensed commercial-stage drug assets, Vyzulta and Zerviate.

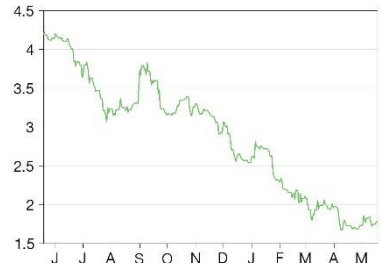
Valuation: rNPV of €298m

We continue to apply a risk-adjusted net present value (nNPV) model with a 12.5% cost of capital. We obtain an rNPV of €298m, up from €294m previously, due to an increase in our NCX-4251 valuation, offset by the pushback in our NCX-470 US launch timing estimate and reduced Vyzulta net pricing estimates. After including €14.6m in Q122 net cash, we obtain an equity valuation of €312.4m or €7.23 per basic share (vs €7.44 previously). We model that Nicox's funds on hand should last through Q423 and that it will need to raise €104m (modelled as illustrative debt) before year-end 2026 (up from €45m previously) before launching NCX-470.

19 May 2022

Price	**€1.84**
Market cap	**€80m**
	$1.05/€
Estimated net cash (€m) at 31 March 2022	14.6
Shares in issue	43.2m
Free float	86%
Code	COX
Primary exchange	Euronext
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	3.0	(11.2)	(57.4)
Rel (local)	6.5	(3.8)	(57.1)
52-week high/low		€4.22	€1.67

Business description

France-based Nicox develops therapeutics for the treatment of ocular conditions. Its lead candidate NCX-470 is in Phase III studies for the treatment of glaucoma, and it is advancing NCX-421 for dry eye disease. Nicox also receives licence revenue for its FDA-approved drugs Vyzulta and Zerviate.

Next events

Mont Blanc Phase III NCX-470 top-line results	Q123
Updates on NCX-4251 development strategy for dry eye disease	H222/H123

Analyst

Pooya Hemami, CFA +1 646 653 7026

healthcare@edisongroup.com

Edison profile page

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Investment summary

Company description: Focusing on eye-care

Based in France, Nicox is a pharmaceutical company with multiple therapeutic 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, originally studied for acute exacerbations of blepharitis, is now being advanced for DED following recently reported promising data in this indication in its prior Phase IIb study. 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.

Exhibit 1: Nicox upcoming catalysts

Event	Timing
NCX-470 Mont Blanc and Denali enrolment updates	H222
NCX-470 Mont Blanc Phase III top-line results	Q123
Updates on DED development strategy for NCX-4251	H222/2023

Source: Edison Investment Research

Valuation: Pipeline rNPV of €298m reflects upside

Our Nicox valuation applies a risk-adjusted nNPV model with a 12.5% cost of capital. We include the prospects for NCX-470 (50% probability of success in the US and 35% in Europe), NCX-4251 (25% probability of success) and the Vyzulta and Zerviate royalties. Altogether, we obtain a pipeline rNPV of €298m, up from €294m previously. The mild increase is due to a higher contribution from NCX-4251 as we believe the acute DED indication can provide much higher revenue potential than the blepharitis indication previously investigated, although this is offset by reductions in our NCX-470 US market (due to the pushback in launch timing) and global Vyzulta (on lower pricing assumptions) valuations. After adding Q122 net cash of €14.6m (excluding lease liabilities), we obtain an equity valuation of €312.4m, or €7.23 per basic share (vs €7.44 previously). Our per-share valuation on a fully diluted basis is €6.75 (versus €6.68 previously).

Financials: Funded into Q423 given recent financing

In Q421, Nicox raised €15m in a private placement and reported gross cash of €41.9m at 31 December 2021 along with €20.5m in gross debt. At 31 March 2022 it reported gross cash of €35.1m and no material change in its debt position and hence we estimate Q122 net debt of €14.6m. We have raised our net operating cash burn rate forecasts to €18.8m and €19.7m in FY22e and FY23e, up from our prior estimates of €15.0m and €18.8m, respectively. We have increased our R&D cost estimates due to recent trends and given our expectations in future study costs needed for the NCX-4251 programme in DED. Nicox indicates that its current funds should finance its operations until Q423 based on NCX-470 development alone. Our forecasts assume a similar funding runway (permitting Nicox to also continue non-clinical activities towards NCX-4251 over the period) and we model €104m in fund-raising needs (modelled as illustrative debt) between 2023 and year-end 2026. This is up from €45m previously, mainly due to the push back in our estimated NCX-470 commercialisation timelines and due to higher anticipated costs with the NCX-4251 programme as it moves into the larger DED indication (from acute blepharitis, previously).

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 versus latanoprost in ongoing pivotal trials. For NCX-4251, the company will still need to demonstrate efficacy in trials and a value benefit compared to other corticosteroid or immunomodulatory drugs used for DED. 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 30 employees (December 2021) 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's NCX-4251, having previously completed Phase IIb studies, is now being advanced as a treatment for DED. Both assets are partnered with Ocumension Therapeutics for the Chinese market and Nicox maintains rights for the more lucrative North American, European and Japanese/Australasian markets. Nicox also has commercialised assets, Vyzulta (latanoprostene bunod) and Zerviate (cetirizine ophthalmic solution), already launched and marketed via commercial partners, enabling it to obtain recurring royalty income. We expect that the potential market introduction of NCX-470 in H226 should 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 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 by Bausch + Lomb (B+L).

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

[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).

