EDISON

Newron Pharmaceuticals

Corporate update

Xadago launched; eyes now on pipeline assets

Pharma & biotech

Following an encouraging year to date we have upgraded our forecasts for Xadago (Parkinson's disease [PD] therapy), and key CNS pipeline assets sarizotan (Rett syndrome) and Evenamide (schizophrenia). Sublicensee partner US WorldMeds launched Xadago into the US market in July 2017; Xadago is now available in the majority of key markets worldwide through partners. Importantly Newron's CNS R&D pipeline is progressing; clinical data and commercial opportunity details presented on Evenamide and sarizotan at the R&D day in May have prompted upgrades to our peak sales forecasts and valuation. Our updated valuation is CHF754m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/15	2.4	(18.3)	(1.17)	0.0	N/A	N/A
12/16	6.7	(15.2)	(1.04)	0.0	N/A	N/A
12/17e	15.1	(13.6)	(0.72)	0.0	N/A	N/A
12/18e	17.9	(15.3)	(0.81)	0.0	N/A	N/A

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

Xadago launches in the key US market

Sublicensee US WorldMeds has launched Xadago (PD) as an add-on therapy to L-DOPA in the US market (July 2017). Xadago is the first NCE to launch in the US for PD in over a decade. The US prescribing detail includes all PD patients (not limited to moderate to severe as per the EU). Pricing in the US is significantly higher than we had expected, leading us to revise upwards our peak sales assumptions for the US market opportunity.

R&D focus on Evenamide and sarizotan

Detailed Phase IIa Evenamide data demonstrate good tolerability and safety profile plus preliminary evidence of efficacy as an add-on therapy in schizophrenia. We have significantly increased our peak sales assumptions for Evenamide to €0.9bn. A confirmatory Phase IIb study will be initiated in 2018 by Newron. The pivotal Phase III sarizotan STARS trial should report top-line data in Q318, supporting a 2019 NDA filing. The 'Burden of disease' study due to read out Q318 should optimise market uptake, access and reimbursement for this orphan product; our orphan drug pricing analysis opportunity has prompted an upgrade on pricing.

Valuation: CHF754m or CHF42.3/share

Our upgraded valuation of Newron is CHF754m (from CHF530m). It includes Xadago in PD and risk-adjusted contributions for the dyskinesia indication, sarizotan in RS and Evenamide in schizophrenia, and reflects June 2017 net cash and short-term investments of €44.9m. The recent CHF27m private placement of 2m new shares will fund Newron through 2019 beyond key inflection points. Our valuation upgrade is driven by increasing our peak estimates across all three assets and updating FX rates. Sarizotan's disproportionate contribution to the valuation reflects the potential higher pricing assumption and high operating margin of this asset, which Newron can commercialise alone with a small but focused salesforce.

13 October 2017

Price	**CHF13.65**
Market cap	**CHF243m**
	€0.87/CHF
Net cash and short-term investments (€m) at 30 June 2017	44.9
Shares in issue (post private placement)	17.8m
Free float	77%
Code	NWRN
Primary exchange	SIX
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(24.2)	(34.2)	(33.6)
Rel (local)	(26.2)	(36.2)	(42.4)
52-week high/low	CHF27.8		CHF13.7

Business description

Newron Pharmaceuticals is an Italian CNS-focused biotechnology company. Xadago (safinamide) for Parkinson's disease has been launched in Europe and the US; Xadago is partnered with Zambon (EU), Meiji Seika (Japan), US WorldMeds (US) and Seqirus (Australia/New Zealand).

Next events

Sarizotan Phase III STARS data	Q318
Evenamide Phase IIb start	2018
Sarizotan NDA filing	2019

Analysts

Dr Susie Jana +44 (0)20 3077 5700

Dr Daniel Wilkinson +44 (0)20 3077 5734

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: Focus on CNS disorders

Newron is an Italian company focused on central nervous system (CNS) disorders. Lead product Xadago (safinamide) for the treatment of PD has been launched in multiple European countries by commercial partner Zambon and in the US by sublicensee US WorldMeds. Additionally, Newron has a pipeline of mid to late clinical stage products, including orphan drug candidate sarizotan for the genetic disorder RS, which could represent the first product for Newron to commercialise alone, and Phase II asset Evenamide, an entirely novel mechanism of action antipsychotic drug for schizophrenia. Newron floated on the SIX at the end of 2006, raising CHF118m (€74.3m) at CHF55/share. In 2008 it acquired UK-based Hunter-Fleming and at the end of 2012 acquired NeuroNova. During 2014-2016 Newron raised gross proceeds of CHF66.9m. A private placement of 2.0m new shares in September 2017 raised gross proceeds of CHF27.0m (post transaction shares outstanding 17.8m). The company's headquarters are in Bresso, Italy, and it employs around 25 people, including in its operations in Morristown, NJ, US.

Valuation: Risk-adjusted NPV of CHF754m or CHF42.3/share

Our updated Newron valuation is CHF754m (from CHF530m). Our valuation includes Xadago in PD and risk-adjusted contributions for the dyskinesia indications, sarizotan in RS and Evenamide in schizophrenia, and reflects end-June 2017 net cash and short-term investments of €44.9m (this excludes the gross proceeds of CHF27m from the recent private placement). The upgrade to our valuation largely reflects an increase to our peak sales expectations for all three assets: Xadago, sarizotan and Evenamide. Sarizotan's disproportionate contribution to the valuation reflects the potential higher pricing assumption and high operating margin of this asset, which Newron can commercialise alone with a small but focused salesforce. A top down analysis of the schizophrenia market highlights the large number of patients that could be eligible for Evenamide; while it is currently in Phase IIa and its valuation is heavily risk adjusted, we believe peak sales of €0.9m as an add-on therapy in schizophrenia to be reasonable

Sensitivities: Xadago US uptake and pipeline evolution

The main near-term sensitivities for Newron relate to safinamide (Xadago) uptake in the US; the Xadago for PD contribution to our valuation is CHF21.8/share (the US PD opportunity represents c 68% of our total Xadago peak sales estimate). Newron's mid to late stage programmes (sarizotan and Evenamide) are advancing into registration and late stage development, respectively. Phase III data for sarizotan should be available Q318, supporting a 2019 launch. A confirmatory Phase IIb study on Evenamide could initiate in 2018 by Newron or with/by a potential partner. Success or failure with any of these compounds could have an impact on our valuation and financial forecasts.

Financials: Cash runway beyond key inflection points

Newron had net cash and short-term investments of €44.9m at end June 2017 (€45.1m in cash and investments, €0.18m in short-term borrowings); reported cash has been bolstered by the €11.3m milestone payment (recognised under IFRS as immediate revenues) from partner Zambon triggered by the US approval of Xadago in March 2017. The recent CHF27m private placement of 2m new shares will fund Newron through 2019 beyond key inflection points including the confirmatory safety and efficacy Phase IIb study for Evenamide, and completion of the STARS Phase III trials for sarizotan. Evenamide will eventually be a partnering candidate, given the potential size of the indication and scope of development and its differentiating mode of action.

Xadago first PD drug to launch in the US for a decade

US pricing ahead of our expectations

Following a protracted regulatory process with the FDA, including a refusal to file letter (May 2014), and issuance of a complete response letter to the subsequent NDA resubmission (March 2016), Newron and its partners Zambon and US WorldMeds finally received the greenlight of approval for Xadago (safinamide) for the treatment of Parkinson's disease in March 2017. Sublicensee US WorldMeds swiftly launched Xadago as an add-on to levodopa therapy for fluctuating mid to late stage PD patients in the US market in July 2017. Xadago is the first new chemical entity (NCE) to launch in the US for PD in over a decade. Xadago has been priced in line with its main competitor Azilect (Teva/Lundbeck) at $600-700 per month, versus our $200 per month prior assumption. We note Xadago's label is narrower than Azilect (Xadago is approved for mid- to late-stage patients compared to Azilect, which is approved for use across the entire PD spectrum including early PD). However, Xadago's multiple mechanisms of action (see below) and lack of dietary restrictions are differentiating factors.

Xadago (partnered with Zambon) is now available in 12 European countries (latest launch in Portugal) as an add-on therapy to levodopa in mid-to-late PD. Newron reported €1.3m in Xadago royalties in H117 (€0.85m in H116) from commercial partner Zambon; given we assume a 12% royalty rate, this implies net sales of c €11m for the first six months of 2017 across the available territories in Europe. Importantly Xadago royalties are ramping up despite the Italian Medicines Agency's (AIFA's) imposed ceiling on 2017 and 2018 sales. Zambon launched Xadago in 2015, but the drug was only commercialised in Germany for seven months. During the course of 2016 Xadago was rolled out to 10 additional countries in Europe; FY17 sales will benefit from the ongoing European market roll-out by Zambon (including France by the end of 2017), plus an undisclosed territory ex Europe. We expect an uplift in the royalty trajectory in 2017 given a full 12 months of product availability for the year in 11 European countries plus initial US sales.

Xadago multiple mechanism of action in PD

Parkinson's disease (PD) is characterised by progressive loss of dopaminergic neurons within the basal ganglia in the brain, leading to a decline in dopamine levels. The most important and debilitating symptoms of PD are those that result from the depletion of dopamine in the substantia nigra of the brain. Dopamine plays a critical role in movement and co-ordination, and a reduction in its levels leads to the characteristic and progressive features of PD: tremor, slowness of movement and rigidity. The current mainstay of drug treatment is limited to oral therapies such as levodopa (L-DOPA), dopamine agonists (DA) and monoamine oxidase-B inhibitors (MAOI) such as Azilect (rasagiline), which aim to increase or substitute for dopamine. However, over time the benefits of drug treatment diminish; L-DOPA provides symptomatic relief of around three to five years. Importantly treatment with L-DOPA can lead to the unpleasant axillary effects of motor fluctuations (ON/OFF effect) and involuntary movements known as L-DOPA induced dyskinesia (LD).

Xadago (safinamide) has multiple mechanisms of action (it acts through both dopaminergic and non-dopaminergic pathways), with reversible inhibition of MAO-B (monoamine oxidase), which blocks the enzyme responsible for breaking down dopamine, inhibition of dopamine uptake, and inhibition of glutamate release. Xadago helps to restore dopamine levels in the brain (by inhibiting dopamine enzymatic breakdown), thereby improving the patient's symptoms. Additionally, by blocking the activity of the voltage-dependent sodium channels and thus inhibiting glutamate release, Xadago helps to avoid the development of dyskinesia linked to long-term levodopa use.

Xadago is used as an add-on to L-DOPA therapy

Xadago is positioned as an oral, once a day add-on treatment in PD patients who are receiving L-DOPA) and experiencing 'OFF' episodes. This means patients can remain on Xadago throughout their life, without physicians having to switch treatment with disease progression, which in our view will facilitate its use. Both DAs and L-DOPA are now generic, hence expensive drug combinations should not be an issue or barrier to Xadago's use. Mylan launched generic rasagiline in June 2017 in to the US market. Both DAs and L-DOPA are well established in treating PD, hence the biggest competition to Xadago, in our view, will likely be new drugs with unique or novel mechanisms of action; however, the majority of such candidates are at an earlier stage of development. Xadago has a long period of market exclusivity; the EU patent runs to 2029 and the US patent to 2031.

Regional partnerships in place to maximise value

Xadago's global development plan will benefit sales in the longer term. In 2012, Newron partnered Xadago with Zambon under a strategic collaboration and licence agreement covering all territories worldwide excluding Japan/Asia, which had already been licensed to Meiji Seika. Zambon is a private Italian company with 2015 reported group turnover of €667m, with the pharmaceutical division contributing 85% and the chemicals division 15%. Zambon holds a 4.4% equity stake in Newron. To date, Zambon has launched Xadago in 12 countries in Europe. Zambon does not have a significant pharmaceutical sales presence outside of Europe and Latin America. Regional partnerships have therefore been actively sought to maximise Xadago's value. Hence, the drug was sub-licensed to US WorldMeds in the US; Xadago is now available in this key market after a protracted regulatory period with a somewhat cautious FDA. Seqirus obtained the licence for Australia and New Zealand in 2017 and will be responsible for regulatory approval submission in those territories and Zambon will supply the product. Valeo Pharma has more recently sublicensed the commercialisation and marketing rights for Xadago in Canada.

Newron is eligible for regulatory related milestone payments from Zambon and for double-digit royalties on sales. As part of any sub-licensing, Newron could be eligible for around 25-30% of milestone payments and 50% of royalties. Financial terms with Meiji Seika have not been disclosed; a Phase II/III confirmatory study and long-term Phase III study have been initiated in Japan by Meiji. In 2017 Newron and Meiji Seika announced a commercialisation agreement with Eisai; Eisai will hold the exclusive rights to market safinamide in Japan and to develop and market the product in seven countries in Asia (South Korea, Taiwan, Brunei, Cambodia, Laos, Malaysia and the Philippines).

We forecast global peak sales of €653m in PD

In the US there are 1.0-1.5 million PD patients (sources: American Parkinson Disease Association, Parkinson's Disease Foundation), with a similar-sized market in Europe (source: European Parkinson's Disease Association) and a smaller market of around 250,000 in Japan (source: Decision Resources 2011). We have added in an additional 1.7 million patients to capture ROW opportunities; this has been triggered by the numerous sublicensing deals made by Zambon across multiple territories. In Europe and in the US we assume 70% qualify for treatment as per the mid to late stage PD as specified on the label. We have modulated our peak penetration assumption to 7% from 10% of treated PD patients six years after launch, as a result of slower than expected sales ramp up in Europe versus our original expectations and the launch of Rasagiline generics by Mylan in the US in June 2017. While we have kept our pricing assumption of €3.7/day in Europe, which compares favourably to other PD products including Azilect, we have materially increased our pricing assumption in the US market from $7/day to $21/day, reflecting Xadago's US pricing. As a result, our peak Xadago sales forecast has increased from €450m to €653m in PD, which

comprises Europe/ROW (ex-Japan) peak sales of €187m and US peak sales of €446m (vs €250m previously). Our royalty rate forecasts are around 12-13%.

Dyskinesia label extension in the US a possibility

Newron and partner Zambon together with academic and regulatory experts are in the process of designing a potentially pivotal efficacy study to support Xadago use in levodopa induced dyskinesia (PD LID). We believe a single Phase III trial could support a label expansion in this indication that would differentiate Xadago from all other classes of PD drug treatments.

A subset analysis of a previous clinical trial (study 018) found that Xadago (safinamide) could improve dyskinesia in patients with moderate dyskinesia at baseline. Although L-DOPA is an effective treatment for PD, its use is associated with the development of dyskinesia. The ability to improve dyskinesia could therefore allow for potentially earlier use of L-DOPA in PD and expand the market opportunity for Xadago. The subset analysis revealed that the third of patients who scored four or higher on the dyskinesia rating scale at the beginning of the study reported an improvement of 24% on 100mg of Xadago (added to L-DOPA) versus placebo. However, there were no significant differences for patients on 50mg of safinamide.

Newron has indicated that the study design (based on previously reported clinical and preclinical data) will be discussed with EU and US regulatory bodies and a trial is expected to start in 2018. We include a risk-adjusted contribution for Xadago in dyskinesia, assuming peak sales of €400m until there is more clarity on the potential magnitude of benefit. It is estimated that dyskinesia affects around 40% of PD patients treated with L-DOPA for four to six years, with limited treatment options aside from L-DOPA dosing adjustment. With around one million PD patients in each of the US and Europe, this represents a large opportunity. We assume the safinamide label could be expanded to include dyskinesia following a single clinical trial, and could lead to potential launch in 2020.

Evenamide Phase IIa data preliminary efficacy signals

At the R&D day Newron elaborated on the Phase IIa Evenamide data (first presented at the International Congress on Schizophrenia Research [ICOSR] on 24-28 March); the Phase IIa proof of concept data so far demonstrate a good tolerability and safety profile and preliminary evidence of efficacy. Discussions with the regulators are ongoing regarding Phase IIb trial design, Newron expects a confirmatory Phase IIb efficacy and safety/tolerability study (six weeks' duration) as an add-on to second-generation antipsychotics in patients experiencing worsening symptoms of psychosis to initiate in 2017/18. Additionally, an international panel of schizophrenia experts has advised the company to evaluate the development of Evenamide for a potential orphan indication in Clozapine-treatment-resistant schizophrenia; the relevance of this is potential for an NDA filing under breakthrough therapy designation.

Evenamide novel MOA for schizophrenia

Schizophrenia is a common chronic and severe mental disorder and many patients are resistant to or refractory to available drug treatments; there is a huge opportunity for novel mechanism of action (MOA) drugs. Evenamide (NW-3509) is an internally developed asset that originates from Newron's ion channel discovery platform. It is a novel, new-generation, oral, antipsychotic drug in development for schizophrenia, which acts through pathways (sodium channel modulator, which regulates the hyperexcitability of neurons) that are not targeted by available antipsychotic drugs, which mainly exert their efforts through dopamine receptor blockade. Evenamide is being evaluated in the first instance as a potential add-on therapy to antipsychotics for treating schizophrenia. Early data in preclinical models demonstrated that Evenamide has a synergistic effect when administered with atypical antipsychotics. The clinical relevance is that the potential to lower the treatment dose

of an atypical drug would reduce the troublesome side effect burden caused by these drugs while increasing overall efficacy versus atypical drug monotherapy, rescuing patients from discontinuing antipsychotic treatment altogether. As Evenamide is the first compound to have an impact on both targets (glutamate modulation and voltage gated sodium channel blockade) it could also have utility as monotherapy.

Schizophrenia is a chronic and severe mental disorder involving a breakdown in the relation between thought, emotion and behaviour, leading to faulty perception and the inability to function normally. Signs and symptoms can vary. Generally, symptoms are classified into three categories:

- Positive symptoms include hallucinations, delusions, thought disorders, movement disorders.
- Negative symptoms include flat effect (reduced expression of emotion), social withdrawal, lack of interest in everyday activities.
- Cognitive symptoms include trouble focusing, poor 'executive functioning' and problems with 'working memory'.

Drug treatments for schizophrenia focus on eliminating symptoms; the current mainstay of these are antipsychotic drugs ('typical antipsychotics' were developed in the 1950s and examples include haloperidol, chlorpromazine and fluphenazine; 'atypical antipsychotics' were developed in the 1990s and examples include aripiprazole [BMS's Abilify], olanzapine [Lilly's Zyprexa] and quetiapine [AstraZeneca's Seroquel]). The first generation of typical antipsychotics was hampered by significant neurological side effects including, in some cases, non-reversible tardive dyskinesia. While the newer generation of atypical antipsychotics improved on the toxicity profile of the typical antipsychotics, drug-related side effects remain troublesome and include sedation, metabolic changes (weight gain, diabetes, hyperlipidemia) and endocrine changes (sexual side effects). Discontinuation of antipsychotics in patients achieving remission leads to a relapse in over 52% of patients in 6.5 months (Gilbert et al, 1995). Long-term drug treatment of schizophrenia has major limitations; the US National Center for Biotechnology Information (NCBI) estimates that 25-33% of patients are treatment resistant and relapse rates remain high (relapse rates over two years in chronic schizophrenia receiving medication approaches 41% [Crow et al, 1986]). There is a clear unmet need in schizophrenia. New classes of medication are required that:

- improve the condition without affecting dopamine,
- reduce persistent psychotic symptoms in antipsychotic-treated patients with fewer side effects than clozapine,
- improve on negative and cognitive symptoms, and
- can reduce the side effects of available antipsychotic medications through dosage reduction.

Evenamide has potential to fit the bill on many of the aforementioned points; it does not affect dopamine; as a selective and use-dependent, voltage-gated sodium channel blocker, it may act synergistically with antipsychotics. Evenamide has the potential to target the abnormal neuronal activity and glutamate transmission and thereby have an impact on the positive, negative and cognitive symptoms of schizophrenia. Evenamide could also have utility in conditions such as mania and depression; these illnesses can also have psychosis symptoms in some patients.

Encouraging preliminary Phase IIa proof-of-concept (POC) Evenamide data

Newron has reported encouraging preliminary Phase IIa proof-of-concept (POC) Evenamide data (good tolerability, safety and preliminary evidence of efficacy) as an add-on to antipsychotics in the treatment of schizophrenia. This Phase IIa study addressed the drug's ability to reduce positive symptoms and psychotic worsening in patients with schizophrenia experiencing breakthrough symptoms while on adequate doses of risperidone or aripiprazole (atypical antipsychotic drugs). This double-blind, placebo-controlled, four-week in/outpatient study evaluated 15-25mg of

Evenamide (twice daily) in a minimum of 90 patients across study centres in the US and India. Interestingly, patients in the study who were showing signs of worsening symptoms of psychosis (while on doses of antipsychotics to which they had responded in the recent past) benefited on all efficacy measures evaluated and the onset of improvement occurred early in treatment. Results of the study are summarised in Exhibit 1.

Exhibit 1: Evenamide Phase IIa trial results

Phase IIa	Notes
Trial design	Phase IIa, double-blind, placebo-controlled, randomised, multinational study (n=89).
Indication	Evenamide (15-25mg BID) as add-on treatment in patients with a DSM-5 diagnosis of schizophrenia (add on to risperidone or aripiprazole).
Efficacy	Patients treated with Evenamide showed improvement on the symptoms of schizophrenia assessed by the Positive and Negative Syndrome Scale (PANSS). The mean (SD) change from baseline at day 28 for the PANSS total score was greater for Evenamide [-5.1 (9.67)] than for placebo [-3.7 (9.65)]. For the PANSS Positive Symptoms subscale, a statistically significant/near significant improvement from baseline (mean baseline score: 14.8 ± 2.8) to day 28 for Evenamide compared to placebo.
Tolerability	Evenamide in the range of 15-25mg bid (30-50mg/day) was well tolerated. Most AEs were of mild severity [Evenamide, 58 of 69 (84%); placebo, 30 of 34 (88%)]; 9 of 69 (13%) AEs for Evenamide and 4 of 34 (12%) for placebo were assessed as moderate. The most frequent (>5% of patients in any group) adverse events (AEs) (Evenamide vs placebo) were somnolence [8 (16.0%) vs 5 (12.8%)], insomnia [5 (10.0% vs 1 (2.6%)], overdose [3 (6.0%) vs 1 (2.6%)], dry mouth [3 (6.0%) vs 2 (5.1%)], headache [3 (6.0%) vs 0] and cold sweat/hyperhidrosis [2 (4.0%) vs 0].
Safety	Two patients in the Evenamide group discontinued treatment due to AEs: seizure (n=1) and atrial fibrillation (n=1).

Source: Newron Pharmaceuticals

Newron believes the Phase IIb/IIIa dose finding efficacy and safety study evaluating Evenamide in schizophrenia could be initiated in 2018. While the CHF27m private equity placement ensures funding of the Phase IIb through to clinical trial read out, Evenamide will eventually be a partnering candidate, given the potential size of the indication and scope of development and its differentiating mode of action. Conducting the confirmatory efficacy and safety Phase IIb alone at this stage should ensure better economics when it comes to partnering than on Phase IIa data alone. Furthermore, following confirmation of Evenamide's therapeutic dose range, a study could be initiated in mania patients who are not adequately controlled on current treatments.

The anti-psychosis market is vast

According to a recent Grand View Research report, the global antipsychotic drug market was $11.7bn in 2015 and is forecast to grow at a 2.1% CAGR from 2017-25. Most of the branded drugs used widely to treat the anti-psychotic symptoms of schizophrenia (eg AstraZeneca's Seroquel, BMS's Abilify, Lilly's Zyprexa) are out of market exclusivity, with generics widely available. Market growth in this segment will be a function of volume growth in underlying patients and the availability of new drugs. Bristol-Myers Squibb's Abilify (aripiprazole) is the number one antipsychotic drug, reporting peak sales of $9.2bn in 2014 (before generics hit the market). Much of Abilify's success is due to its better tolerability profile (lower incidence of weight gain, QTc prolongation, sedation) versus second-generation compounds such as risperidone. Abilify's reported sales are across multiple indications including schizophrenia, bipolar disorder (including maintenance) and autistic disorders. The opportunities for novel MOA drugs including Evenamide are wide and could extend beyond schizophrenia; much of this will be dependent on conducting a wide range of clinical trial programmes and this highlights the eventual need to seek a partner for this asset.

Peak sales of €0.9bn as add-on therapy in schizophrenia alone

Following the initial positive POC data and a deeper understanding of where Evenamide could fit into the current schizophrenia treatment paradigm, we have revisited our peak sales forecast. According to the US National Institutes of Health, the prevalence of schizophrenia in the US adult population is 1.1%. We apply the same prevalence rate to the European population to derive US/EU schizophrenia patient numbers of 5.6 million. According to the National Institute of Mental Health's Clinical Antipsychotic Trials of Intervention Effectiveness (the 'CATIE' program), 75% of

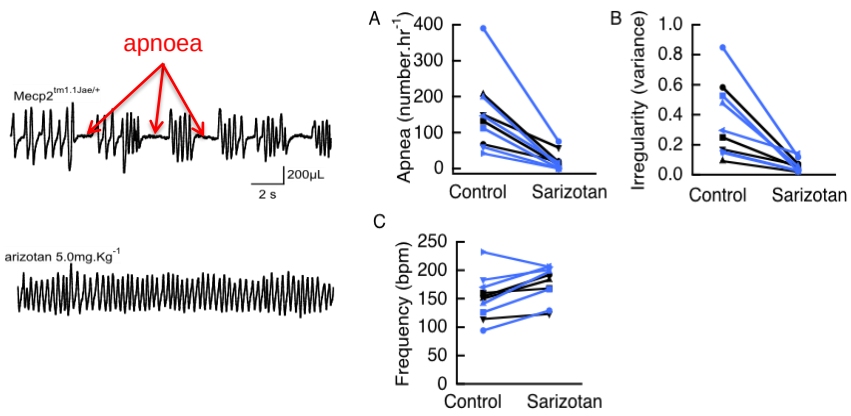
patients are incomplete responders (including drug discontinuation due to side effects) and 33% of incomplete responders are on combination therapy. This derives our Evenamide eligible patient population as defined as incomplete responders on combination treatment. We apply a peak penetration rate of 8% (six years from our assumed 2022 launch year) to these patients who would be eligible for Evenamide as an add on to an atypical anti-psychotic drug. We price in line with Abilify in the US at $12,000 per annum and assume an average $6,000 per annum price in Europe. As a result, our peak sales for Evenamide have increased to €0.9bn (from $500m) as add-on therapy. Furthermore, its potential would be dependent on the breadth of clinical trials conducted including as monotherapy, in clozapine resistant patients as well as mania and depression patients suffering psychosis symptoms. While we assume a 20% royalty rate on sales, we do not book any partnering milestones at this point; the announcement of a partnering deal and or compelling Phase IIb efficacy data could represent upside to our numbers.

Sarizotan the first orphan drug for Rett syndrome

Sarizotan is a highly selective serotonin (5-HT1a) and dopamine (D2) antagonist, which in preclinical studies demonstrated activity in normalising the abnormal breathing patterns in animal models of Rett syndrome (RS), a rare, genetic, incurable, neurodevelopmental disorder that generally affects girls. Sarizotan is not being developed to address the underlying cause of RS but as a potential treatment for these life-threatening breathing disorders. 70-90% of RS patients have respiratory abnormalities, motor and intellectual impairment, sleep abnormalities and seizures. 25% of sudden deaths in RS may be due to cardio-respiratory abnormalities. See our note Back on track, published in September 2016, for more detail on sarizotan.

STARS (Sarizotan Treatment of Apneas in Rett Syndrome), a potentially pivotal Phase II/III clinical study to evaluate breathing disorders associated with RS, is underway. STARS is a global study that will recruit around 129 RS patients across centres of excellence in the US, Italy, UK, Australia and India. The FDA recently lowered the age criteria to six years and over; the primary endpoint of the study is the reduction in the number of clinically significant apnoea (>10 seconds) episodes at 24 weeks. The lowering of the age eligibility criteria is important given that afflicted children start to show signs and symptoms of the disorder at around two years of age. Newron has sought advice from both regulators and key opinion leaders in the design of this study. Data from STARS are expected in mid-2018. Newron is planning to apply for a global filing and approval strategy once the STARS data are available.

Exhibit 2: Sarizotan reduced apnoea and breathing irregularities in preclinical studies



Source: Newron Pharmaceuticals

In preclinical studies, sarizotan has demonstrated reduced apnoea and corrected irregular breathing in RS mouse models. These data are shown in Exhibit 2. On the left, the RS mouse model shows recurring instances of apnoea, which are corrected when treated with sarizotan, with apnoea reduced by 70-85% overall. It is this profile that has encouraged Newron to pursue pivotal development of sarizotan in RS – the 'STARS' study as described above.

Burden of disease study outcome to aid in pricing and reimbursement decisions

Importantly, a c 750-patient, c 210-caregiver burden of disease study (Health Economics and Outcome Research study) is ongoing. This study enables Newron to foster partnerships and collaborations with Rett advocacy groups, thought-leading physicians and governing payers. By identifying the unmet need for improving RS disease management and aligning economic and clinical outcomes, the company believes this study will aid in the pricing reimbursement discussions, access and market take-up of the drug once the approval process has been initiated.

Newron received sarizotan's IND approval in May 2016; both the FDA and the European Commission have designated sarizotan with orphan drug status for the treatment of RS. The introduction of the Orphan Drug Act 1983 by US congress has encouraged the industry to develop drugs for rare disease and disorders, defined as "those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug." Japan and the European Union adopted the Orphan Drug Act in 1993 and 2000, respectively.

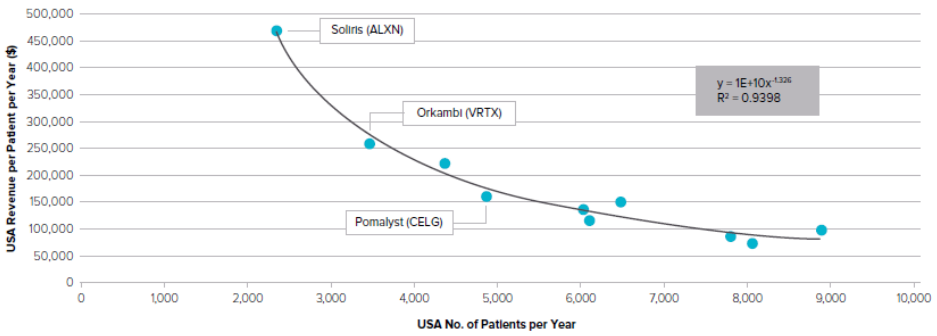
Orphan drug status can provide financial incentives such as market exclusivity (7.5 years from approval in the US, 12 years in the EU), reduced R&D costs (eg through tax credits, R&D grants) and substantial pricing incentives. According to EvaluatePharma's Orphan Drug Report 2017, the average cost per patient per year for an orphan drug in the US was ~$140k in 2016 compared to ~$28k for a non-orphan drug (top 100 drugs). Exhibit 3 highlights the prices of the top 10 orphan drugs in the US and the correlation that exists between price and number of patients; the lower the market potential in terms of patient volumes, the higher the price per annum.

Exhibit 4 demonstrates that the median cost per year for an orphan drug in 2016 was $84k. We note that many of the orphan drugs are treatments aimed at oncology or immune mediated conditions; AbbVie's Imbruvica pricing in 2016 was $114k/annum.

Rare paediatric disease voucher a possibility

Newron could be eligible to qualify for an FDA 'Rare Paediatric Disease Priority Review Voucher', a transferable voucher that allows for an accelerated FDA approval process. The voucher would not have to be used for sarizotan or by Newron and could be sold to a third party. For example, priority review vouchers either for paediatric or for tropical diseases have been purchased for $67-350m. United Therapeutics monetised its rare paediatric voucher (received when Unituxin was approved by FDA for the treatment of neuroblastoma) by selling the voucher to AbbVie in August 2015 for $350m).

Exhibit 3: Top 10 US orphan drugs in 2016 by sales revenue per patient vs no. of patients treated



Sales represent company reported sales where available, otherwise based on an average of equity analyst estimates.

USA sales represent sales for all indications.

EvaluatePharma® analysed the Top 10 selling USA drugs which treated fewer than 10,000 patients in 2016.

*Revenues per patient: An estimate of the dollar ($) revenues per year received, by a company, per patient for a drug in the USA market. This takes into account the cost per patient (average mg per year multiplied by the cost per mg), off-invoice discount and patient compliance.

All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

Prices for products in the US are sourced from Medicare Part B, NADAC, FSS and Medicaid. Availability of a price point determines choice of source. The source is kept consistent across years to reflect a clear trend in pricing.

Source: EvaluatePharma Orphan Drug Report, February 2017

Exhibit 4: Average and median cost per patient per year, 2012-16

Average Cost per Patient ($) per year	2012	2013	2014	2015	2016	CAGR
Orphan	116,216	123,464	137,545	140,352	140,443	4.8%
Growth per Year		6.2%	11.4%	2.0%	0.1%	
Median price	64,099	69,203	88,503	80,124	83,883	
Non-orphan	18,680	20,677	22,736	26,405	27,756	10.4%
Growth per Year		10.7%	10.0%	16.1%	5.1%	
Median price	6,543	8,017	9,065	13,402	15,239	
Median Price Differential (orphan/non-orphan)	9.8	8.6	9.8	6.0	5.5	
				Median price increase 2012-2016:		
					Orphan:	1.31
					Non-orphan:	2.33

Note: All sales analysis based on EvaluatePharma®'s clean 'Orphan' sub-set of products, as defined in the Overview section.

Cost per patient is an estimate for the retail cost of a drug to a patient, for a given year, based on a 100% compliance to the treatment guidelines outlined in the FDA label. Does not include off-invoice discounts. The Top 100 orphan and non-orphan drugs were ranked by USA sales for 2016.

Prices for products in the US are sourced from Medicare Part B, NADAC, FSS and Medicaid. Availability of a price point determines choice of source. The source is kept consistent across years to reflect a clear trend in pricing.

Source: EvaluatePharma Orphan Drug Report, February 2017

Conservative assumptions drive €558m peak sales forecasts

Our forecasts assume first approval in the US during 2019, delayed from 2018 given slower than expected patient recruitment in the STARS trial, which is a function of the rarity of the disease, and the challenges in recruiting paediatric patients to centres that can be a huge distance from home. Phase III data, due in 2018, could support an NDA filing in 2019, with sarizotan potentially eligible for accelerated review given the unmet medical need.

Due to the small size of the indication (US 16,000 patients, EU 20,000 patients), Newron will commercialise sarizotan alone in key markets, including the US and major European countries. We have revised our peak sales forecasts upwards to €558m (from €260m), based on a higher pricing assumption of €75,000 a year ($88,000 per annum) versus €60,000 a year. Our $88,000 per annum estimate is based on the median orphan drug price in the US in 2016 (+5% price rise for launch in 2019) as described above. Newron believes 70-90% of patients with RS suffer from breathing abnormalities; as described above, we model 70% as the target patient population versus our prior

estimate of 25%. We assume 25% peak penetration of this target patient population. We note that both our penetration and pricing assumptions are on the conservative side, and highlight that pricing and penetration will ultimately depend on sarizotan's magnitude of benefit demonstrated in the ongoing STARS trial. Newron could achieve higher pricing than our per annum assumption. We provide a sensitivity analysis (Exhibit 6) under the valuation section to demonstrate how each swing factor (pricing and penetration) could affect our valuation.

Valuation

Our increased valuation of Newron (see Exhibit 5) is CHF754m from CHF530m, or CHF42.3 per share. The breakdown of our rNPV valuation, which uses a 12.5% discount rate, is shown in Exhibit 5. Our valuation includes Xadago peak sales in PD, in addition to risk-adjusted contributions for Xadago for the PD-related dyskinesia indication, sarizotan in RS and Evenamide in schizophrenia, which Newron is planning to partner. We have increased our probability of success for Xadago in dyskinesia to 50% (from 40%) given the recent communication that the clinical trial in dyskinesia will initiate in 2018, and now apply a 25% probability of success for Evenamide (from 20%), reflecting the initial efficacy data from the Phase IIa study. Our valuation of Newron has been updated to reflect a number of revised assumptions across all three assets, in addition to updating for prevailing spot FX rates, and the increased number of shares outstanding post the 2m new share offering (post transaction 17.8m shares outstanding). Our valuation has been rolled forward in time and includes H117 net cash and short-term investments of €44.9m.

Exhibit 5: Newron sum-of-the-parts valuation

Product	Indication	Launch	Peak sales (€m)	Value (€m)	Value (CHFm)	Probability	rNPV (€m)	rNPV (CHFm)	NPV/share (CHF/share)
Xadago	Parkinson's disease	2015	653	343.2	393.6	100%	343.2	393.6	22.1
	Dyskinesia	2020	400	83.0	95.2	50%	42.2	48.4	2.7
Sarizotan	Rett syndrome	2019	558	654.5	750.8	30%	187.7	215.3	12.1
Evenamide	Schizophrenia	2023	898	214.7	246.3	25%	39.4	45.2	2.5
Net cash at June 2017				44.9	51.5	100%	44.9	51.5	2.9
Valuation				**1,340.3**	**1,537.4**		**657.4**	**754.0**	**42.3**

Source: Edison Investment Research

The major source of valuation uplift relates to sarizotan, which now contributes CHF12.1/share vs CHF5.4/share before. We have significantly increased our pricing assumption to €75,000 a year ($88,000 per annum) versus €60,000 a year and assume 25% penetration of the targeted patients (as discussed above). Exhibit 6 highlights the impact on valuation per share if actual pricing or penetration for sarizotan is higher or lower than our estimates. We apply a 30% probability of success; this appears conservative given the pivotal nature of the trial. However, to date there is limited efficacy data in the proposed target group of patients, with only data from preclinical models available; this makes assessing the likelihood of success in RS more challenging, and hence we apply a heavy risk-adjustment to this programme. Sarizotan's disproportionate contribution to the valuation reflects the potential higher pricing assumption and high operating margin of this asset, which Newron can commercialise alone with a small but focused salesforce. We have modelled a long-term operating margin of 65% for this asset, taking into account royalty pay away to Merck KGa, in addition to COGS and SG&A expenses.

Exhibit 6: Sarizotan rNPV sensitivity to changes in pricing and penetration (CHF/share)

		Pricing per annum				
		€60,000	€75,000	€100,000	€125,000	€150,000
Penetration	20.0%	6.0	8.8	13.2	17.6	22.1
	25.0%	8.8	**12.1**	17.6	23.2	28.7
	30.0%	11.4	15.4	22.1	28.7	35.3
	40.0%	16.7	22.1	30.9	39.8	48.6

Source: Edison Investment Research

For Xadago in PD we have made numerous changes to our assumptions, including US price and peak penetration rates worldwide as discussed above. The net impact is an uplift of contribution to CHF22.1/share from CHF20.9. Evenamide peak sales have been increased to €0.9bn from €0.4bn, however given the early stage of development and need for additional trials to support this initial Phase IIa data, we have applied a 25% probability of success to our unadjusted NPV.

Financials

Newron reported cash and equivalents of €45.1m at end June 2017 (cash has benefited from an €11.3m milestone payment [recognised under IFRS as immediate revenues] from partner Zambon, triggered by the US approval of Xadago in March 2017) and has debt of only €0.1m. With the additional proceeds from the recent private placement (gross proceeds of CHF27.0m) cash should be sufficient to fund ongoing clinical development of the Phase II/III trial for sarizotan and the Phase IIb trial for Evenamide (that is to 2019 beyond key inflection points). Longer-term funding requirements will depend on the royalty income levels from Xadago, the extent of the clinical development plans for Evenamide and whether Newron choses to actively partner Evenamide.

Our FY17 revenue forecast of €15.1m consists of the net €10.4m milestone income already received plus €4.6m based on royalty income related to Xadago sales in Europe and the US. We forecast net R&D for FY17 of €19.5m, mainly related to the ongoing pivotal sarizotan Phase II/III trial (which could conclude in Q118) and initiation of the Evenamide Phase IIb trial in schizophrenia. Our forecast €23.8m in R&D expenses for 2018 reflects the Phase IIb trial for Evenamide in schizophrenia. Any delays to the pipeline development in 2017 could result in a phasing of R&D costs from 2017 to 2018. In addition, if the regulatory bodies request further clinical trials for sarizotan, and depending on the breadth of the Evenamide Phase IIa trial and whether or not a partner is involved to share costs of the trial, our 2018 R&D forecasts may need to be materially upgraded. If the latter were to materialise, we would highlight the need for additional capital requirements.

Newron is based in Italy and reports in euros. It is listed in Switzerland on the SIX with the share price quoted in Swiss francs (CHF). Our valuation is based on an FX rate of CHF/€0.87, which is in line with spot.

Exhibit 7 Financial summary

€000s	2014	2015	2016	2017e	2018e	2019e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	1,557	2,380	6,726	15,088	17,949	28,393
Cost of Sales	0	0	0	0	0	0
Gross Profit	1,557	2,380	6,726	15,088	17,949	28,393
Research and development (net)	(3,892)	(11,724)	(12,398)	(19,500)	(23,800)	(21,160)
EBITDA	(9,057)	(17,604)	(15,290)	(14,016)	(15,935)	(3,353)
Operating Profit (before amort. and except.)	(9,077)	(17,668)	(15,318)	(14,038)	(15,957)	(3,377)
Intangible Amortisation	(13)	(7)	(7)	(24)	(24)	(24)
Exceptionals	(2,125)	(6,725)	0	0	0	0
Other	0	0	0	0	0	0
Operating Profit	(11,215)	(24,400)	(15,325)	(14,062)	(15,981)	(3,400)
Net Interest	492	(583)	121	401	648	1,305
Profit Before Tax (norm)	(8,585)	(18,251)	(15,197)	(13,637)	(15,309)	(2,072)
Profit Before Tax (reported)	(10,723)	(24,983)	(15,204)	(13,661)	(15,333)	(2,095)
Tax	628	2,167	(33)	0	0	0
Profit After Tax (norm)	(7,957)	(16,084)	(15,230)	(13,637)	(15,309)	(2,072)
Profit After Tax (reported)	(10,095)	(22,816)	(15,237)	(13,661)	(15,333)	(2,095)
Average Number of Shares Outstanding (m)	12.7	13.7	14.7	18.8	18.8	19.8
EPS - normalised (€)	(0.63)	(1.17)	(1.04)	(0.72)	(0.81)	(0.10)
EPS - (reported) (€)	(0.80)	(1.66)	(1.04)	(0.73)	(0.81)	(0.11)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET						
Fixed Assets	7,686	406	451	478	504	529
Intangible Assets	6,993	265	261	240	219	198
Tangible Assets	67	79	120	168	215	261
Investments	626	62	70	70	70	70
Current Assets	29,388	43,974	56,140	67,233	55,843	56,844
Stocks	102	38	5	98	98	98
Debtors	3,320	3,005	9,667	3,883	3,883	3,883
Cash	25,702	40,931	46,468	63,252	51,862	52,863
Other	264	0	0	0	0	0
Current Liabilities	(4,489)	(6,513)	(6,645)	(6,785)	(8,468)	(9,304)
Creditors	(4,131)	(6,151)	(6,281)	(6,772)	(8,468)	(9,304)
Short term borrowings	(358)	(362)	(364)	(13)	0	0
Long Term Liabilities	(3,324)	(755)	(199)	(199)	(199)	(199)
Long term borrowings	(729)	(364)	0	0	0	0
Other long term liabilities	(2,595)	(391)	(199)	(199)	(199)	(199)
Net Assets	29,261	37,112	49,747	60,728	47,680	47,870
CASH FLOW						
Operating Cash Flow	(9,370)	(10,695)	(19,616)	(5,541)	(11,954)	(232)
Net Interest	107	121	102	401	648	1,305
Tax	(628)	(2,167)	33	(8)	0	0
Capex	(22)	(60)	(69)	(69)	(69)	(69)
Acquisitions/disposals	0	0	0	0	0	0
Financing	17,547	28,392	25,448	22,363	0	0
Other	0	(4)	(3)	(3)	(3)	(3)
Dividends	0	0	0	0	0	0
Net Cash Flow	7,634	15,587	5,895	17,142	(11,377)	1,001
Opening net debt/(cash)	(16,981)	(24,615)	(40,205)	(46,104)	(63,239)	(51,862)
HP finance leases initiated	0	0	0	0	0	0
Other	0	3	4	(7)	0	0
Closing net debt/(cash)	(24,615)	(40,205)	(46,104)	(63,239)	(51,862)	(52,863)

Source: Newron Pharmaceuticals accounts, Edison Investment Research

Contact details	Revenue by geography
via Ludovico Ariosto 21 Bresso (Mi) 20091 Italy +39 02 610 3461 www.newron.com	N/A

Management team

Chairman: Dr Ulrich Köstlin	CEO: Stefan Weber
Dr Köstlin was a member of the board of management of Bayer Schering Pharma until 2011. He was responsible for multiple regions globally: Europe, Asia-Pacific, Latin America, Japan and North America. He began his pharmaceutical career with Schering. In 1994 he was appointed to the former Schering AG's executive board. He holds a doctorate from Tübingen University and a master of law degree from the University of Pennsylvania Law School.	Mr Weber was appointed CEO in 2012, having been CFO since 2005, successfully executing the 2006 IPO. Mr Weber has more than 25 years' industry experience in general management and finance and has been responsible for numerous equity, debt, mezzanine and grant funding transactions. He holds a master's degree in business management from Fern Universität Hagen.
CMO: Ravi Anand	**VP finance: Roberto Galli**
Mr Anand has been Newron's CMO since 2005. He has over 20 years of experience in drug development, including positions at Roche and Sandoz/Novartis. These were focused on CNS and incorporated all stages of clinical development and post-marketing. He completed his medical training in the US, specialising in psychiatry and neurology.	Mr Galli has held various positions within finance at Newron since joining in 2002 and has more than 16 years of experience in biotech, finance and auditing. He holds a degree in business economics from the University Luigi Bocconi, Milan, and is a chartered auditor.

Principal shareholders	(%)
Investor AB	9.4
Aviva	7.8
Zambon	4.4

Companies named in this report

Merck KGaA (MRK GR); Meiji Seika Pharma, part of Meiji Holdings (2269 JP); Zambon Group (private), US WorldMeds (private)

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
295 Madison Avenue, 18th Floor
10017, New York
US

Sydney +61 (0)2 8249 8342
Level 12, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia