EDISON

Pharnext

Initiation of coverage

New efficacy and new indications from old drugs

Pharma & biotech

Pharnext is a pharmaceutical company that develops new therapies leveraging pleiotropism, which is the idea that drug combinations can have effects outside of their individual canonical mechanisms. This provides access to novel methods of treating disease, which the company has used to develop its lead drug PXT3003 for Charcot-Marie-Tooth disease type 1A (CMT1A, entering Phase III in Q121). We initiate with a valuation of €239.5m or €12.48/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/18	6.8	(21.7)	(1.83)	0.00	N/A	N/A
12/19	3.6	(23.4)	(1.61)	0.00	N/A	N/A
12/20e	2.9	(18.1)	(0.98)	0.00	N/A	N/A
12/21e	1.8	(26.4)	(1.38)	0.00	N/A	N/A

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

Pleiotropism: Drug effects only seen in combination

The company's Pleotherapy platform is an in silico and in vitro discovery and screening protocol that starts by examining a large array of drugs for how they may affect the transcriptional profile of the disease of interest. A series of drug combinations is then screened in vitro for synergistic effects. The medications developed this way, such as PXT3003 and PXT864, have activities that none of the constituent drugs have, which opens the potential to treat diseases that are otherwise unaddressed, with molecules that have already been individually vetted.

Phase III interrupted; still manages to show efficacy

PXT3003 was previously studied in a Phase III clinical trial, which unfortunately had to be interrupted for reasons unrelated to the drug's effect (a manufacturing issue with no safety impact) and prevented it from being applicable as a pivotal study. However, the trial still managed to demonstrate a statistically significant improvement in the primary endpoint (p=0.04) even under the strictest intent-to-treat analysis (where all the discontinuations were imputed as placebo). This improved to p=0.008 when just including completers and drug-related dropouts.

New study for 2021

The company is planning on starting a new pivotal Phase III study of PXT3003 in Q121. It is currently submitting a special protocol assessment (SPA) to the FDA (planned for Q320), which will pre-establish how the Phase III will be evaluated. The drug also has both an orphan designation and fast track status.

Valuation: €239.5m or €12.48 per share

We are initiating at €239.5m or €12.48 per share based on a risk adjusted NPV analysis. We only value PXT3003 and we assume it will have an above average probability of success of 60% based on the previous Phase III results. The company ended 2019 with €1.3m net cash and we forecast it will need additional capital in 2020 (an estimated €30m) with €95m in total before 2024.

29 September 2020

Price	**€3.07**
Market cap	**€59m**
	€0.85/US$
Net cash (€m) at 31 December 2019	1.26
Shares in issue	19.2m
Free float	41%
Code	ALPHA
Primary exchange	Euronext Paris
Secondary exchange	OTC Pink

Share price performance

%	1m	3m	12m
Abs	(16.6)	(9.7)	(39.3)
Rel (local)	(14.0)	(9.2)	(29.7)
52-week high/low	€6.46		€2.75

Business description

Pharnext is developing new therapies for neurological disorders using its proprietary Pleotherapy platform that unearths new therapeutic effects from drug combinations. Its lead program is PXT3003 for Charcot-Marie-Tooth disease, which is entering Phase III. It also has PXT864 for Alzheimer's disease, which has completed Phase IIa.

Next events

SPA submission to FDA	Q320
Phase III initiation	Q121

Analysts

Nathaniel Calloway +1 646 653 7036

Wiktoria O'Hare +1 646 653 7028

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: Finding hidden functions in old drugs

Pharnext is a French pharmaceutical company that uses its proprietary Pleotherapy platform to design novel therapies using drug combinations. The platform is based on the concept that a drug combination can have effects that none of the constituent dugs have. The company has developed an in silico and in vitro system for systematically examining these relationships. Pharnext used the platform to design PXT3003, which is in Phase III testing for Charcot-Marie-Tooth type 1A (CMT1A), a rare peripheral demyelinating neuropathy. The program is slated to re-enter the clinic for a second Phase III in Q121. Additionally, Pharnext has used the platform to design the Phase II drug PXT864, for Alzheimer's, which the company is looking to partner for further development.

Valuation: Initiated at €239.5m or €12.48 per share

We arrive at an initial valuation of €239.5m or €12.48 per share based on a risk adjusted NPV analysis of PXT3003. We forecast that the drug will have $626m peak sales. We have a 60% probability of success for the program based on the results from the previous Phase III study. We are not valuing PXT864 at this time because the company is not advancing its clinical development, although it is seeking partners to support the program.

Financials: Spending to increase in 2021 with new study

The company reported a loss of €23.3m for 2019, driven by R&D spending of €15.2m. We forecast less R&D spending in 2020 (€9.3m) because the company is not currently engaged in any clinical studies, but we expect R&D spending to rise again in 2021 (€16.6m) as the company re-enters the clinic with PXT3003. The company ended the year with €1.3m in net cash, and subsequently raised €7.7m gross in a private placement, but we forecast the company will need additional capital in 2020. We expect the company to need €95m to reach profitability in 2024 (recorded as illustrative debt: €30m in H220, €30m in 2021, €35m in 2022). We only include the costs associated with developing PXT3003 at this time as the company intends to out-license PXT864.

Sensitivities: Unique to the pleotherapy approach

The company faces a series of risks, many of which are particular to its unique platform. The drugs the company is currently investigating in combination are all widely available generics with very well understood safety and tolerability profiles. However, these molecules are being used in roles wholly outside of their approved indications and new safety considerations may emerge, not unlike the novel effects being investigated. There is relatively little information to evaluate if the Pleotherapy platform can reproducibly generate useful drug combinations, but we are very encouraged by the activity seen in PXT3003 clinical studies to date. The positive result from the previous Phase III clinical study, although not applicable as pivotal data for regulatory purposes, has de-risked the upcoming study, in our view. The clinical impact may be perceived as small, but has a meaningful effect given there are no medications approved (or routinely used off label) to treat CMT1A. There is uncertainty regarding how it will be seen by regulatory agencies, but the company is seeking a special protocol assessment from the FDA, which may provide insight. If approved the drug may face competition from new market entrants or from the generic versions of the drugs of which they are composed. Finally, the company faces financing risk because it needs significant additional capital to run its planned Phase III study of PXT3003, and share issuances over the next few years could potentially be greater than the current shares outstanding (if there is no sharp increase in the market valuation). We expect the company to address its funding needs through a range of methods including potentially licensing the product or its geographic marketing rights.

Company description: New uses for old drugs

Pharnext is a French specialty pharmaceutical company founded in 2007 that went public in 2016. The company was founded with a focus on developing therapies for neurodegenerative disorders, and it has developed a platform for identifying drug combinations that show novel functionality. This platform is based upon the concept of pleiotropism, the idea that a specific gene, gene product or drug can have phenotypic impacts outside of its canonical function (more details below). The company's Pleotherapy platform parses the effect of drugs on genetic and biochemical networks, and is able to predict the pleiotropic effects of certain drugs and drug combinations. The effect of these combinations may have little resemblance to the canonical functions of the individual drugs.

Pharnext has used this platform to develop two drug candidates that are in clinical testing. It is focused on the development of drugs for neurodegenerative disorders. The lead program is PXT3003, a combination of three drugs, for the treatment of CMT1A, an orphan chronic peripheral neuropathy. The company is planning to initiate a second Phase III study for the drug in Q121.

The company has also developed PXT864, a combination of two drugs, which is being investigated for Alzheimer's disease (Phase IIb ready), as well as potentially other degenerative disorders of the central nervous system (amyotrophic lateral sclerosis, ALS, and Parkinson's).

Exhibit 1: Pharnext pipeline

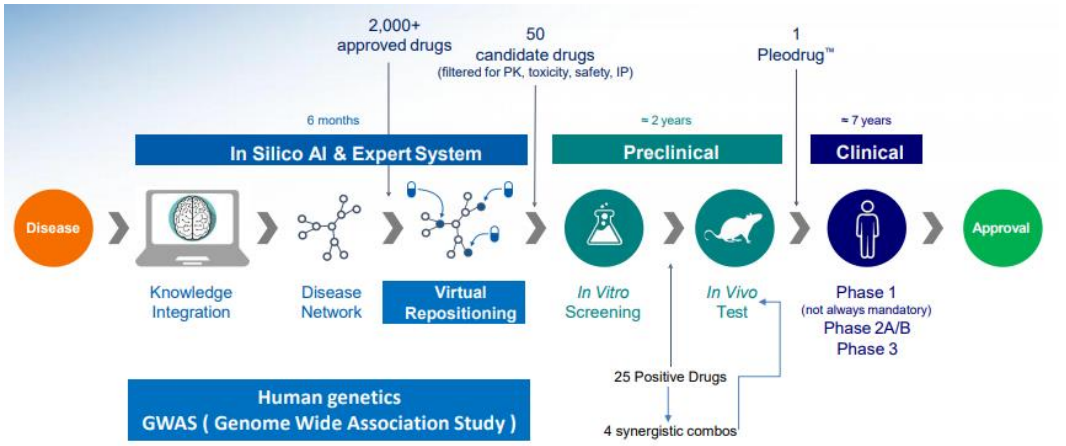
Product	Drug combination	Indication	Stage	Notes
PXT3003	naltrexone, baclofen, sorbitol	CMT1A	2nd Phase III ready	First Phase III complicated by CMC issue
PXT864	acamprosate, baclofen	Alzheimer's	Phase IIb ready	Phase IIa completed but missed endpoint, seeking partner for further development
		ALS	Planned	
		Parkinson's	Planned	

Source: Pharnext

The Pleotherapy platform

The central premise surrounding Pharnext's development activities and its core value driver as a company is its ability to leverage pleiotropism to develop new combination drug therapies. The company has developed a proprietary platform (the Pleotherapy platform) that combines in silico modelling of biochemical and genetic networks with a preclinical screening protocol to identify synergistic combinations of drugs.

Exhibit 2: The Pleotherapy platform



Source: Pharnext

Pleiotropy was coined as a term to encapsulate the idea of unintended consequences. The central premise is that perturbations in a biochemical network can have phenotypic impacts outside of the function of the specific node of the network that was perturbed. These perturbations can be driven by mutations to the genes that specify that network, drugs targeting individual proteins in that network, or other effects. Many genetic diseases are examples of pleiotropy. For instance in the inherited enzyme deficiency phenylketonuria, patients lack the ability to convert the amino acid phenylalanine into another amino acid tyrosine. The downstream effect of this is that phenylalanine builds up in these patients to toxic levels and can cause damage in the central nervous system and intellectual disabilities. By perturbing these genetic and biochemical networks, drugs similarly can have pleiotropic effects, many of which are unexplored, as well as others that are characterized as 'adverse effects' if they are detrimental.

It is perhaps obvious from these examples that the idea of pleiotropy is loosely defined, and which effects of a perturbation are considered central and which ones are considered secondary is a matter of perspective. However, it is undeniable that there are a wide range of effects from any biochemical perturbation that go largely uncharacterized. For instance, a drug may cause changes to gene expression patterns, but because there are no detrimental effects of these changes they may go unnoticed or uncharacterized. These drugs may therefore have a use outside of their initial design if these other pathways are implicated in a disease. The goal of Pharnext and its Pleotherapy platform is to characterize these otherwise unnoticed effects and find new uses for these existing drugs.

Many of the pleiotropic effects of drugs may go unnoticed because they have either no or very little phenotypic impact. Biochemical networks have evolved to be resilient and in many cases resist perturbation. However, by targeting multiple axes of a network, these effects can become more pronounced. This is similar to the idea of synthetic lethality, where one drug or perturbation can have no effect, but the effect becomes pronounced when combined with a different drug or other perturbation. The company's Pleotherapy platform both predicts these interactions in silico and then screens for beneficial synergistic activity between drugs in vitro and in vivo. This synergy is demonstrated in the company's preclinical data, such as Exhibit 5 below.

PXT3003

The company's lead program, PXT3003, is being developed as a treatment for the orphan disease CMT1A. CMT is a group of genetic disorders characterized by progressive peripheral neuropathy in motor and sensory neurons. It typically presents as gait difficulties in early childhood to early adulthood and as it progresses, patients can develop muscular deformities and wasting in the feet, legs and hands, resulting in progressive disability. The disease is not considered life threatening, and historically patients have been considered to have a normal lifespan, although a recent report from Denmark found a 36% higher risk of death among affected individuals.[1] The causes of the neuropathy vary depending on the disease subtype, but most forms are caused by issues in the myelination of peripheral axons. Myelination is the 'insulation' of nerve cells, which allows for signals to progress quickly down an axon and is mediated by Schwann cells in the peripheral nervous system. The 1A subtype of the disease (CMT1A) is caused by duplication of the PMP22 gene, leading to overexpression of the PMP22 protein. Too much of this protein in the Schwann cells disrupts the formation of the myelin sheath, leading to loss of nerve function. When developing PXT3003, the Pleotherapy platform was used to identify a drug combination that would significantly reduce the overexpression of PMP22. CMT is the most common inherited peripheral neuropathy

[1] Vaeth S, et al. (2017) Charcot-Marie-Tooth disease in Denmark: a nationwide register-based study of mortality, prevalence and incidence. *BMJ Open* 7, e018048.

and one of the most common inherited neurological disorders, affecting approximately 126,000 individuals in the US.[2]

CMT1A is well established as the most common genetic subtype of the disease, but there has been some variability in the rates reported in different studies, but with most reporting rates in the range of 40-50% of all CMT patients. One complicating factor is that there is a large population of patients diagnosed with CMT who lack a definitive genetic diagnosis. For instance in one representative study it was found that CMT1A was present in 61.6% of patients with genetically defined disease, but this number was 43.0% when the genetically uncertain patients confirmed to have CMT were included.[3] These patients may lack a genetic diagnosis because either genetic testing was performed but was inconclusive or because they were not tested. Ultimately, more patients with CMT1A may be discovered with better diagnostic screening. A survey conducted by the company in collaboration with digital healthcare research company Vitaccess found 55.4% of CMT respondents had CMT1A,[4] (although survey data should not be taken as definitive demographic data).

There are not currently any approved medications to treat CMT or alter its course. Pharmaceutical intervention is typically limited to palliative pain care and the only method of managing disease progression is physical therapy to reduce the formation of contractures. There are a small number of drugs currently in development, of which PXT3003 is the most advanced (Exhibit 3). The next most advanced program is MD1003 from MedDay, which is a formulation of purified biotin that recently failed in Phase III as a treatment for multiple sclerosis. The status of this program and the company is currently uncertain. One program to keep a close eye on is the gene therapy scAAV1.tMCK-NTF3. The therapy is being studied in a nine-patient proof-of-concept Phase I/II being performed by Nationwide Children's Hospital, and Sarepta Therapeutics currently has an option to license the asset. The therapy introduces a gene for the nerve growth factor neurotrophin 3 to encourage nerve proliferation and myelination. If it is successful it would be the only potentially curative treatment in development, but right now very little information is available.

Exhibit 3: CMT1A clinical programs

Drug	Company	Stage	CMT type	Drug description	Notes
PXT3003	Pharnext	Phase III	1A	Naltrexone, baclofen and sorbitol	Most advanced CMT program
MD1003	MedDay	Phase II	1	Purified biotin	Recently failed Phase III in MS, status uncertain
Sephin1	InFlectis	Phase I	1A, 1B	Targets stress response	Phase I completed Jan 2020
MT-002/MP-188	Myotherix	Phase I	1A	P2X7 antagonist	Licensed from AstraZeneca, also being tested for DMD, cannot confirm if the trial is active
scAAV1.tMCK-NTF3	Sarepta	Phase I/IIa IST	1A	Neurotrophin 3 gene therapy	Sponsored by Nationwide Children's Hospital, Sarepta has option to license
$GABA_B$ PAM	Addex	Preclinical	1A	$GABA_B$ modulator	Candidate selection to be done by end of 2020

Source: Evaluate Pharma, CMT Research Foundation. Note: MS: multiple sclerosis; DMD: Duchene's muscular dystrophy.

The design of PXT3003

PXT3003 is a combination of three active molecules, naltrexone, baclofen, sorbitol, which were identified using the Pleotherapy platform screening protocol. In a true example in pleiotropism, canonically none of these molecules target the peripheral demyelination characteristic of CMT1A,

[2] NIH. Charcot-Marie-Tooth Disease Fact Sheet.

[3] Fridman V, et al. (2015) CMT subtypes and disease burden in patients enrolled in the Inherited Neuropathies Consortium natural history study: a cross-sectional analysis. *J Neuol Neurosurg Psychiatry* 86, 873-878.

[4] Zeissman T, et al. (2019) Diversity in the Charcot–Marie–Tooth disease population in the United Kingdom and United States: insights from a digital real-world observational study. American Association of Neuromuscular & Electrodiagnostic Medicine 2019 meeting.

but each has been separately implicated as having an effect on the peripheral nervous system. However, we caution against drawing too many conclusions from the activities of these individual drugs because it is their combined synergistic action that is being tested in PXT3003.

Exhibit 4: PXT3003 active components

Drug	Class	Medical use	Link to myelination
Naltrexone	opiate antagonist	Treatment of opiate use disorder	Off label use for symptomatic relief in MS patients
Baclofen	GABA analogue	Treatment for spasticity	May inhibit proliferation of Schwann cells, or contrarily induce proliferation of oligodendrocytes
Sorbitol	sugar alcohol	Laxative*	May inhibit myelination in diabetic neuropathy

Source: Various, see footnotes. Note: *Laxative mechanism of action unrelated to mechanism in PXT3003.

Naltrexone is an opiate antagonist, meaning it binds to and blocks the activation of μ-opioid receptors. The primary use of this in practice is for the treatment of opiate use disorder, because it prevents patients from getting high. It has also been approved for weight loss in combination with bupropion (Contrave, Currax Pharmaceuticals). Low doses of the drug have been used off label for the treatment of the symptoms of multiple sclerosis, another demyelination disorder, and it appears to show some symptomatic benefit in clinical trials.[5]

Baclofen is an analogue of the neurotransmitter gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the nervous system. Its action is predominantly on the peripheral nervous system, where it inhibits the activation of skeletal muscle and is used as an antispasmodic. The impact of baclofen on myelination has previously been explored but has produced some contradictory results of either inhibiting or enhancing myelination, depending on the context.[6,7]

Of the three active molecules included in PXT3003, sorbitol is the most curious. It is a sugar alcohol most commonly used as a sugar substitute sweetener. Its primary medical use is as a laxative, but this is likely unrelated to its activity in PXT3003. However, it has been studied in the context of diabetic neuropathy, where it appears to induce Schwann cell de-differentiation.[8]

As part of the Pleotherapy platform, these drugs have been screened both alone and in combination for a range of biochemical markers of clinical activity. It was confirmed via tissue culture that this combination was effective at reducing the expression of PMP22[9] and the combination (and none of the individual drugs or two-way combinations) increased myelination in cultured neurons by over 20% (Exhibit 5, left). Finally, when the combination was tested in animal models of CMT1A, it was shown to improve grip strength (Exhibit 5, right).

5 Gironi M, et al. (2005) A pilot trial of low-dose naltrexone in primary progressive multiple sclerosis. *Multiple Sclerosis J* 14, 1076-1083.

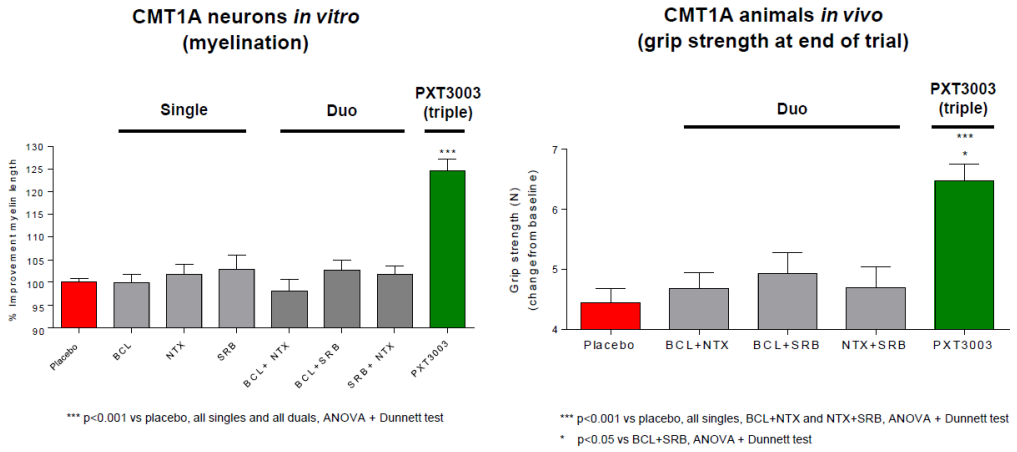
6 Magnaghi V, et al. (2004) GABAB receptors in Schwann cells influence proliferation and myelin protein expression. *Euro J Neurosci* 19, 2641-2649.

7 Serrano-Regal MP, et al. (2020) Oligodendrocyte Differentiation and Myelination Is Potentiated via GABAB Receptor Activation. *Neurosci* 439, 163-180.

8 Hao W, et al. (2015) Hyperglycemia Promotes Schwann Cell De-differentiation and De-myelination via Sorbitol Accumulation and Igf1 Protein Down-regulation. *J Biol Chem* 290, 17106-17115.

9 Chumakov I, et al. (2014) Polytherapy with a combination of three repurposed drugs (PXT3003) down-regulates Pmp22 over-expression and improves myelination, axonal and functional parameters in models of CMT1A neuropathy. *Orphanet J Rare Dis* 9, 201.

Exhibit 5: PXT3003 improves myelination in vitro and animal grip strength



Source: Pharnext. Note: BCL = Baclofen, NTX = Naltrexone, SRB = Sorbitol.

PXT3003 is protected by patents until 2031 in the US (US8992891B2) and 2028 in Europe (EP2211846B1). However, we expect the drug to be protected primarily through orphan drug exclusivity. It has received orphan designation in both the US and Europe that would provide seven and 10 years exclusivity respectively after approval. We therefore expect the company to have exclusivity on the product until 2031 in the US and 2034 in Europe.

Phase II: Signs of improvement seen

PXT3003 was initially studied in humans in a randomized Phase II study looking at three dosing levels compared to placebo.[10][11] The clinical trial enrolled 80 patients with mild to moderate CMT1A and followed them for a year. Patient improvement was gauged using the Charcot-Marie-Tooth Neuropathy Score (CMTNS) and the Overall Neuropathy Limitations Scale (ONLS) as the primary endpoints, as well as a range of other functional metrics. The CMTNS is a 36-point symptomatic scoring assessing both motor and sensory disability, whereas the ONLS is a 12-point functional assessment of the ability to perform tasks with the arms and legs (Exhibit 6).

Exhibit 6: CMT rating scales

CMTNS	ONLS	
Symptomatic assessment	**Body part**	**Functional assessment**
Sensory symptoms	Arms	Wash hair
Motor symptoms (legs)		Turn key
Motor symptoms (arms)		Use Knife
Pinprick sensibility		Undo buttons and zippers
Vibration detection		Dress upper body
Strength (legs)	Legs	Climb stairs
Strength (arms)		Walking difficulty
Ulnar CMAP		Gait abnormality
Ulnar SAP		Need for walking aid
		Ability to walk one meter
		Purposeful leg movement
		Need for leg braces

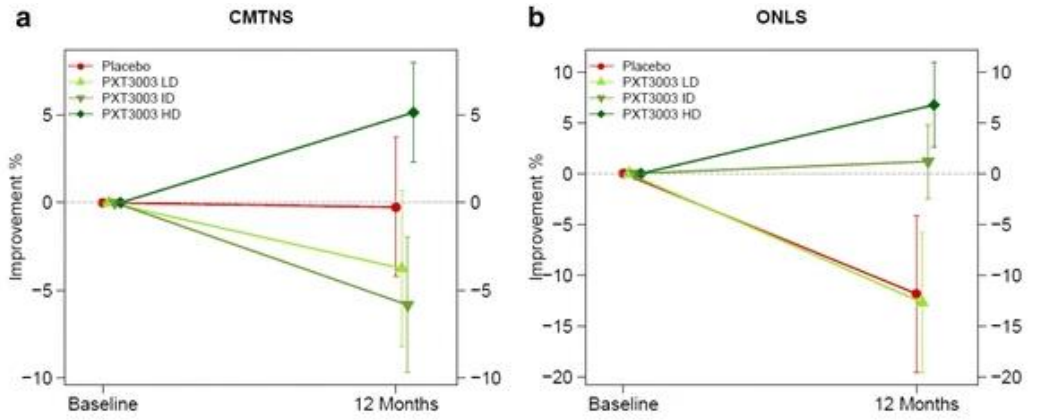
Source: Murphy SM (2011) *J Peripher Nerv Syst* 16, 191–198.Graham RC (2006) *J Neurol Neurosurg Psychiatry* 77, 973–976. Note: CMAP: compound muscle action potential; SAP: sensory action potential.

[10] Attarian S, et al. (2014) An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A. *Orphanet J Rare Dis* 9, 199.

[11] Attarian S, et al. (2016) Errata to: An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A. *Orphanet J Rare Dis* 11, 92.

The study showed statistically significant improvement in ONLS at the high dose (0.7mg naltrexone, 6mg baclofen, 210mg sorbitol) versus placebo. Patients on the high dose improved an average of 6.8% on the ONLS scale, compared to placebo patients worsening by 11.8% (p=0.043). Additionally, statistically significant correlations were seen in measures of nerve conductance to dosing levels. The study did not reach statistical significance for CMTNS in the per-protocol analysis but it did when the high dose was compared to the combined cohort of placebo, low and intermediate doses (p=0.042), although caution should always be exercised when interpreting post hoc analyses. The CMTNS has been a subject of criticism due to ceiling and floor effects as well as the fact that scores naturally worsen with age (in the absence of CMT) and a second version of the scale has been developed since the trial was performed.

Exhibit 7: PXT3003 Phase II: Improvement in CMTNS and ONLS



Source: Attarian S et al. (2016)[11]

These results are encouraging for a number of reasons. The measurements of improved nerve conduction suggest the therapy is having the intended effect of improving myelination (although this is impossible to confirm without biopsy) and the improvement in ONLS shows a clear dose-response relationship. We are not particularly worried that the CMTNS results did not reach significance due to the perceived limitations to this scale. ONLS is also a functional assessment, which is generally preferred when evaluating drugs for approval and we assume this will be the approvable endpoint (based on the FDA's engagement with the company in following studies). Moreover, although the p values in this study were close to the threshold for significance (0.05), this is also based on a small number of patients and typically functional assessments for movement disorders show a high degree of variability.

The first Phase III: Ended prematurely

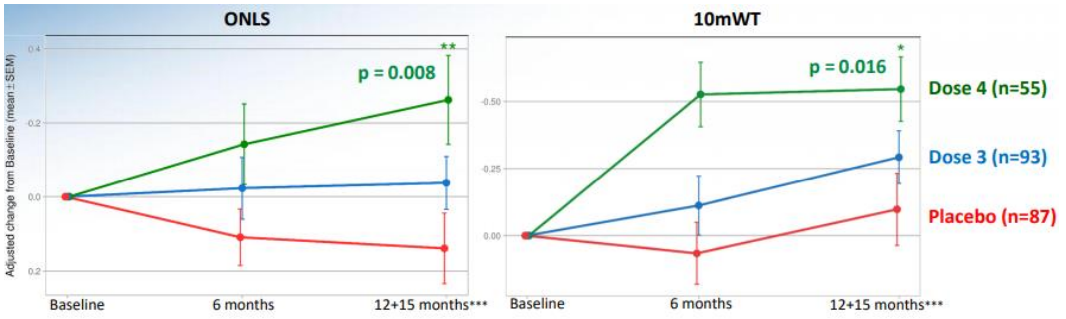
Following completion of the Phase II, the company initiated a pivotal global Phase III study (PLEO-CMT) enrolling 323 mild to moderate CMT1A patients. This study continued to explore dosing and included two drug cohorts: the low dose, which was the high dose from the Phase II study (0.7mg, 6mg, 210mg) and a high dose at twice the concentration (1.4mg, 12mg, 420mg). The primary endpoint was improvement in ONLS after 12–15 months.

In an unfortunate turn of events, the high dose arm (n=113) had to be halted due to manufacturing issues. The drug (in both dosing arms) was provided as an oral solution and some batches of high dose bottles showed formation of precipitate in the solution. This was later demonstrated to be a reaction between the baclofen and a preservative (paraben) and unlikely to be a source of risk, but regardless the halt prevented further dosing with the high dose arm, resulting in 53 patients discontinuing the trial. Additionally, this also caused interruptions in the dosing of the low dose and placebo arms as the protocol was amended. This rendered the trial non-viable to serve as a pivotal

study for approval, but the results from the patients that were able to complete the study before the high dose arm was halted can be analyzed for efficacy (with some statistical caveats).

Despite major disruption to the study, the company reported in October 2018 that the patients on the high dose arm who were unaffected by the halt showed a placebo-adjusted improvement of 0.37 points on the ONLS scale vs placebo (p=0.008; Exhibit 8, left). Additionally, a half-second improvement on the 10-meter walk test was observed (p=0.016) in this population (Exhibit 8, right). These data used a modified (but prespecified) statistical analysis plan that included only study completers and those who dropped out due to treatment related adverse events. However, the company was also able to achieve a p=0.04 of improvement in ONLS vs placebo in the original per-protocol intent-to-treat (ITT) analysis, which in this case was very strictly defined as imputing all dropouts at the same values as placebo. Given that 53 of the 113 patients on the study dropped out because of the halt (as well as 11 others due to other reasons), it is a testament to the statistical strength of the treatment effect that it was still able to achieve this p-value. Further details from the ITT analysis such as effect size have not been reported as these may not be meaningful numbers (because of all of the imputed dropouts).

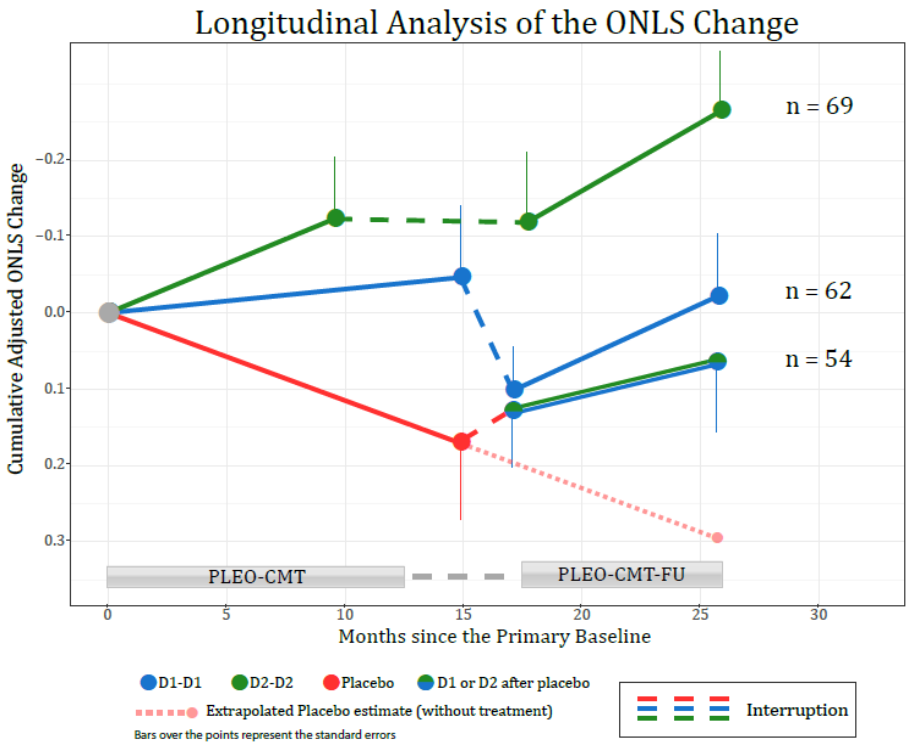
Exhibit 8: PXT3003 Phase III results using modified SAP



Source: Pharnext. Note: Dose 3=0.7mg, 6mg, 210mg; Dose 4=1.4mg, 12mg, 420mg; *, **=Dose 4 vs Placebo, ANCOVA with multiple imputation (Missing data implemented by multiple imputations following the placebo trend); ***=Average of 12 and 15 Month, or 12 Month if 15 Month is missing

The PLEO-CMT study was followed by a nine-month open label extension study, in which all patients received treatment (patients from the placebo arm were selected to receive either a high or low dose), and Pharnext presented the results from the extension in January 2020. The halt in the Phase III study led to some variability among patients in the extension as well, as many had disruptions to dosing as the manufacturing issue was addressed. However, interesting results were observed in the 187 patients fit for evaluation, which showed improvements in ONLS across all three original trial cohorts (Exhibit 9). When these patients were pooled in a post-hoc analysis, the trend showed a statistically significant improvement compared to the prior placebo arm of the study (0.30 points, p=0.001).

Exhibit 9: PX13003 open-label extension



Source: Pharnext

Although it is disappointing the PLEO-CMT study had to be interrupted and cannot be used as a pivotal study, the data gathered are highly suggestive of PXT3003 having a clinical impact. However, it is worth discussing if the magnitude of this impact is clinically meaningful. All of the improvements seen in OLNS are on the scale of a fraction of a point for a metric that ranges from 0 to 12. The company has stated that a mean improvement of 0.3 on the scale represents a clinically meaningful outcome, based on feedback from key opinion leaders. However, it is difficult to gauge what regulators will consider a meaningful result for this particular indication because no product has been approved for this indication yet. ONLS has not been used to support an approval before in the US. However, Octagam (intravenous immunoglobulin, Pfizer) has been approved in Europe for chronic inflammatory demyelinating polyneuropathy (CIDP) based on the finding that 41.7% of patients had a 1 point improvement or better from baseline, which corresponds to an average effect of 0.42.[12] We also note the improvements in ONLS seen in the clinical studies of PXT3003 have been similar in scale to the deterioration seen in the placebo group over the same year-long period, meaning that even if the effect sizes appear small, it is on the same scale as the deterioration from CMT that occurs over the course of a year or more. If this improvement can be maintained or if further deterioration can be prevented over the course of multiple years, this would be a major improvement in quality of life, and this trend appears to be supported in the extension study data.

Safety

Over the course of the clinical trials, PXT3003 has shown a safe and tolerable adverse event profile. The doses of the individual active molecules in the therapy are lower than those used for their primary indications (eg naltrexone is approved in 50mg tablets, Phase III high dose was 1.4mg), so the relatively benign profile is not surprising. The most detailed safety data have been released with the Phase II data, which showed lower rates of treatment emergent adverse events

[12] Belmokhtar C, et al. (2019) Efficacy and Safety of Octagam in Patients With Chronic Inflammatory Demyelinating Polyneuropathy. *Neurol Ther* 8, 69-78.

(TEAE) in the treatment arms than in placebo. Pharnext confirmed that a similar profile was seen in Phase III and that TEAEs were similar between drug and placebo (and majority mild), although further data were not provided.

Direction forward

The next logical step for the company is to run another Phase III clinical trial to serve as a pivotal study for approval. Although it was disappointing the high dose arm had to be interrupted in PLEO-CMT, the data are supportive of a drug effect. Pharnext is finalizing the protocol for a follow-up pivotal Phase III study with the FDA and it plans on initiating enrolment in early Q121. The company provided an update in June 2020 on discussions it had with the FDA regarding the planned study. The agency agreed that ONLS could serve as the primary endpoint. The study will be largely similar to the prior PLEO-CMT study, but with a single active drug arm (at the high dose). Several relatively simple changes have been made to the plan to avoid the manufacturing issues that were previously encountered. Additionally, the company has noted that it will be seeking a SPA from the FDA. An SPA is a clinical plan that the FDA agrees to before a trial is conducted and lays out the specific criteria for approval beforehand. This would remove a large degree of the uncertainty in the regulatory process. Moreover, even if the FDA does not approve the SPA, feedback from the agency from the process can provide substantial insight into what it is looking for. The company intends to have its plan for the SPA submitted to the FDA before the end of Q320. Additionally, the drug has a fast-track designation from the FDA, which increases the amount of interaction with the agency and allows the company to submit its NDA on a rolling basis as each section is completed (and potentially receive feedback before the submission is complete). This should both reduce upcoming surprises from the agency and generally speed the regulatory process. Based on our assumptions, we forecast that the study will take between two and three years to complete.

PXT864

Pharnext's second asset in development, PXT864, which the company is primarily focusing on developing the asset for use in mild Alzheimer's disease and later intends to move into Parkinson's disease and ALS. The drug is protected by patents until 2032 (US9636316B2), which we expect to be extended to 2037.

Alzheimer's disease is a progressive neurodegenerative disease generally characterized by the impairment of cognition, along with behavioral changes that can eventually interfere with an individual's ability to complete simple tasks associated with daily life. While Alzheimer's disease can affect people of all ages, it predominately presents in individuals over the age of 65 and the doubling of prevalence of the disease occurs every five years over the age of 50.[13] Alzheimer's disease has become the most prevalent neurodegenerative disorder in the world and is the most common cause of dementia. In 2020, an estimated 5.8 million people aged 65 years and older are suffering from Alzheimer's disease in the US, while 8.8 million individuals were affected in Europe (in 2018).[14,15] The associated economic burden of Alzheimer's disease worldwide was an estimated $1trn in 2018 and is expected to double by 2030.[16] The need for adequate treatment is becoming

[13] GBD 2016 Dementia Collaborators (2016) Global, Regional, and National Burden of Alzheimer's Disease and Other Dementias, 1990-2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *Lancet Neurology* 18, 88-106.

[14] Alzheimer's Association (2019) Alzheimer's Disease Facts and Figures. *Alzheimer's Dement* 15, 321-387.

[15] Alzheimer Europe (2019) *Dementia in Europe Yearbook 2019*.

[16] Cummings J, et al. (2020) Alzheimer's Disease Drug Development Pipeline: 2020. *Alzheimer's Dement* 6, e12050.

more dire as projections of prevalence and the subsequent economic and social burden are expected to be quite significant.

Alzheimer's disease has been an extremely difficult indication for the development of new drugs. This is due in a large part because the exact pathophysiology of the disease is not completely understood. There are a number of different competing theories of its pathogenesis (Exhibit 10), the most prominent theory in recent years has been the amyloid hypothesis, where the toxic accumulation of β-amyloid (Aβ) peptides, or plaques, in the extracellular surface of neurons leads to cell death. Nearly all drugs targeting this mechanism have failed in the clinic and there remains a single prominent Aβ-targeting program in the clinic, aducanumab (Biogen), which has a BLA filed in July 2020 for approval following mixed Phase III results. Little traction has been made targeting other mechanisms either. The only drugs that have been successfully approved for Alzheimer's disease are the cholinesterase inhibitors donepezil, galantamine and rivastigmine, and the NMDA antagonist memantine. These drugs belong to the so-called neurotransmitter treatment axis and although they can improve cognition, they do not modify the course of the disease. Despite the difficulties in getting new drugs approved for this indication, there remains a very large development effort with over 120 drugs in development.[16]

Exhibit 10: Selected AD mechanisms and treatment strategies

Treatment axis	Drug mechanism	Treatment strategy
Neurotransmitters	Enhancement of acetylcholine response	Cholinesterase inhibitors, α7nAChR agonists
	Inhibition of glutamate cytotoxicity	NMDA receptor antagonists
Amyloid-β	Inhibition of Aβ production	β-secretase-1 (BACE1) inhibitors, GSM
	Inhibition of Aβ aggregation	Metal protein attenuating compounds
	Aβ clearance	Anti-Aβ antibodies
Tau	Inhibition of tau phosphorylation	Glycogen synthase kinase (GSK)-3β inhibitors
	Enhancement of microtubule stabilization	Microtubule stabilizers
	Inhibition of tau aggregates	Tau aggregation inhibitors
Inflammation	Inhibition of neuroinflammation	NSAIDs, Microglial activation inhibitors

Source: Edison Investment Research, Lao et al. 2018 [17]

A new approach

PXT864 was developed to target the excitatory/inhibitory balance in the Alzheimer's disease brain using the Pleotherapy platform. It is a combination of acamprosate and baclofen, which respectively inhibit the excitatory (glutaminergic) nervous system and potentiate the inhibitory (GABAergic) nervous system. The hyperactivation of the excitatory nervous system has been proposed as a potential cause of cognitive dysfunction and progressive degeneration.[18] Acamprosate is an anti-craving agent commonly used in alcohol addiction and is thought to affect the glutamatergic system thereby influencing the excitatory/inhibitory imbalance caused by alcoholism. Baclofen, as described above, is used to treat spasticity and has been a commonly used therapeutic for that indication for several decades. Results from the Chumakov pre-clinical study implied several promising characteristics of the combination therapy including protective effects against Aβ toxicity and oxidative stress, reduction of Tau phosphorylation and alleviation of cognitive deficits. In an in vitro model using neuronal cell cultures, the drug provided about 50% neuronal protection from cytotoxicity induced by Aβ oligomers treatment. A mouse model was used to assess the effects of the drug following injection of Aβ oligomers to induce cognitive impairment similar to Alzheimer's disease and working memory was significantly preserved in these animals.

[17] Lao K, et al. (2018) Drug Development for Alzheimer's Disease: Review. *Journal of Drug Targeting* 27, 164-173.

[18] Chumakov I, et al. (2015) Combining Two Repurposed Drugs as a Promising Approach for Alzheimer's Disease Therapy. *Scientific Reports* 5, 7608.

Clinical program

A Phase I trial with 24 healthy volunteers was completed and Pharnext reported a positive safety and tolerability profile. Following these results, an additional Phase I trial was conducted in 20 healthy volunteers and the company stated that PXT864 demonstrated initial efficacy in a scopolamine-induced dementia model. Pharnext then moved to an exploratory open-label Phase II PLEODIAL trial in 2013 to assess the safety, tolerability and preliminary efficacy of PXT864. The trial tested three doses of PXT864 over a 36-week period in 45 patients with mild Alzheimer's disease who had not been previously treated with any anti-dementia medications. Patients were evaluated for efficacy as a change from baseline scores using the 11 item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-11). The study had two portions. In the first, patients received the drug for four weeks, placebo for four weeks and finally four more weeks of drug. The company has stated that patients improved when they were on the active drug during this section of the study, but to our knowledge, no detailed data on this portion of the study have been released. The second portion of the study was an extension that kept patients on the drug for an additional 24 weeks (36 weeks total, 32 on the drug). The study was completed in 2015, and the company reported that '[ADAS-Cog-11] appeared to decline less in the pooled PXT864 dose 1 and 2 groups as compared to historical placebo for mild to moderate patients with AD at week 36,' which leads us to assume it did not show a statistical improvement in this endpoint. The company has separately presented the results of the study evaluated with a different cognitive disability scale, Clinical Dementia Rating - Sum of Boxes score, which showed a statistical improvement over a historical control on an intent to treat basis (p=0.013). It is difficult to draw any conclusions about efficacy from these results without being able to look at the totality of the data. Additionally, there are limitations to what conclusions can be drawn when comparing to historical controls. Regarding safety, the company noted that no alarms were raised and it could be safely co-administered with donepezil. The company intends to out-license PXT864 to a partner for further development.

Sensitivities

The risks to Pharnext's business are unique compared to many other development-stage pharmaceutical companies. The company's unique approach to repurposing drugs allows it to investigate new functions of these otherwise well-understood medications. The indications the company is examining are far outside of the scope of activity that these drugs have been tested in before and the ability to demonstrate clinical efficacy with PXT3003 or PXT864 is wholly dependent on the predictive capacity of the company's Pleotherapy platform, which has not yet produced an approved drug. Despite the fact that the company's previous Phase III for PXT3003 was interrupted, we are encouraged that it was still able to demonstrate a benefit with the limited dataset. This has significantly de-risked the follow-up Phase III study, in our view. The greatest risk with PXT3003 is that the size of the clinical benefit appears to be small. This may affect how the drug is reviewed at the FDA, but we think the company's decision to seek an SPA is wise as it would, if accepted by the agency, remove a substantial portion of this regulatory uncertainty. If successful, it would be the first drug approved for the treatment of CMT1A, which we expect to both streamline the approval process as well as improve market uptake even if the clinical benefit is small.

PXT864 is a higher-risk program for a range of reasons, which include the fact that Alzheimer's disease is a notoriously difficult indication for new drugs. Moreover, the drug did not reach its primary endpoint in Phase II. Finally, the company has indicated it is seeking a partner to advance the program, which while this will defray the high costs of running clinical programs in Alzheimer's disease carries its own set of risks.

These products will also face a range of commercial risks if approved. The intellectual property for these drugs is comparatively weaker as combination therapies than for a novel compound and there may be challengers to the IP if these programs are successful. Additionally, because these drugs are composed of commonly available generic medications, there is the potential for some market share to be lost to these generic alternatives. This may be compounded in the case of PXT3003 due to the small effect sizes. Finally, although there is little competition in these markets currently (especially for CMT1A with no approved medications), there are multiple programs in development, which might change this in the future.

Finally, the company faces significant financing risk. The company ended 2019 with €1.3m in net cash (excluding €8.4m in refundable advance liabilities) and we expect it will need €95m in additional capital to reach the approval decision for PXT3003 (not including the cost to develop PXT864). The company may finance this program through licensing the product, but if it is financed through capital markets, this may result in substantial dilution. Share issuances over the next few years could potentially be greater than the current shares outstanding (assuming no sharp increase in the market valuation).

Valuation

We arrive at an initial valuation of €239.5m or €12.48 per basic share. Our valuation is based on a risk adjusted NPV analysis of PXT3003 and is made with a series of assumptions (Exhibit 11). We model commercialization in US and European markets and we assume pricing in Europe will be 40% lower than the US. We also assume a 30% gross/net sales discount. The drug will likely face pressure from payers because the active molecules are inexpensive generics and we expect negative pressure on pricing and market share as a result.

We are assuming a launch price of $55,000 per year in the US for PXT3003. We acknowledge that when considering pricing for PXT3003, there are few comparators, as few drugs have been repurposed successfully for rare genetic diseases. This pricing is on par with tetrabenazine ($57,000/year minimum), a generic drug approved for Huntington's disease, a different movement disorder (albeit more severe).

We assume a 60% probability of success for the drug, which we consider above average for the current stage and indication. We were encouraged that it demonstrated a statistical benefit in the previous Phase III even given its limitations. The bigger risk for the drug is that its clinical benefit may be small, which may have an impact on approvability and is reflected in our penetration assumptions (20%) along with the effect of payer pressure. We may adjust these values as more data become available.

We have not included PXT864 in our valuation as the company is not currently advancing its clinical development, although we may change this in the future if the company can secure a partner to support the program. This being said, we consider the program high risk given the previous clinical results and the difficulty developing drugs for Alzheimer's.

We record a pro forma net cash position of €8.4m, which includes the company's €15.0m in debt obligations, but not OSEO repayable advances, and the estimated net proceeds (€7.2m) from the company's €7.7m March private placement (more information below). The repayment of the advance associated with the CMT1A program (€2.4m) is included in the valuation of the PXT3003 program.

Exhibit 11: Valuation of Pharnext

Development Program	Indication	Clinical stage	Prob. of success	Launch year	Patent/ Exclusivity Protection	Launch Pricing ($/year)	Peak sales (US$m)	rNPV (€m)	Assumptions
PXT3003	CMT1A	Phase III	60%	2024	2031-2034	55,000	626	231.0	Target population: mild-moderate CMT1A, approximately 110,000 in the US and Europe combined. R&D: 330 patient Phase III (based on previous Phase III) at $50,000 per patient + $4m per year overhead. COGS: 5%. SG&A: $10m fixed, 10% variable costs of selling. Peak penetration: 20% assuming moderate treatment effect. Pricing: $55,000 per year at launch, includes 2% growth per year.
Total								**231.0**	
Net cash (YE19 + private placement) (€m)								8.42	
Total equity value (€m)								239.5	
Total basic shares (m)								19.2	
Value per basic share (€)								**12.48**	
Dilutive options and warrants (m)								5.24	
Total diluted shares								24.42	
Value per diluted share								11.16	

Source: Pharnext reports, Edison Investment Research

Financials

The most recent financial report for the company was for the year ending 2019. Pharnext reported a loss of €23.3m for 2019, driven by R&D spending of €15.2m. This is before R&D rebates of €3.2m for the year (recorded as revenue). 2018 revenue was higher (€6.83m) because it included the sale of Chinese rights to PXT3003 to Tasly Pharmaceuticals for €2m. We forecast a reduction in R&D spending for the year 2020 (€9.3m) because PXT3003 is not currently in the clinic, but to increase again in 2021 (€16.6m). We only forecast the costs associated with developing PXT3003 in our forecasts, as we do not expect the company to advance PXT864 without the support of a partner.

The company ended 2019 with €16.2m in cash and €15.0m in debt (bond due in 2023 at Euribor+11%). In addition, the company records repayable advances from OSEO (French sovereign fund development corporation) in the amount of €8.7m under loans and borrowings, although repayment of these are contingent on the success of the company's development programs and their commercialization. Of this, €2.4m is associated with the PXT3003 program and the remainder with PXT864. Subsequent to the end of 2019, the company had a private placement in March 2020 for €7.7m gross (1.8m new shares at €4.28). Hence, we calculate an adjusted FY19 net cash position of €1.3m, or adjusted pro forma net cash of €8.4m after adjustment for the March private placement.

We forecast the company will need €95m in additional capital to complete the development of PXT3003 (in Phase III from 2021 to 2023) and reach approval (in 2024) and expect it will need additional capital before the end of 2020. We record this as illustrative debt in our model (€30m in 2020, €30m in 2021, €35m in 2022). We expect the company will attempt to meet these financing needs through licensing and other business development, but it may seek it on the capital markets, which can lead to dilution.

Exhibit 12: Financial summary

€'k	2018e	2019e	2020e	2021e
31-December	IFRS	IFRS	IFRS	IFRS
INCOME STATEMENT				
Revenue	6,829.0	3,597.4	2,873.8	1,759.9
Cost of Sales	0.0	0.0	0.0	0.0
Gross Profit	6,829.0	3,597.4	2,873.8	1,759.9
R&D	(17,664.7)	(15,178.1)	(9,294.8)	(16,587.3)
Admin & Marketing	(7,072.1)	(8,444.6)	(8,529.1)	(8,614.4)
EBITDA	(17,754.9)	(19,501.6)	(14,830.2)	(23,334.0)
Normalised operating profit	(18,310.9)	(20,093.0)	(14,785.1)	(23,276.8)
Amortisation of acquired intangibles	0.0	0.0	0.0	0.0
Exceptionals	0.0	0.0	0.0	0.0
Share-based payments	403.1	67.7	(165.0)	(165.0)
Reported operating profit	(17,907.8)	(20,025.3)	(14,950.1)	(23,441.8)
Net Interest	(3,408.8)	(3,283.9)	(3,316.7)	(3,139.7)
Joint ventures & associates (post tax)	0.0	0.0	0.0	0.0
Exceptionals	0.0	0.0	0.0	0.0
Profit Before Tax (norm)	(21,719.8)	(23,376.9)	(18,101.8)	(26,416.5)
Profit Before Tax (reported)	(21,316.7)	(23,309.2)	(18,266.8)	(26,581.5)
Reported tax	0.0	0.0	0.0	0.0
Profit After Tax (norm)	(21,719.8)	(23,376.9)	(18,101.8)	(26,416.5)
Profit After Tax (reported)	(21,316.7)	(23,309.2)	(18,266.8)	(26,581.5)
Minority interests	0.0	0.0	0.0	0.0
Discontinued operations	0.0	0.0	0.0	0.0
Net income (normalised)	(21,719.8)	(23,376.9)	(18,101.8)	(26,416.5)
Net income (reported)	(21,316.7)	(23,309.2)	(18,266.8)	(26,581.5)
Basic average number of shares outstanding (m)	11.8	14.5	18.5	19.2
EPS - basic normalised (€)	(1.83)	(1.61)	(0.98)	(1.38)
EPS - diluted normalised (€)	(1.83)	(1.61)	(0.98)	(1.38)
EPS - basic reported (€)	(1.80)	(1.61)	(0.99)	(1.39)
Dividend (€)	0.00	0.00	0.00	0.00
BALANCE SHEET				
Fixed Assets	1,333.7	1,526.5	1,406.6	1,298.8
Intangible Assets	32.3	12.1	0.0	0.0
Tangible Assets	401.0	293.2	185.4	77.6
Investments & other	900.5	1,221.2	1,221.2	1,221.2
Current Assets	29,663.9	21,645.1	39,664.1	45,177.6
Stocks	0.0	0.0	0.0	0.0
Debtors	0.0	0.0	472.4	289.3
Cash & cash equivalents	22,761.4	16,246.6	33,793.2	39,489.7
Other	6,902.5	5,398.5	5,398.5	5,398.5
Current Liabilities	(9,361.8)	(9,959.6)	(8,165.8)	(9,988.0)
Creditors	(9,173.7)	(5,792.7)	(4,324.7)	(6,146.8)
Tax and social security	0.0	0.0	0.0	0.0
Short term borrowings	0.0	(3,806.3)	(3,480.6)	(3,480.6)
Other	(188.1)	(360.5)	(360.5)	(360.5)
Long Term Liabilities	(47,981.3)	(20,457.9)	(50,783.7)	(80,783.7)
Long term borrowings	(38,772.8)	(11,181.4)	(41,507.1)	(71,507.1)
Other long term liabilities	(9,208.5)	(9,276.6)	(9,276.6)	(9,276.6)
Net Assets	(26,345.4)	(7,245.9)	(17,878.8)	(44,295.3)
Minority interests	0.0	0.0	0.0	0.0
Shareholders' equity	(26,345.4)	(7,245.9)	(17,878.8)	(44,295.3)
CASH FLOW		**0**		
Op Cash Flow before WC and tax	(18,158.0)	(19,569.3)	(14,665.2)	(23,169.0)
Working capital	2,532.2	(1,523.1)	(1,940.4)	2,005.3
Exceptional & other	(285.2)	(476.0)	0.0	0.0
Tax	0.0	0.0	0.0	0.0
Net operating cash flow	(15,911.1)	(21,568.4)	(16,605.6)	(21,163.7)
Capex	0.0	0.0	0.0	0.0
Acquisitions/disposals	(401.5)	193.5	0.0	0.0
Net interest	(1,827.2)	(1,412.9)	(3,316.7)	(3,139.7)
Equity financing	6,110.1	16,494.9	7,469.0	0.0
Dividends	0.0	0.0	0.0	0.0
Other	(1,267.5)	0.0	0.0	0.0
Net Cash Flow	(13,297.3)	(6,292.9)	(12,453.4)	(24,303.5)
Opening net debt/(cash)	2,714.1	16,011.4	(1,258.8)	11,194.6
FX	0.0	0.0	0.0	0.0
Other non-cash movements	0.0	23,563.0	0.0	0.0
Closing net debt/(cash)	16,011.4	(1,258.8)	11,194.6	35,498.0

Source: Pharnext reports, Edison Investment Research

Contact details	Revenue by geography
46 rue Saint-Lazare 75009 Paris France +33 (0) 1 41 09 22 30 www.phamext.com	N/A

Management team

CEO: David Horn Solomon	CFO and CBO: Peter Collum
Mr Solomon has more than 30 years of experience within the life sciences industry. He previously served as CEO of Silence Therapeutics, Akari Therapeutics, Bionor Parma and Zealand Pharma. He was a former managing partner at Sund Capital and previously headed healthcare investments at Carrot Capital Healthcare Ventures. He is also a former board member of TxCell (acquired by Sangamo Therapeutics), Onxeo and Promosome, and is now chairman of the board for Advicenne Pharma and Rexgenero.	Mr Collum has more than 22 years of experience within the pharmaceutical industry, with 17 of those years in healthcare investment banking focused on M&A, financing and business development transactions for public and private life sciences companies both in the US and abroad. He was previously a partner at MTS Health Partners, and prior to MTS was a director in the healthcare investment banking group at Bank of America, and he began his career at Roche as an engineer.
CMO: Adrian Hepner	**CCO: Xavier Paoli**
Dr Hepner has over 30 years of experience in US and international biomedical research and clinical drug development. He previously served as executive vice president and chief medical officer at Eagle Pharmaceuticals and was former vice president of clinical research at Avanir Pharmaceuticals, vice president of Clinical Research and Medical Affairs at BioDelivery Sciences International (BDSI), and senior medical director at UCB BioSciences. He is the author of multiple publications and inventor of several patents and has practiced neuropsychiatry for about 17 years.	Mr Paoli has held various marketing positions in biotech and big pharma companies (GlaxoSmithKline, UCB Pharma, Alexion). He brings 18 years of experience in the commercialization of innovative drugs notably for rare diseases. He graduated from HEC Paris with a master of marketing and from the University Paris 7 with masters of science in genetics and immunology.

Principal shareholders	(%)
CB Lux	21.57
Tasly Pharmaceutical	12.48
Lohas	12.28
Truffle Capital	5.05

General disclaimer and copyright

This report has been commissioned by Pharnext and prepared and issued by Edison, in consideration of a fee payable by Pharnext. Edison Investment Research standard fees are £49,500 pa for the production and broad dissemination of a detailed note (Outlook) following by regular (typically quarterly) update notes. Fees are paid upfront in cash without recourse. Edison may seek additional fees for the provision of roadshows and related IR services for the client but does not get remunerated for any investment banking services. We never take payment in stock, options or warrants for any of our services.

Accuracy of content: All information used in the publication of this report has been compiled from publicly available sources that are believed to be reliable, however we do not guarantee the accuracy or completeness of this report and have not sought for this information to be independently verified. Opinions contained in this report represent those of the research department of Edison at the time of publication. Forward-looking information or statements in this report contain information that is based on assumptions, forecasts of future results, estimates of amounts not yet determinable, and therefore involve known and unknown risks, uncertainties and other factors which may cause the actual results, performance or achievements of their subject matter to be materially different from current expectations.

Exclusion of Liability: To the fullest extent allowed by law, Edison shall not be liable for any direct, indirect or consequential losses, loss of profits, damages, costs or expenses incurred or suffered by you arising out or in connection with the access to, use of or reliance on any information contained on this note.

No personalised advice: The information that we provide should not be construed in any manner whatsoever as, personalised advice. Also, the information provided by us should not be construed by any subscriber or prospective subscriber as Edison's solicitation to effect, or attempt to effect, any transaction in a security. The securities described in the report may not be eligible for sale in all jurisdictions or to certain categories of investors.

Investment in securities mentioned: Edison has a restrictive policy relating to personal dealing and conflicts of interest. Edison Group does not conduct any investment business and, accordingly, does not itself hold any positions in the securities mentioned in this report. However, the respective directors, officers, employees and contractors of Edison may have a position in any or related securities mentioned in this report, subject to Edison's policies on personal dealing and conflicts of interest.

Australia

Edison Investment Research Pty Ltd (Edison AU) is the Australian subsidiary of Edison. Edison AU is a Corporate Authorised Representative (1252501) of Crown Wealth Group Pty Ltd who holds an Australian Financial Services Licence (Number: 494274). This research is issued in Australia by Edison AU and any access to it, is intended only for 'wholesale clients' within the meaning of the Corporations Act 2001 of Australia. Any advice given by Edison AU is general advice only and does not take into account your personal circumstances, needs or objectives. You should, before acting on this advice, consider the appropriateness of the advice, having regard to your objectives, financial situation and needs. If our advice relates to the acquisition, or possible acquisition, of a particular financial product you should read any relevant Product Disclosure Statement or like instrument.

New Zealand

The research in this document is intended for New Zealand resident professional financial advisers or brokers (for use in their roles as financial advisers or brokers) and habitual investors who are 'wholesale clients' for the purpose of the Financial Advisers Act 2008 (FAA) (as described in sections 5(c) (1)(a), (b) and (c) of the FAA). This is not a solicitation or inducement to buy, sell, subscribe, or underwrite any securities mentioned or in the topic of this document. For the purpose of the FAA, the content of this report is of a general nature, is intended as a source of general information only and is not intended to constitute a recommendation or opinion in relation to acquiring or disposing (including refraining from acquiring or disposing) of securities. The distribution of this document is not a 'personalised service' and, to the extent that it contains any financial advice, is intended only as a 'class service' provided by Edison within the meaning of the FAA (i.e. without taking into account the particular financial situation or goals of any person). As such, it should not be relied upon in making an investment decision.

United Kingdom

This document is prepared and provided by Edison for information purposes only and should not be construed as an offer or solicitation for investment in any securities mentioned or in the topic of this document. A marketing communication under FCA Rules, this document has not been prepared in accordance with the legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of investment research.

This Communication is being distributed in the United Kingdom and is directed only at (i) persons having professional experience in matters relating to investments, i.e. investment professionals within the meaning of Artide 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the 'FPO') (ii) high net-worth companies, unincorporated associations or other bodies within the meaning of Article 49 of the FPO and (iii) persons to whom it is otherwise lawful to distribute it. The investment or investment activity to which this document relates is available only to such persons. It is not intended that this document be distributed or passed on, directly or indirectly, to any other class of persons and in any event and under no circumstances should persons of any other description rely on or act upon the contents of this document.

This Communication is being supplied to you solely for your information and may not be reproduced by, further distributed to or published in whole or in part by, any other person.

United States

Edison relies upon the 'publishers' exclusion' from the definition of investment adviser under Section 202(a)(11) of the Investment Advisers Act of 1940 and corresponding state securities laws. This report is a bona fide publication of general and regular circulation offering impersonal investment-related advice, not tailored to a specific investment portfolio or the needs of current and/or prospective subscribers. As such, Edison does not offer or provide personal advice and the research provided is for informational purposes only. No mention of a particular security in this report constitutes a recommendation to buy, sell or hold that or any security, or that any particular security, portfolio of securities, transaction or investment strategy is suitable for any specific person.

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