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, and IOP reduction remains the most widely accepted measure of treatment efficacy in decelerating disease progression. Neuroprotective treatment approaches (whereby the proposed treatment would aim to reduce the propensity for RGC injury) have not generally been shown to be successful in reducing progression in large-scale randomised clinical trials (RCTs). The US National Eye Institute (NIH) estimates the US glaucoma prevalence at over 2.7 million people. Over 120,000 Americans go blind each year from glaucoma. Glaucoma is the second leading cause of blindness 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 usage of topical eye drop medications to lower IOP. We estimate 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 $2.8bn in 2020 across seven major markets (including the US and Japan) and projected that it would grow to $3.5bn in 2030. 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	MoA	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 (AE) 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 unlikely to cause systemic side effects). PGAs command c 50% of the topical

[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.

[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 glaucoma cases are 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.

glaucoma market in the United States, and US PGA sales reflect about $1.5bn in gross yearly sales.

In 2017, Vyzulta, which is a modified form of latanoprost designed to donate 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 increasing AH outflow through the TM/SC pathway. As explained below, Vyzulta was first developed by Nicox then partnered with B+L.

NCX-470 could be a more potent 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, derived from an analogue of bimatoprost, and releases that molecule and NO when instilled into the eye. Bimatoprost is a second-generation PGA marketed as Lumigan 0.01% by AbbVie and is the best-selling branded glaucoma drug in the United States in terms of revenue. Bimatoprost is considered the most effective approved base PGA molecule for glaucoma, with meta-studies[5] suggesting incremental IOP reductions in of c 0.5mmHg to c 1.2 mmHg compared to latanoprost or travoprost, albeit with a higher incidence of hyperaemia. Given the NCX-470 formulation in current trials has a higher drug concentration (0.1%) than Vyzulta (0.024%), it provides a higher effective NO dose release per eye drop, which could potentially augment the therapeutic effect compared to Vyzulta.

NCX-470 was studied in a 433-patient US multicentre 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 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 versus 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 AEs. If comparable results are confirmed in Phase III trials, NCX-470 could potentially become the first non-combination glaucoma drug product to show statistical superiority to a standalone PGA drug in its registration-enabling pivotal trials.

Preclinical study shows possible neuroprotection

In Q321 Nicox reported encouraging preclinical data showing NCX-470 may also provide benefit in glaucoma patients through a mechanism other than IOP reduction, namely by potentially improving ocular perfusion. We believe there is much interest in alternative methods to provide neuroprotection to the retinal ganglion cells affected in glaucoma. The results, discussed in a prior note, suggest possible non-IOP-mediated mechanisms of neuroprotection for NCX-470, which could bode well for the product's perception among eye-care practitioners. No approved glaucoma product has definitively shown non-IOP-mediated methods of neuroprotection, to our knowledge, and we believe more substantive (and likely head-to-head) post-approval NCX-470 human studies demonstrating neuroprotection will be needed n order for any such claim to be reliably made.

Top-line data from first Phase III study guided for Q123

In mid-2020, Nicox started the Mont Blanc Phase III multisite study for NCX-470 (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

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

an adaptive design, where the adaptive phase consists of two NCX-470 arms (0.065% or 0.1%), and latanoprost (0.005%). In Q320, after completing the adaptive phase a 0.1% NCX-470 dose was selected, so for the remaining portion of the trial, patients would randomly 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 it is likely the incremental IOP reduction to latanoprost 0.005% that can be shown could be higher than the 1.4mm amount shown in the Dolomites study.

A small number of sites in China will be included in the Mont Blanc trial. The company recently reported enrolment has been faster than anticipated and 98% of the required study participants been recruited. Top-line data continue to be guided for Q123. The second Phase III study in glaucoma, Denali, started in Q420. The Denali trial is being equally funded by Nicox and Ocumension (Nicox's commercial partner for the Chinese market, explained below) and is evaluating NCX-470 ophthalmic solution (0.1%), versus latanoprost (0.005%). It will include c 60 clinical sites in the US and China, with c 80% of the patients to be recruited in the United States (and the remainder from China). 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. The first patient from China was recruited in Q421 and in April 2022, the company indicated that due to COVID-19 and other hurdles, top-line data will not be available until after 2023 (versus its prior guidance of before year end FY23). Given the predominantly US-based Mont Blanc study is recruiting ahead of schedule, we believe the delay in Denali is likely due to challenges within the China-based components of the study.

Ocumension partnership for China, Korea and South-East Asia

In 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. Nicox will be entitled to tiered royalties of between 6% and 12% on net sales in the covered regions. In March 2020, the two parties amended their agreement resulting in Ocumension immediately paying Nicox €15m (in place of potential milestones from the original agreement), gaining additional rights to NCX-470 for Korea and South-East Asia and agreeing to pay 50% of the costs of the Denali study.

Market considerations for glaucoma therapeutics

Fortune Business Insights[6] 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,[7] and Nicox[8] and others[9] have estimated total US prescriptions for glaucoma medications (TRx) at more than 35 million annually.

[6] Fortune Business Insights. https://www.fortunebusinessinsights.com/industry-reports/glaucoma-therapeutics-market-100312 Accessed 21 February 2022

[7] Market Scope. www.market-scope.com/pages/news/3476/glaucoma-drugs-continue-to-battle-for-market-share. Accessed 21 February 2022.

[8] Nicox annual information form. https://www.nicox.com/wp-content/uploads/EN-_Nicox-2020-Document-dEnregistrement-Universel-%E2%80%93-Overview-of-the-activities-%E2%80%93-free-translation-1-1.pdf Accessed 21 February 2022.

[9] Skye Bioscience. https://ir.skyebioscience.com/news-events/press-releases/detail/20/emerald-bioscience-to-present-research-data-related-to-its Accessed 21 February 2022.

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 first, changes at the RGC level over time or second, change in visual function. 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, glaucoma drainage implants 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 implants such as Durysta (bimatoprost implant by Allergan/AbbVie, approved by the FDA in H120) or Glaukos's iDose TR (in Phase III with NDA planned in 2022) 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,[10] rho kinase (ROCK) inhibitors, with the only molecule on the US market being netarsudil (Rhopressa from Aerie Pharmaceuticals), launched in Q218. Aerie reported combined US Rhopressa and Rocklatan (netarsudil/latanoprost, launched in 2019) sales were $$112.1m in FY21 (+35% y-o-y). Rhopressa is generally viewed as having a milder effect on IOP than PGA drugs, of up to 5mmHg versus baseline, compared to 6–8mmHg from latanoprost. One potential benefit of ROCK inhibitors could be neuroprotection,[11] 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).[12]

Competitive landscape considerations for NCX-470

Generic latanoprost accounts for about 74%[13] of US PGA prescriptions, compared to 13% for Lumigan, whereas Lumigan leads by value. Net US Lumigan sales (after all discounts) were

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

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

[12] Rhopressa Prescribing Information.

[13] MIDAS T-Rx data provided by Nicox.

reported by Abbvie at $273m in 2021 and its international sales, including Ganfort (bimatoprost/timolol combination) were $306m.

Among current US approved products, we perceive the most direct competitors to NCX-470 as Lumigan, Vyzulta and Rocklatan. One further competitive advantage versus 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 $306m in peak global sales in 2026. However, it is a combination drug (and thus has the AE profiles of both constituent molecules) and as with Rhopressa, can lead to hyperaemia (59% incidence in registration trials)[14] and corneal verticillata. This is in addition to the AE associated with a PGA drug, which may limit Rocklatan's uptake.

Emerging pipeline considerations

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 United States or Europe. In the pipeline, we believe Santen's DE-117, already launched in Japan, could be an interesting entrant. DE-117 targets prostanoid receptor EP2 (unlike currently 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. Santen had filed an NDA with the US FDA, with two of the three included Phase III studies meeting the non-inferiority statistical endpoint. However, Santen received a complete response letter (CRL) in November 2021, citing manufacturing deficiencies, and announced it is working to resolve the stated issues and file a resubmission in H122. Santen/Ona's sepetaprost (DE-126) is a dual agonist of the prostanoid EP3 and FP receptors and a dose-ranging Phase IIb (ANGEL) study found sepetaprost 0.002% delivered a similar IOP reduction to latanoprost 0.005% across all time points through three months and a lower rate of AEs. A subsequent Phase IIb (ANGEL-2) study was initiated comparing DE-126 to timolol 0.5% and was completed near YE21 but to our knowledge results have not yet been published. Cenegermin (recombinant human nerve growth factor), already approved for neurotrophic keratitis, represents a unique treatment approach, given it directly aims for neuroprotection (rather than IOP control), but remains at a very early stage.

[14] Rocklatan Prescribing Information.

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

Product	Company	Stage or Status	Description	Notes
Omidenepag isopropyl (DE-117)	Santen	NDA/CRL in Nov 2021; launched in Japan in 2018	Selective agonist for prostanoid receptor EP2 versus currently approved PGA drugs, which act on an 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 (NCT02981446, NCT03691649 and NCT03691662) were designed to assess whether DE-117 is non-inferior to timolol or latanoprost at reducing IOP. Two of these three met the non-inferiority endpoint. Prior Phase III study in Japan (NCT02623738) found 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. FDA CRL received in November 2021
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 versus baseline (29% drop) versus 6.8mmHg (26% drop) for latanoprost comparator arm; 0.002% DE-126 arm was well tolerated with lower AE than latanoprost arm. Subsequent Phase IIb (NCT04742283, n=323) is comparing the drug to timolol 0.5%
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-patient Phase II (NCT02250612) showed non-inferiority versus twice-daily timolol in patients with baseline IOP over 25 mmHg, but did not show non-inferiority in total study population
Razuprotafib (AKB-9778)	Aadi Bioscience (Aerpio Pharmaceuticals)	Phase II	Inhibitor of vascular endothelial protein tyrosine phosphatase, 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 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 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 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 still account for the majority of US glaucoma drug prescriptions, suggesting 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. We believe if NCX-470 can show a c 1.5–2mmHg improvement versus latanoprost in the pivotal programme (and if the AE profile remains favourable), it can be 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 maintain a 50% probability of success estimate in the United States. With the company recently withdrawing its guidance for the completion of Denali by YE23, we now assume Denali will be completed in 2024, pushing back our estimate for NDA submission into 2025 and NCX-470 US launch to H226 (from H225, previously). We also assume a launch in China by partner Ocumension in H226. For Europe, we anticipate 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 H223, leading to a potential European launch in 2027 (unchanged). We continue to apply a lower 35% probability of success for Europe, given our forecast need for a separate pivotal study. We continue to model an initial gross (pre-discount) price of $220/bottle, comparable to Vyzulta's current (pre-discount) price, and 50% net to gross. Our commercial forecasts are summarised below and there is little change from our prior estimates other than pushing back of our launch timing forecasts (the anticipated duration from launch to reaching peak market share is unchanged).

Exhibit 5: Financial forecasts for NCX-470

	2026	2027	2028	2029	2030
US market					
Estimated number of glaucoma drop bottles dispensed per year (000)	72,376	75,271	78,282	81,413	84,670
Market share for NCX-470 (%)	0.14	0.42	0.71	1.21	2.04
Estimated price per bottle ($), net of discounts/rebates	110.00	113.11	118.76	124.70	130.94
Net sales ($000)	11,261	36,008	66,452	122,636	226,321
Ex-US markets					
Net sales for Europe and regions not covered by Ocumension agreement (€000)	0	15,108	27,882	51,455	94,960
Net licence and royalty revenue from Ocumension for China (€000)	75	244	459	863	1,664
Assumed $/€ rate	1.05	1.05	1.05	1.05	1.05
Worldwide total NCX-470 related revenue (€000)	10,800	49,645	91,628	169,114	312,168

Source: Edison Investment Research

We assume 55 million (as estimated by IQVIA) glaucoma drop bottles were dispensed in 2019[15] in the US and this will grow at 4% a year. We estimate that, at peak share, NCX-470 will account for 3% of such prescriptions, resulting in nearly $395m net US sales in 2032. NCX-470's primary US patent expires in 2029 (with up to five years of term extension), with its formulation patent expiring in 2039. We assume gradual erosion of sales after 2035.

NCX-4251 for DED

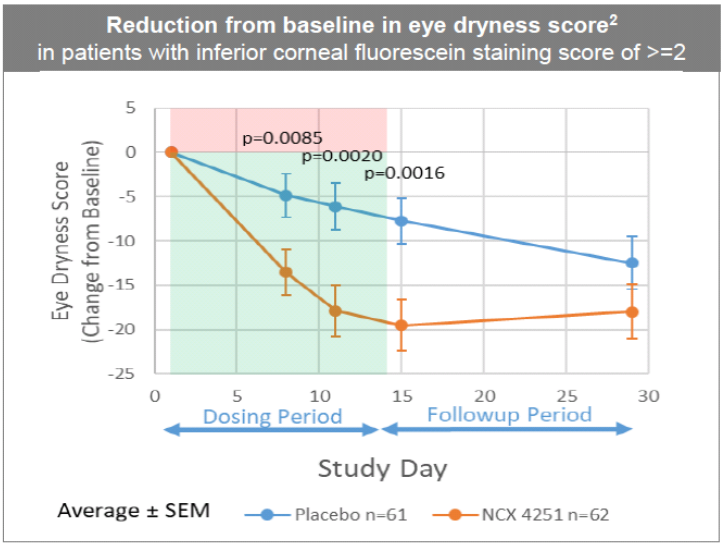
Previously investigated for acute blepharitis, after a post-hoc analysis of the Mississippi Phase IIb trial showed an improvement in dry eye symptoms and subsequent positive discussions with the FDA in Q122, Nicox will now advance the candidate as a treatment for DED. NCX-4251 is a proprietary ophthalmic suspension of fluticasone propionate nanocrystals, designed to be placed directly on the eyelids using an applicator. Fluticasone propionate is an established approved corticosteroid drug and an inhaled formulation is sold in the United States under the Flonase brand. Fluticasone has high affinity for the glucocorticoid receptor and was reported to have over 14x higher affinity than dexamethasone,[16] 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 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, and hence the intended treatment regimen for NCX-4251 is for acute (short term) therapy of c 14 days. NCX-4251 is licensed to Ocumension for mainland China, Hong Kong, Macau and Taiwan, and Nicox retains NCX-4251 rights for the remaining regions including the US and Europe.

[15] 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).

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

While signals of efficacy in blepharitis were shown in Mississippi, the trial did not meet its primary outcome measure in terms of the proportion of patients achieving complete cure in all three assessed blepharitis measures (eyelid redness, eyelid debris and eyelid discomfort). However, in Q421 the company reported a post-hoc analysis showed potentially promising data that NCX-4251 could provide clinical benefit in patients with DED (c 70–80% of blepharitis patients generally also have DED). Given blepharitis is commonly associated with DED, of the 224 enrolled patients in Mississippi, 123 were found to have inferior corneal staining (by a score of at least two on a five-point scale), a key sign of DED. Among these 123 patients, there was a statistically significant difference versus placebo in the change from baseline in eye dryness scores (assessed on a validated Visual Analog Scale). Significant differences were also observed in other DED symptoms (including photophobia, blurred vision, burning/stinging, pain and others) at all measured time points in the 14-day treatment, and for some, the effects persisted for up to two weeks after the end of treatment.

Exhibit 6: NCX-4251 Phase IIb data showing efficacy in reducing signs and symptoms of DED



Post hoc subset analysis

- 123 of the overall 224 patients had inferior corneal fluorescein staining scores ≥2 on a scale of 0 (none) to 4 (severe)
- In this subset, patients had **statistically significant difference against placebo for change from baseline in eye dryness scores**
- Statistically significant differences against placebo were also observed in other symptoms of dry eye disease (photophobia, blurred vision, burning/stinging, foreign body sensation, ocular itching, pain) at all timepoints during treatment. In some symptoms the effects of treatment persisted up to two weeks after the end of dosing treatment
- Treatment group differences in change from baseline in inferior corneal fluorescein staining approached significance and could potentially reach that with a larger sample size

Source: Nicox. Note: 1. Mississippi: US multicenter, randomised, double-masked, placebo-controlled, Phase IIb study evaluating the safety and efficacy of NCX 4251 ophthalmic suspension, 0.1% once daily (QD) for the treatment of acute exacerbations of blepharitis, ClinicalTrials.gov identifier: NCT04675242. Eye dryness measured on a visual analogue scale (0 to 100).

It is not surprising a corticosteroid-based product such as NCX-4251 could provide benefit for DED, given inflammation is a well-known contributor to the disease, and we note Eyesuvis, a formulation of corticosteroid loteprednol, was approved in Q420 for the short-term treatment of DED. The DED market could provide a substantial opportunity for NCX-4251, as it is estimated to be worth c $5bn worldwide by Research and Markets and Fortune Business Insights, and c $1.6m in the United States according to Aerie Pharma. DED has been estimated as affecting between 30 million and 38 million people in the United States,[17] and although its pathophysiology is not fully understood, it is viewed as multifactorial and chronic, often with an inflammatory component where the eye produces insufficient tears (aqueous deficiency), or tears have an unbalanced composition (often related to meibomian gland dysfunction). First-line DED therapy relies on over-the-counter (OTC) topical lubricants, eyelid hygiene-related supportive treatments and omega-3 fatty acid supplementation, but these are often not adequate in moderate to severe cases. The only FDA-approved topical drugs (cyclosporine in Restasis and Cequa, lifitegrast in Xiidra, and loteprednol in Eyesuvis) for DED rely on controlling or modulating inflammation. Restasis, Xiidra and Cequa have been estimated to account for c $1.5bn in combined total revenue.

[17] According to research cited by Aerie Pharmaceuticals and Kala Pharmaceuticals in their respective 2021 10-K filings

Given the risks associated with prolonged corticosteroid usage, we anticipate that Nicox will advance NCX-4251 as a short-term therapy (c 14 days) for acute exacerbations of DED, similar to Eyesuvis (which recorded $6.3m in FY21 product sales its Q121 launch). Only c 10% of US patients with DED are estimated to be taking chronic prescription drugs[20] and, according to research cited by Kala Pharmaceuticals, c 75–90% of surveyed DED patients experience episodic dry eye flares, lasting around four to five days and occurring around five to six times per year.

The company is currently assessing how to best advance NCX-4251 in DED, and we anticipate that it will start a Phase IIb study in acute exacerbations of DED in 2024. We have removed blepharitis from our NCX-4251 forecasts and are now modelling future development of the candidate for short-term exacerbations (or 'flares') of DED. We project the Phase IIb in DED (to start in 2024) will be designed in such a way that if the primary endpoint is met, it could count as one of two pivotal trials required by the FDA for NDA submission. We anticipate Nicox will start a separate Phase III trial in 2025. We model potential US market approval and launch in H227.

Given that over 30 million people in the United States have DED and over 75% experience short-term exacerbations (which we model at an average of four events per year), we view the acute DED market as a substantial opportunity and considerably larger than the acute blepharitis indication previously investigated. We consider a sizeable portion of DED patients will not seek medical care for every acute DED episode and we estimate the addressable market to be c 24m potential acute DED episodes per year in the US. Given the self-limited nature of most such flares and that treatment would be primarily for ameliorating comfort (rather than preventing ocular damage), we assume a peak penetration for NCX-4251 of 5%. Assuming a gross price at launch of $320 per bottle or treatment course (a c 10% discount to Eysuvis), we now model peak US sales of c $400m in the US market in 2032 and c €460m in global sales and royalties to Nicox (compared to our prior estimates of €55m in peak global revenue to Nicox in acute blepharitis).

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 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 inhibition. Further optimisation of the NCX-1278 formulations will proceed before the formal start of pre-IND enabling studies. We 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. It is now commercialised in the United States, Canada, Argentina, Mexico, Hong Kong, Taiwan and Ukraine, and approved in nine other countries. Nicox is entitled to tiered net royalties[18] 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.

[18] 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 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.

Vyzulta has shown up to c 1.2mmHg superior IOP reduction versus 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 remain positive until 2030.

Vyzulta showed 32% US prescriptions growth reported in FY20 and over 40% in Q122, supported by increased demand and coverage. However, gross royalties received by Nicox (predominantly due to Vyzulta but also from Zerviate, as described below) have been flat (€3.9m in FY20 and €3.8m in FY21) despite the prescriptions growth. This is due to higher rebates in FY21 (and lower realised net prices following changes in the insurance plan reimbursement mix as described previously), hence we are lowering our peak Vyzulta sales estimates to reflect a lower realised net drug price. We now assume peak global Vyzulta net sales of c $130m in 2030, down from our prior estimate of c $217m. We estimate peak net Vyzulta royalties to Nicox will be €11m in FY30, down from our prior estimate of €21m in FY31. We have also pushed back our estimate of a €5m milestone payment to Nicox (triggered on global yearly Vyzulta sales reaching $100m) to FY27, from FY24 previously. We have also substantially reduced (by c 70%) our post-2030 Vyzulta royalty estimates to reflect that B+L would no longer be required to pay Nicox any further royalties on net US sales once US market exclusivity ends (expected in 2030).

Zerviate

Zerviate (cetirizine 0.24%) is an antihistamine drug approved by the FDA for treating ocular itching associated with allergic conjunctivitis. Zerviate is licensed by Nicox in the United States to Eyevance (acquired by Santen in Q320) and was launched there in Q120. Zerviate is also licensed to Ocumension in the Chinese market, to Samil in South Korea, ITROM in certain Gulf and Arab markets and to Laboratorios Grin in Mexico. In Q321, Nicox received $2m from Ocumension as an advance payment for development and regulatory milestones for the product and remains eligible to receive sales milestones of up to $17.2m from Ocumension along with tiered royalties of between 5% and 9% of net sales recorded by Ocumension. We also note positive Phase III results in China were reported in Q122, whereby Zerviate was found to be non-inferior to emedastine difumarate.

The ocular allergy market is very competitive, but what sets Zerviate apart is it is the only topical US anti-allergy drug based on an existing approved oral product and this familiarity may potentially help its positioning with primary care providers. We see limited clinical advantage in Zerviate compared to the existing ocular allergy alternatives, as discussed in our initiation report. However, we anticipate Eyevance (Santen) 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 c $47m in 2032 (in line with our prior forecasts), or c 2.5% of ophthalmic anti-allergy prescriptions.

To our knowledge, Zerviate has only been launched in the United States and Nicox has reported an increase of more than 120% y-o-y in prescriptions each quarter since Q221, but specific royalties have not been disclosed. Nicox's effective royalty from Eyevance is c 5% until certain manufacturing costs are covered, after which the royalty rate rises to 8–15%.

Valuation

Our Nicox valuation applies a risk-adjusted nNPV model with a 12.5% cost of capital. For NCX-470, the lead asset, we separate the contributions for the United States, Europe and the Ocumension arrangement. We continue to apply a 50% probability of success for the United States and China and a lower probability (35%) for Europe. For NCX-4251 in Acute DED, we use a 25% probability of success (lower than our prior estimate of 30% for the acute blepharitis indication) given at least two more studies will be needed for approval, and the product has yet to be assessed in a specific DED human study. We are optimistic for NCX-4251's ability to be effective in DED given that before

Eysuvis's approval, corticosteroids were often used off-label for DED, and we will reassess our probability estimates as NCX-4251 progresses in further development. As Vyzulta and Zerviate are already on the market, we apply a 100% probability of success assumption for their contributions. We have also adjusted our forex assumption to $1.05/€, from $1.13/€ previously and rolled forward our estimates.

Compared to our prior valuation, our rNPV for NCX-470 in the US market has decreased (from €158.8m to €146.0m) due to pushing back our expectation for launch into H226 (from H225 previously) given the delay in the Denali trial. We have also reduced the rNPV of global Vyzulta royalties from €99.2m to €36.8m, given the revisions to our net pricing estimates described above and the reduction in our post-FY30 forecasts. Compensating for these decreases is a significant upward revision to our NCX-4251 rNPV to €95.1m, up from €9.3m, previously, due to the substantially larger opportunity we anticipate for acute exacerbations of DED (compared to acute blepharitis). We believe acute DED flares can potentially generate peak global sales of over €460m, which still only represents a single-digit percentage of the potential addressable market (given the substantial incidence of DED flare-up episodes as described above). We note our global NCX-470 valuation (c €207m) still drives most of our valuation for the company.

Exhibit 7: Nicox SA rNPV assumptions

Product contribution	Indication	Stage	NPV (€m)	Prob of success	rNPV (€m)	rNPV/ basic share (€)	Launch year	Peak sales (€m)*
NCX-470 (net of R&D and SG&A costs) in US market	Glaucoma	Phase III ongoing	299.9	50%	146.0	3.38	H226	377
NCX-470 (net of R&D and SG&A costs) in Europe and unpartnered regions	Glaucoma	Phase III	165.6	35%	56.8	1.31	2027	216
NCX-470 licence fees from Ocumension (China and other)	Glaucoma	Phase III ongoing	8.1	50%	3.9	0.09	H226	3.6**
NCX-4251 (net of R&D and SG&A costs) sales and licence fees/royalties	Acute exacerbations of dry eye	Phase IIb	394.8	25%	95.1	2.20	H227	463
Vyzulta royalties from B+L	Glaucoma	Commercial	36.8	100%	36.8	0.85	2017	10.6*
Zerviate royalties from Eyevance and others	Allergic conjunctivitis	Commercial	24.8	100%	24.8	0.57	2020	6.4*
Corporate costs			(65.5)	100%	(65.5)	(1.52)		
Total			864.5		297.8	6.89		
Net cash (Q122e) excluding lease liabilities			14.6		14.6	0.34		
Total equity value			879.1		312.4	7.23		
Basic shares outstanding (000)			43,223					
Outstanding options and warrants (000)			6,142					
FD shares outstanding (000)			49,365					

Source: Edison Investment Research. Note: *Peak projected sales shown for year 2032 except for Vyzulta where peak anticipated royalties are shown for year 2030. **Reflects net licence and royalties received by Nicox and not commercial sales by licensee(s).

We now obtain an rNPV valuation for Nicox of €297.8m (versus €294.0m previously). After updating for Q122e net cash of €14.6m, we obtain an equity value of €312.4m, or €7.23 per basic share (down from €7.44 previously given the reduction in net cash compared to the €26.9m pro forma October 2021 amount previously applied). After considering the potential dilutive effect of options and warrants and their effects on net cash, our fully diluted valuation would be €6.75 (up from €6.68 previously) per fully diluted 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. In addition, management recently extended the Denali study completion timelines and if further delays occur, this could push back our commercialisation timeline forecasts.

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 it shows versus latanoprost in Phase III. For NCX-4251, Nicox will need to demonstrate 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/Santen and Ocumension for most of its partnered revenue. Nicox may also decide to license NCX-470 or NCX-4251 in markets outside the United States and, if so, it would depend the commercial efforts and partnership terms of such potential agreements.

Financing risk: we expect Nicox will need to raise additional capital before commercialising NCX-470 and model €104m in financing between 2023 and year-end 2026. 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 prices 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 to at least 2034, 2038, 2030 and 2035, respectively. Comparable protections exist for Europe.

Financials

Nicox reported cash and equivalents of €42.0m at 31 December and outstanding debt of €20.5m (consisting of an €18.5m Kreos loan and a €2m French-state guaranteed loan), excluding €1.0m in lease liabilities. At 31 March 2022, it reported gross cash of €35.1m and no material change in its debt position, hence we estimate Q122cash net debt of €14.6m. In December 2021 the company announced it had raised €15m in gross proceeds (€13.7m net) through a private placement of shares (and attached warrants), which extended its cash runway guidance to Q423 (assuming development of NCX-470 alone) and thus comfortably past the top-line Mont Blanc study data readout, expected in Q123.

The company had a FY21 net operating cash burn rate (including finance income) of €18.5m, up from €5.4m in FY20, compared to our prior forecast of €17.3m. FY20 had benefited from a €15m payment from Ocumension as part of their licensing agreement involving NCX-470. The company recognised €10.5m of this licence payment as part of FY20 revenue, compared to €4.8m in licence payments recognised in FY21. Gross royalties, which are predominantly derived from Vyzulta sales and are before the consideration of royalties paid to Pfizer, decreased slightly from €3.9m in FY20 to €3.8m in FY21, due to Vyzulta pricing considerations discussed previously. R&D costs (net of tax credits) increased to €17.2m (from €12.0m in FY20), primarily due to the ramping up of the Mont Blanc, Denali and Mississippi clinical trials.

Following FY21 results, we have raised our net operating cash burn rate forecasts to €18.8m and €19.7m in FY22 and FY23, up from our prior estimates of €15.0m and €18.8m, respectively. The increases are due in part to the R&D cost run-rate being higher than expected in FY21, with us revising future costs in line with more recent expenditure rates. We also raised our R&D cost expectations for the NCX-4251 programme, particularly after FY22, as we expect acute DED study trials to be larger than we previously expected for the prior acute blepharitis programme (which is now being put aside in favour of the acute DED indication). We continue to expect current funds on-hand to be sufficient for Nicox to maintain operations through Q423, but given the increase in our R&D cost expectations – particularly due to NCX-4251 and the push back in our NCX-470 launch

expectations – we now expect the company will require €104m in added funding before the anticipated launch of NCX-470 (which we now expect in H226), up from €45m previously. We assume the company will raise €26m in each year between 2023 and 2026 (all these fundraisings are modelled as illustrative debt). Our projections do not include any potential proceeds from the exercise of options or warrants, which if exercised, would lower our funding forecasts accordingly.

Following the anticipated NCX-470 launch, we do not expect Nicox to require additional capital, as we expect its royalty streams plus NCX-470 sales should enable it to start achieving consistent positive operating income starting in 2027.

Exhibit 8: Financial summary

€'000s	2018	2019	2020	2021	2022e	2023e	2024e
31-December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS							
Revenue	4,717	8,260	14,423	8,583	5,312	6,979	9,270
Cost of Sales	(690)	(1,405)	(1,516)	(1,350)	(1,288)	(1,667)	(2,058)
Gross Profit	4,027	6,855	12,907	7,233	4,024	5,312	7,213
General & Administrative	(9,506)	(7,666)	(6,677)	(7,000)	(7,261)	(9,579)	(17,961)
Net Research & Development	(15,491)	(16,883)	(11,991)	(17,194)	(14,250)	(14,100)	(19,650)
Amortisation of intangible assets	0	(659)	(1,252)	(1,205)	(993)	(968)	(944)
Operating profit before exceptionals	(20,970)	(18,353)	(7,013)	(18,166)	(18,480)	(19,336)	(31,343)
EBITDA	(20,718)	(17,230)	(5,270)	(16,505)	(17,103)	(18,068)	(30,139)
Depreciation & other	(252)	(464)	(491)	(456)	(384)	(299)	(260)
Operating Profit (before amort. and except.)	(20,970)	(17,694)	(5,761)	(16,961)	(17,487)	(18,367)	(30,399)
Exceptionals including asset impairment	302	(6,115)	(6,621)	(30,658)	0	0	0
Other	0	0	0	0	0	0	0
Operating Profit	(20,668)	(23,809)	(12,382)	(47,619)	(17,487)	(18,367)	(30,399)
Net Interest	2,390	1,690	(4,436)	1,419	(1,189)	(1,456)	(3,642)
Profit Before Tax (norm)	(18,580)	(16,004)	(10,197)	(15,542)	(18,676)	(19,823)	(34,041)
Profit Before Tax (FRS 3)	(18,278)	(22,778)	(18,070)	(47,405)	(19,669)	(20,792)	(34,986)
Tax	(113)	3,856	(28)	3,644	0	0	0
Profit After Tax and minority interests (norm)	(18,693)	(12,148)	(10,225)	(11,898)	(18,676)	(19,823)	(34,041)
Profit After Tax and minority interests (FRS 3)	(18,391)	(18,922)	(18,098)	(43,761)	(19,669)	(20,792)	(34,986)
Average Basic Number of Shares Outstanding (m)	29.6	30.3	33.7	37.5	43.9	44.7	45.5
EPS - normalised (€)	(0.63)	(0.40)	(0.30)	(0.32)	(0.43)	(0.44)	(0.75)
EPS - normalised and fully diluted (€)	(0.63)	(0.40)	(0.30)	(0.32)	(0.43)	(0.44)	(0.75)
EPS - (IFRS) (€)	(0.62)	(0.62)	(0.54)	(1.17)	(0.45)	(0.47)	(0.77)
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	89,745	66,871	65,640	64,547	63,574
Intangible Assets	71,397	72,120	64,848	39,974	38,981	38,012	37,068
Tangible Assets	25,628	27,517	24,829	26,660	26,422	26,297	26,269
Investments in long-term financial assets	15,473	11,023	68	237	237	237	237
Current Assets	26,092	32,146	52,521	47,738	29,099	35,653	27,833
Short-term investments	0	0	0	0	0	0	0
Cash	22,059	28,102	47,195	41,970	23,058	29,168	21,227
Other	4,033	4,044	5,326	5,768	6,041	6,485	6,606
Current Liabilities	(8,069)	(9,828)	(15,404)	(8,000)	(6,308)	(5,038)	(3,679)
Creditors	(8,069)	(7,751)	(10,115)	(8,000)	(6,308)	(5,038)	(3,679)
Short term borrowings	0	(2,077)	(5,289)	0	0	0	0
Long Term Liabilities	(16,868)	(23,681)	(26,027)	(31,057)	(31,057)	(57,057)	(83,057)
Long term borrowings	0	(9,045)	(12,687)	(20,520)	(20,520)	(46,520)	(72,520)
Other long term liabilities	(16,868)	(14,636)	(13,340)	(10,537)	(10,537)	(10,537)	(10,537)
Net Assets	113,653	109,297	100,835	75,552	57,374	38,105	4,671
CASH FLOW							
Operating Cash Flow	(21,533)	(17,741)	(956)	(19,900)	(17,576)	(18,260)	(30,067)
Net interest and financing income (expense)	2,390	1,690	(4,436)	1,419	(1,189)	(1,456)	(3,642)
Tax	0	0	0	0	0	0	0
Net Operating Cash Flow	(19,143)	(16,051)	(5,392)	(18,481)	(18,765)	(19,716)	(33,709)
Capex	(268)	(95)	(20)	(8)	(146)	(174)	(232)
Acquisitions/disposals	0	0	0	0	0	0	0
Financing	0	11,290	13,321	13,804	0	0	0
Dividends	0	0	0	0	0	0	0
Net Cash Flow	(19,411)	(4,856)	7,909	(4,685)	(18,911)	(19,890)	(33,941)
Opening net debt/(cash)	0	(37,532)	(28,003)	(29,287)	(21,687)	(2,775)	17,115
HP finance leases initiated	0	0	0	0	0	0	0
Other	56,943	(4,673)	(6,625)	(2,915)	0	0	0
Closing net debt/(cash)	(37,532)	(28,003)	(29,287)	(21,687)	(2,776)	17,115	51,056
Lease debt	N/A	1,527	1,099	986	986	986	986
Closing net debt/(cash) inclusive of IFRS16 lease debt	(37,532)	(26,476)	(28,188)	(20,701)	(1,790)	18,101	52,042

Source: Company reports, Edison Investment Research

Contact details	Revenue by geography
Nicox Drakkar 2 – Bât D 2405 route des Dolines – CS 10313 Sophia Antipolis – 06560 Valbonne +33 (0)4 97 24 53 00 www.nicox.com	N/A

Management team

Chairman: Michele Garufi	Executive vice president and chief business officer: Gavin Spencer
Before founding Nicox in 1996, Mr Garufi was vice president (VP) of the international division and director of licensing at Recordati Italy and managing director of its Spanish subsidiary. He previously served as director of the international division at Italfarmaco (1988–1992), assistant to the general manager at Poli Chimica (1984–1988), assistant to the president at Medea Research (1983) and technical director of one of the Italian subsidiaries of the Lipha Group (1978–1982). 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. He previously served as senior manager, new technology and product innovation at Novartis Consumer Health. 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. Dr Spencer holds a BSc in chemistry with first-class honours and a PhD in chemistry from the University of Aberdeen.
Chief Scientific Officer: Doug Hubatsch	**Incoming CEO (with effect from 1 June 2022): Andreas Segerros**
Prior to joining Nicox in December 2021, Mr Hubatsch was global medical head of Ocular Surface Disease and Digital Medicines within Global Medical Affairs at Novartis Pharmaceuticals. He has more than 25 years' experience in discovery research, development and medical affairs at Novartis, Alcon, Roche and AstraZeneca. He has been involved in the launch of more than 10 products through his career including Simbrinza (Alcon) for glaucoma and Xiidra (Novartis) for dry eye disease.	Andreas Segerros has spent most of his career in global pharma, with executive positions (R&D, marketing and business development) in the US, Europe and Japan, at Pharmacia, Pharmacia & Upjohn and Ferring, with the focus on speciality pharma, particularly ophthalmology. As global head of ophthalmology at Pharmacia, he oversaw the launch of Xalatan (latanoprost), which became a billion-dollar ophthalmic drug. His venture capital experience comes from his role as partner at the Scandinavian group Sunstone Capital, and he co-founded Eir Ventures. Andreas holds an MSc in Organic Chemistry from The Royal Institute of Technology in Stockholm, Sweden, and an MBA in International Financing from The University of Uppsala, Sweden.
Vice president, Finance: Sandrine Gestin	**General Counsel and Head of Legal: Emmanuelle Pierry**
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. 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.	Ms Pierry joined Nicox in 2002. Previously, she was a member of the Paris Bar (Avocat au Barreau de Paris) for 10 years and practised business counselling and litigation at international law firms. Ms Pierry holds the French Bar diploma (Certificat d'Aptitude à la Profession d'Avocat) and degrees in specialised studies in business law from Paris-Sorbonne University (DESS—Master 2 Paris I) and the Business Law Institute of Paris (Panthéon Assas University).

Principal shareholders	(%)
HBM Partners	7.0
Armistice Capital	6.0
Michele Garufi	1.3
Banque Publique d'Investissement	0.9

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia