EDISON

Newron Pharmaceuticals

FY18 results

Moving towards R&D inflection points

Pharma & biotech

Newron's FY18 highlights the steady progression of its CNS R&D pipeline. STARS the pivotal Phase II/III (Sarizotan for Rett's Syndrome) has completed enrolment and data are expected in Q419. Newron is planning to apply for a global filing and approval strategy once data are available. Evenamide (schizophrenia), developed internally through Newron's ion channel discovery platform, could enable a paradigm shift in the treatment of refractory schizophrenia patients; in Q219 Newron will initiate two pivotal Phase IIb/III trials. We value Newron at CHF714m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/17	13.4	(5.3)	(0.32)	0.0	N/A	N/A
12/18	4.0	(15.0)	(0.84)	0.0	N/A	N/A
12/19e	8.5	(30.2)	(1.69)	0.0	N/A	N/A
12/20e	21.6	(8.7)	(0.49)	0.0	N/A	N/A

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

Xadago ramp up required

Newron reported €4.0m in Xadago royalties in FY18 (vs €2.9m in FY17). We assume 8–15% royalty rate depending on country, this implies gross sales of c €50m for the period generated in countries launched in Europe and initial US sales. A ramp-up in sales is required if it is to reach our global peak sales of €672m (in PD alone), which comprises Europe/ROW (ex-Japan) peak sales of €197m and US peak sales of €466m. Newron and partner Zambon will initiate a label extension study for Xadago in levodopa (L-DOPA) induced dyskinesia (LID) in H119; this study is important to differentiate Xadago in a genericised US PD market.

Sarizotan STARS data expected Q419

The pivotal Phase II/III Sarizotan Treatment of Apnoeas in Rett Syndrome (STARS) trial is now expected to report top-line data in Q419, supporting a 2020 NDA filing with sarizotan potentially eligible for accelerated review (six months). Due to the small size of the RS population, Newron will commercialise sarizotan alone in key markets, including the US and major European countries.

Evenamide novel MOA for schizophrenia

Newron will initiate two pivotal Phase IIb/III clinical trials (for evenamide) as an add on in patients inadequately controlled on current atypical antipsychotic drugs (APDs) and as an add-on to clozapine for treatment-resistant schizophrenia (TRS) patients. We believe Evenamide's mechanism of action (MOA) could change the treatment paradigm in inadequately responsive or TRS patients, by targeting a different pathway to available drugs. This is a $1.1bn (€0.9bn) plus opportunity.

Valuation: CHF714m or CHF40.1/share

Our valuation of Newron has decreased to CHF714m from CHF788m. We have tweaked our royalty rate assumptions for Xadago in the US, increased the probability of success for Evenamide to 50%, and pushed back sarizotan launch to 2021 from 2019. Newron is funded well into FY20 key inflection points and has access to a further €40m from the European Investment Bank (EIB) through a loan.

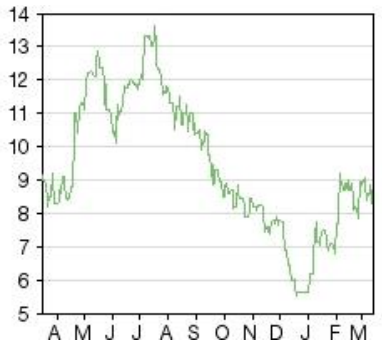
14 March 2019

Price	**CHF8.29**
Market cap	**CHF148m**

€0.88:CHF; $1.00:CHF; $1.13:€

Net cash (€m) at 31 December 2018	43.9
Shares in issue	17.8m
Free float	95%
Code	NWRN
Primary exchange	SIX
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(5.8)	32.0	(8.9)
Rel (local)	(8.0)	24.0	(13.8)
52-week high/low	CHF13.64		CHF5.41

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), Seqirus (Australia/New Zealand) and Medison Pharma (Israel).

Next events

Evenamide Phase IIb/III start	Q219
Sarizotan Phase III STARS data	Q419
Sarizotan NDA filing	2020

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Edison profile page

Investment summary

Company description: Focus on CNS disorders

Newron is an Italian company focused on CNS disorders. Lead product Xadago (safinamide) is approved for the treatment of Parkinson's disease (PD) and 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 late-stage clinical products; including orphan drug candidate sarizotan for the genetic disorder RS and Phase II/III 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 acquired NeuroNova at the end of 2012. Over 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). In October 2018, Newron secured a long-term funding facility from the European Investment Bank (EIB) for €40m. The company's headquarters are in Bresso, Italy and it employs around 25 people.

Valuation: CHF714m or CHF40.1/share

Our valuation of Newron has decreased to CHF714m from CHF788m. Our valuation includes Xadago in PD (CHF17.4share) and risk-adjusted contributions for the dyskinesia indication, sarizotan in RS and Evenamide in schizophrenia, and reflects December 2018 net cash of €43.9m. We make no change to our peak sales forecasts but have pushed back sarizotan launch by two years to 2021 and increased the probability of Evenamide succeeding to 50% from 25% reflecting its transition to pivotal Phase IIb/III trials in H119. We have reduced our royalty rate forecast for the US Xadago to 8% from 12%, given Newron receives a portion of the royalties received by Zambon; we forecast this to increase to 10% on a broader dyskinesia label. Additionally, we have rolled forward our model and updated FX rates. Our valuation of Newron remains skewed to Xadago and sarizotan. 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. Our top-down analysis of the schizophrenia market highlights the large number of patients that could be eligible for Evenamide; its valuation is risk adjusted and we believe peak sales of €0.9bn ($1.1bn) as an add-on therapy in schizophrenia are reasonable, with further upside potential depending on the outcome of the Phase IIb/III clinical trials (likely 2020).

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 CHF17.4/share. Newron's mid- to late-stage programmes (sarizotan and Evenamide) are advancing towards registration and late-stage development, respectively. Phase III data for sarizotan should be available in Q419, supporting a 2021 launch. Two Phase IIb/III studies evaluating Evenamide will commence recruitment in Q219. Success or failure with any of these compounds will impact our valuation and financial forecasts.

Financials: Cash runway beyond key inflection points

Newron had net cash and short-term investments of €43.9m at end December 2018 (€27.6m in cash and investments, €16.2m in short-term investments), which will enable funding through key inflection points including the confirmatory safety and efficacy Phase IIb/III study for Evenamide, and completion of the STARS Phase III trials for sarizotan. Evenamide will be a partnering candidate for the non-treatment resistant patient populations, given the potential size of the

indication; Newron may elect to market the drug alone in the TRS subpopulation. Additionally, Newron has access to a further €40m loan from the EIB to help fund R&D activities.

Xadago regional partnerships to maximise value

Newron's flagship product Xadago (safinamide) was the first PD drug to be approved in the US market in a decade when it launched (by sublicensee US WorldMeds) as an add-on to L-DOPA therapy for fluctuating mid- to late-stage PD patients in July 2017. Xadago (partnered with Zambon) is now available in 14 European countries (first European launch 2015) as an add-on therapy to L-DOPA in mid- to late-stage PD. Newron reported €4.0m in Xadago royalties in FY18 (vs €2.9m in FY17). Newron do not publish the Xadago revenue number but publish the net royalty received. The 41% increase in royalty received in is attributable to a growth in sales in available European countries, new launches and initial contributions from the US market. Further growth in sales is expected as Zambon and regional partners launch in recently approved territories (Australia, Canada, Brazil and Colombia). Xadago is making slow progress, but a ramp-up in sales is required if it is to reach our global peak sales of €672m (in PD alone), which comprises Europe/ROW (ex-Japan) peak sales of €197m and US peak sales of €466m (based on launch pricing assumption of $21/day). The US market is critical if Xadago is to achieve our peak sales expectations and we shall be monitoring sales evolution here. The anticipated label extension study for Xadago in levodopa (L-DOPA) induced dyskinesia (LID) will be an important differentiating factor as it competes in a genericised US PD market. Our royalty rate forecasts are around 8–15%. Under the 2012 agreement Newron is due to receive 'double-digit royalty payments on future sales'. In October 2018, partners Meiji Seika and Eisai filed a marketing authorisation application in Japan (following positive Phase II/III data in Japanese patients) and approval is expected by year end. Filings are also in place in Mexico and Israel by regional partners. For more details on our Xadago forecasts, see our October 2017 note, Xadago launched; eyes now on pipeline assets.

Xadago multiple mechanism of action in PD

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 L-DOPA, dopamine agonists and monoamine oxidase-B inhibitors 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 LID.

Xadago (safinamide) has multiple mechanisms of action (through both dopaminergic and non-dopaminergic pathways), with reversible inhibition of 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), improving the patient's symptoms.

New label US study in LID

Newron and partner Zambon are designing a potentially pivotal efficacy study to support Xadago use in 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 treatment.

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 (abnormal, uncontrolled, involuntary movement). 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. The ability to improve dyskinesia could therefore allow for potentially earlier use of L-DOPA in PD and expand the market opportunity for Xadago. Newron expects that Xadago will be the first add-on therapy to L-DOPA, thus improving Parkinsonism (motor function) and delaying/reducing onset of LID.

Zambon has completed discussions with the FDA on study design and intends to initiate the study in H119 in Europe and the US. We include a risk-adjusted contribution for Xadago in LID, assuming peak sales of €351m ($400m) until there is more clarity on the potential magnitude of benefit. Newron will co-fund the study up to a capped investment (c €10m), and in return receive an increased share of the economics under the licence agreement with Zambon.

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 2021. Furthermore Newron expects dyskinesia on the label to enable Xadago use earlier in the treatment paradigm.

STARS readout Q419 a significant R&D inflection point

Patient enrolment has now completed in Newron's pivotal clinical trial investigating Sarizotan for the Treatment of Apneas in Rett Syndrome (STARS). With over 130 patients recruited in the study, Newron has been a pioneer in developing a drug-based treatment for RS and is the first to conduct a Phase III study; top-line data are now expected in Q419. Newron is planning to apply for a global filing and approval strategy once STARS data are available. If approved, sarizotan will be the first drug for RS to reach the market and Newron will commercialise this asset alone in the US with a small but targeted salesforce; a European and broader commercialisation strategy is yet to be considered.

STARS is a pivotal Phase II/III study being performed by Newron to evaluate the ability of sarizotan to control the awake breathing disorders associated with RS. It is a global study spread across 14 centres in the US, Italy, UK, Australia and India. Enrolment was slower than originally anticipated; this is a function of the rarity of the disease and of the challenges in recruiting paediatric patients to centres far from home.

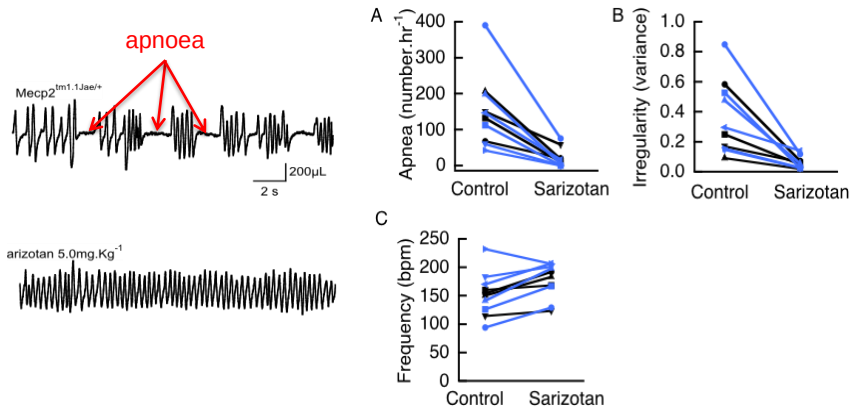
RS is characterised by waxing and waning symptoms that include gastrointestinal dysfunction, seizures and breathing dysfunction. These breathing abnormalities are characterised by three different patterns; hyperventilation, breath holding and air swallowing. RS is a rare, genetic, incurable, neurodevelopmental disorder that generally affects girls for the duration of their life. Mutations that occur to the methyl CpG binding protein 2 (MECP2) gene is indicative of the disease in ~95% of cases. Sarizotan is not being developed to address the underlying cause of RS, but as a potential treatment for these potentially life-threatening breathing disorders. Results from the RS Natural History study which followed 778 girls with classic RS (MECP2 mutation) over nine years, showed almost 100% had respiratory abnormalities, leading to higher odds of poor motor function, seizures and QT prolongation; analysis of the same data set showed survival for classic RS was greater than 70% at 45 years but the majority of deaths thought to be due to presumed cardiorespiratory abnormalities.

Preliminary baseline data from the first 102 patients enrolled in the STARS trial indicate that breathing abnormalities persist lifelong in patients, with ~70% of patients experiencing clinically significant apnoea (~10% of their time not breathing) leading to frequent incidence of low oxygen saturation (hypoxaemia). Given STARS is a pioneering trial for RS, it has been designed such that a clear, objective benefit from sarizotan in reducing both incidence and duration of apnoea can be determined; a primary endpoint, reduction in awake apnoea, will be determined by means of an BioRadio device worn by patients whilst awake. A secondary endpoint of caregiver impression of change, as determined by the primary caregiver, is also likely to be considered by regulatory bodies given STARS is the first Phase III trial for RS.

In-licensed from Merck in 2011, sarizotan is a serotonin (5-HT_{1A}) agonist originally developed to treat dyskinesia induced during the treatment of PD with L-DOPA. In preclinical studies performed by Newron, sarizotan demonstrated a strong reduction in apnoea and irregular breathing in mouse models (mutant MECP2 gene). These data are shown in Exhibit 1. 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 with the STARS study.

Exhibit 1: Sarizotan reduced apnoea and breathing irregularities in preclinical studies

Effect of 5mg/kg ip of sarizotan on respiratory pattern in heterozygous females



Source: Newron Pharmaceuticals

Although Newron is the first to embark on a Phase III study for a pharmacotherapy in RS, Neuren Pharmaceuticals (an Australia-based CNS-focused company that has partnered with ACADIA) plans to initiate a Phase III study for its lead asset (trofinetide) as a treatment for RS in H219. We note that trofinetide elicits its effect through a distinctly different mechanism of action to sarizotan; given the underlying pathology of RS is not well defined, it is far too early to ascertain which could be more beneficial to RS patients.

Rare paediatric disease voucher a possibility

Sarizotan has received orphan drug designation in both the US and EU for the treatment of RS. Newron could be eligible to qualify for an FDA Rare Paediatric Disease Priority Review Voucher, which is transferable and allows for an accelerated FDA approval process. The voucher does not have to be used for by Newron and could be sold to a third party. Priority review vouchers either for paediatric or for tropical diseases have been purchased for $67–350m; Spark Therapeutics monetised its rare paediatric voucher earlier this year (received during the regulatory approval of gene therapy Luxturna) by selling the voucher to Jazz Therapeutics in April 2018 for $110m).

Conservative assumptions drive €574m peak sales forecasts

We have delayed our forecast of sarizotan's launch in the US to 2021 from 2019, reflecting the delays in trial recruitment. Pivotal Phase III data, now expected Q419, could support an NDA filing with the FDA in 2020, with sarizotan potentially eligible for accelerated review (six months).

Due to the small size of the indication (US 16,000 patients, EU 20,000 patients), Newron has indicated it will commercialise sarizotan alone in these key markets, with 25–30 medical liaison managers. We forecast peak sales of €574m based on a pricing assumption of €75,000 a year ($88,000 per year). Our $88,000 per year estimate is based on the median orphan drug price in the US in 2016 (+5% price rise for launch in 2020) as described above. Newron believes 70–90% of patients with RS suffer from breathing abnormalities; we model 70% as the target patient population are eligible. We assume 25% peak penetration of this population. We note that both our penetration and pricing assumptions are conservative and highlight that pricing and penetration will ultimately depend on sarizotan's magnitude of benefit (demonstrated in the ongoing STARS trial) and outcomes from a separate ongoing burden of illness (BOI) study (health economics and outcome research study), which Newron is sponsoring in parallel to STARS. The objective of the BOI study is to better understand the relative burden of each symptom in this multi-symptom disease and quantify how breathing abnormalities affect the quality of life in patients with RS. 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 could achieve higher pricing than our current per year assumption; we have provided a sensitivity analysis (Exhibit 7) to demonstrate how both pricing and penetration of sarizotan could affect our valuation.

Evenamide: A novel approach to schizophrenia

Newron announced plans for a pivotal Phase IIb/III clinical trial programme for Evenamide, as an add-on therapy to atypical antipsychotic drugs (APD) for the treatment of schizophrenia. Schizophrenia is a common, chronic and severe mental disorder with many patients resistant or refractory to available drug treatments; there is a huge opportunity for novel MOA drugs given the unmet need in patients who do not adequately respond to current treatment options.

Evenamide (NW-3509) is an internally developed asset that originates from Newron's ion channel discovery platform. It is a novel, oral, APD in development for schizophrenia and acts through pathways that are not targeted by available APDs, which mainly exert their efficacy through blockade of dopamine receptor. Evenamide's differential feature is that it does not target the same dopamine pathways as current (atypical) APDs, it is a selective voltage-gated sodium channel blocker that inhibits post-synaptic glutamate release. Evenamide may act synergistically with antipsychotics drugs as it targets the abnormal neuronal activity (excessive glutamatergic signalling) thought to play a role in the pathology of patients that do not respond to current APDs. The hypothesis is that combination of Evenamide therapy would enable better efficacy with minimal safety impact and provide a new era of treatment options for inadequately treated or TRS patients.

Pivotal Phase IIb/III clinical trial programmes planned to start in Q219

Newron has been in active discussions with multiple regulatory bodies including Spain, Denmark, Sweden, Germany, UK (CHMP), US FDA (end of Phase II meeting) and Canada. The upshot of these meetings is the design of two Phase IIb/III clinical trials has been agreed, investigating Evenamide in two schizophrenia patient population:

- **Study 003/005 for non-treatment resistant patients**: chronic schizophrenic patients inadequately responding to atypical antipsychotic monotherapy (risperidone, aripiprazole, paliperdone, olanzapine or quietipine). This trial will evaluate efficacy, safety and tolerability of three fixed doses of Evenamide (or placebo) as an **add-on to the patient's current atypical antipsychotic medication**. The trial will aim to recruit 520 patients (across the four groups) monitoring patients (double-blinded) for six weeks before moving into a separate 46-week double-blind extension maintaining patients on the same dose regiment.
- **Study 004/006 for treatment resistant patients**: defined as TRS patients whose psychotic symptoms have failed two or more prior lines of pharmacotherapy and are not adequately responding to clozapine after 12 weeks. This trial will evaluate efficacy, safety and tolerability of two fixed doses of Evenamide (or placebo) as **add-on to clozapine**. The trial will aim to recruit 450 patients (across the three groups) monitoring patients (double-blinded) for eight weeks before moving into a separate 44-week open-label extension, transitioning all patients to dose-titrated Evenamide.

Newron believes both trials could complete in H220. Both trials will have a primary endpoint of efficacy, looking at improvement in positive and negative symptom score with a secondary endpoint looking for an improvement in clinical global impression of change. Regulatory bodies have indicated that both efficacy endpoints are likely to be considered prior to approval with a positive result in study 004/006 likely to lead to breakthrough designation as an add on to clozapine for treatment-resistant patients. Positive results in both 003/005 and 004/006 would be enough to cover the efficacy requirements for submitting an NDA across both indications; if study 003/005 is positive alone, another confirmatory Phase III trial would be needed for the larger patient subset, we note this scenario would require us to revisit our forecast 2022 US and EU launch date (Exhibit 2).

Exhibit 2: Likely pathways following Phase IIb/III trial readouts in 2020

		Study 003/005 Non-treatment-resistant patients (add-on to any atypical APD)	
		Negative readout	**Positive readout**
Study 004/006 Treatment-resistant patients (add-on to clozapine)	**Negative readout**	No regulatory approval	Confirmatory Phase III trial of similar design
	Positive readout	Approval for TRS as an add-on to clozapine (breakthrough designation)	Approval for both treatment-resistant and non-TRS as an add-on to any atypical antipsychotic drug

Source: Edison Investment Research

As an add-on to atypical APDs in wider schizophrenia patient populations, the scope for Evenamide is potentially huge and Newron would need to partner for the wider schizophrenia indication as an add on to APD. Newron, however, could elect to market the smaller sub indication of TRS as defined by resistant to clozapine. An estimated 20–50% of schizophrenia patients become resistant to treatment after 10–20 years; these patients are eligible for clozapine. Newron estimates only 70k schizophrenia patients are on clozapine (we discuss clozapine later in the note) and 30% of these patients are resistant to drug. This translates to 21k patients in the US who could be eligible for Evenamide plus clozapine in TRS. Newron could potentially commercialise for this indication alone without partnering, and would rapidly capture this subset of patients if breakthrough designation was granted.

Unmet needs in schizophrenia

According to the National Institute of Mental Health's Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 74% of schizophrenia patients discontinue treatment with atypical APDS after 18 months (including drug discontinuation due to side effects). As such, new classes of antipsychotic drugs are required that can:

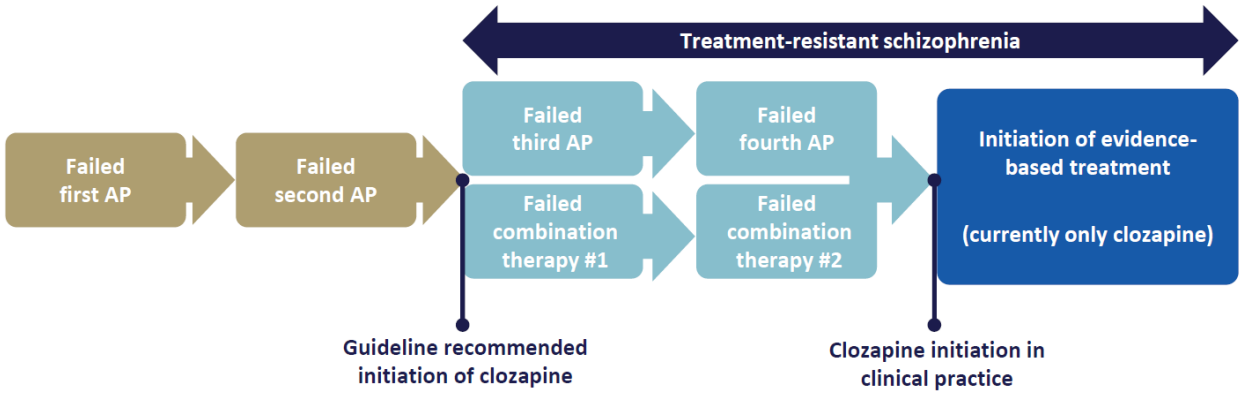
- improve the negative and cognitive symptoms which are not managed well with current pharmacotherapies, reducing the disease burden
- reduce the side effects of atypical antipsychotic medications through dosage reduction, improving patient compliance and clinical response
- reduce persistent psychotic (positive) symptoms in treated patients that do not respond adequately to atypical antipsychotics, where the underlying pathology is thought to be driven by other mechanisms

All currently marketed APDs used in the treatment of schizophrenia primarily work by attenuating dysregulated dopaminergic signalling by either antagonism (ie risperidone or clozapine) or low efficacy, partial agonism (ie aripiprazole) at post-synaptic dopamine D_2 receptors. The current generation of APDs is largely effective in treating the positive symptoms of schizophrenia, delusions and hallucinations (stemming from elevated dopaminergic signalling within the mesolimbic pathway of the brain). These have an episodic pattern and can be effectively controlled for the majority (~80–90%) of treatment-naive patients that initially present with symptoms. Negative and cognitive symptoms show limited improvement to current APDs and tend to persist despite treatment with these drugs; this leads to reduced emotional expression, social withdrawal, problems with working memory and trouble focusing, causing patients difficulties reintegrating back into communities and further burdening primary caregivers. As such, there is a need for drugs with novel mechanisms of action that can effectively manage the negative and cognitive symptoms. The two Phase IIb/III studies planned for Evenamide will determine whether its unique mechanism of action can also benefit patients who are not adequately responding to their current treatment.

Side effects from current APDs (which target dopaminergic pathways) tend to cause patient dissatisfaction and poor compliance, perpetuating difficulties in managing the disease. These include on-target side effects such as Parkinsonian-like motor symptoms (extrapyramidal side effects) and sexual-dysfunction (caused by hyperprolactemia), and off-target side effects including weight gain and abnormal heart rhythms (QT prolongation). Although second generation, atypical antipsychotics have significantly improved side-effect profiles (compared to first-generation, typical antipsychotics), novel treatments that can maintain or improve the efficacy with a lower dose of atypical APDs could be beneficial in improving patient compliance and treatment response.

Although there is a strong response to APDs initially in 80–90% of patients, 30–60% of these treatment-responsive patients become resistant or partially responsive to APDs. Schizophrenia patients that do not respond adequately to two (or more) dopaminergic antipsychotics (after an adequate dose and duration) are defined as having TRS. The effective management of TRS has been a longstanding challenge to clinicians and clozapine (Clorazil) is the only approved drug treatment (recommended as a third-line treatment in clinical guidelines issues by American Psychiatric Association, NICE and the World Federation of Societies of Biological Psychiatry). Clinically, clozapine is underutilised for a variety of reasons, but primarily this is due to the potential risk (black box warning) for agranulocytosis, which occurs in ~1% of patients, a potentially severe and life threatening condition due to lower white blood cell count and patients require monthly blood testing. Even though clinical guidelines recommend starting clozapine after two APD treatment failures, clozapine treatment is often delayed by several years (Exhibit 3) and 30% of TRS patients do not respond adequately.

Exhibit 3: Points of clozapine intervention in TRS

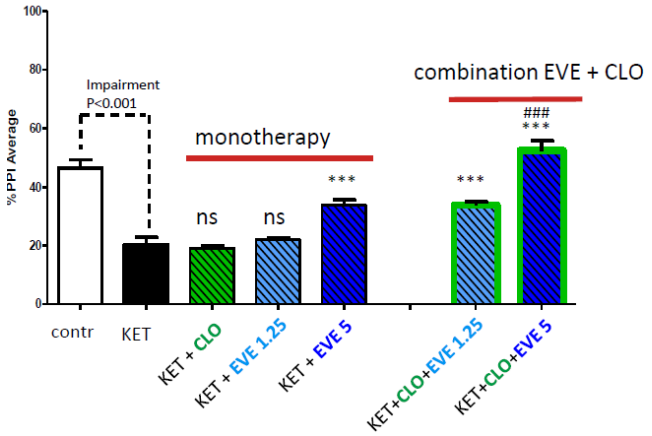


Source: Newron

Persistence of symptoms in TRS may be associated dysregulation of glutamatergic pathways as patients have been shown to exhibit higher levels glutamate in certain areas of the brain (the anterior cingulate cortex) while maintaining relatively normal dopamine function in comparison to treatment-responsive patients (who have an abnormally high dopamine function). Newron believes Evenamide could have an incremental impact in treatment without any additional safety issues given its unique mechanism of action of modulating excessive post-synaptic glutamate release (via inhibition of VGSC. Positive data from the Phase II proof of concept study indicated Evenamide was effective and well tolerated as an add-on therapy for patients who were not adequately responding to atypical antipsychotics (risperidone and aripiprazole).

During previous R&D days, Newron has presented preclinical data that have demonstrated the ability of Evenamide to treat numerous symptoms of schizophrenia (both as a mono- and combination therapy). Highlighted in Exhibit 4, and what we feel most relevant, is a preclinical model that demonstrates Evenamide exhibiting a synergistic effect when administered with clozapine in a ketamine induced model for schizophrenia (which induces glutamate dysfunction). Notably, full reversal was achieved when Evenamide was co-administered with clozapine at a dose where clozapine was ineffective by itself. How well this translates into the clinic will be established following the readout of study 004/006 (expected in H220), but could provide the much-needed breakthrough for patients that do not respond to clozapine treatment.

Exhibit 4: Preclinical schizophrenia models demonstrating synergistic effects of Evenamide with clozapine



- Significant attenuation of KET detrimental effect by EVE 5mg/kg monotherapy (reconfirms the previous study)
- Significant attenuation of KET detrimental effect by the combination of inactive dose of EVE 1.25mg/kg + inactive CLO 3mg/kg;
- Full reversal produced by the combination of EVE 5mg/kg + inactive CLO 3mg/kg; this combination is also significantly different from EVE 5mg/kg alone

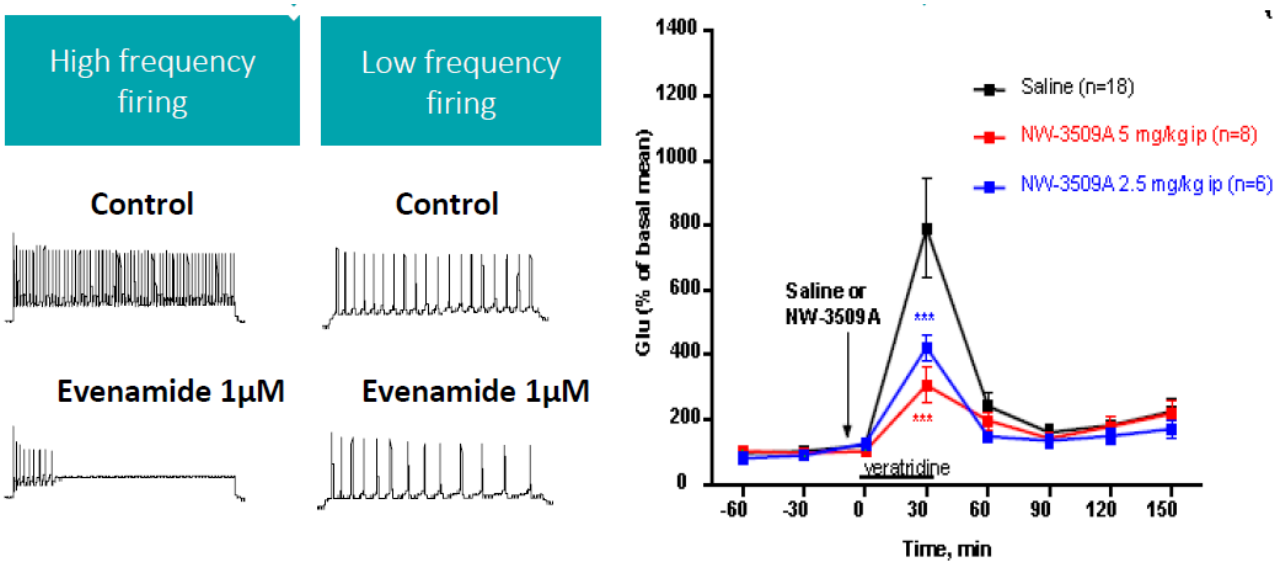
Source: Newron. Note: EVE: Evenamide; CLO: clozapine; KET: ketamine.

A unique mechanism of action for the treatment of schizophrenia

Evenamide (NW-3509) is one of Newron's proprietary assets, developed internally during a discovery programme conducted between 2003 and 2006 to identify small-molecule inhibitors of VGSC; Newron has been granted patent protection for composition of matter, retaining exclusive rights for Evenamide across a range of countries (including US and Europe) until 2028 and could extend with a five-year patent term extension, should regulatory approval be given.

From screening against over 130 targets, Newron has established that Evenamide works exclusively at VGSCs (also known as Na_V1 channels). VGSCs play a crucial role in the CNS, mediating neuronal signal transduction and cycle through three states: closed (resting), open and inactive. Conformational changes that occur between these states mean inhibitors can bind and inhibit one preferentially; rapidly firing channels will exist longer in an inactive state than a resting state, as such inhibitors can preferentially modulate a channel based on the frequency it is firing. It is these features that enable Evenamide to attenuate excessive signalling in glutamatergic systems. This is exemplified with a set of preclinical models performed by Newron: on the left of Exhibit 5 shows the ability of Evenamide (NW-3509) to selectivity attenuate high frequency firing neurons over low frequency and on the right, shows how this translates in vivo to a reduction in excessive glutamate release caused by high frequency firing (induced by veratridine), without causing a reduction to normal (basal) levels of glutamate release.

Exhibit 5: Evenamide attenuates glutamate release from hyperexcitable neurons



Source: Newron

No other marketed antipsychotic drugs have the same MOA as Evenamide. If this preclinical efficacy translates into the clinic, Evenamide could shift treatment paradigms, particularly in treatment-resistant patients. We note the recent Phase III failure of Lundbeck's asset (Lu AF35700) highlights the need for drugs with novel MOAs for the treatment of TRS patients; Lu AF35700 acted primarily through blockade (antagonism) of dopamine receptors (D_2 and D_1).

The anti-psychosis market is vast

According to a 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) was 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, QT 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

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 (CATIE), 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 ASD. We price in line with Abilify in the US at $12,000 per year and assume an average $6,000 per year price in Europe. We therefore forecast peak sales for Evenamide of €0.9bn as add-on therapy. In a real-life setting 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/III efficacy data could represent upside to our numbers.

Valuation

Our valuation of Newron has decreased CHF714m from CHF788m. The breakdown of our rNPV valuation, which uses a 12.5% discount rate for clinical stage assets and 10% discount rate for commercially available asset Xadago, is shown in Exhibit 6. 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.

Exhibit 6: Newron sum-of-the-parts valuation

Product	Indication	Launch	Peak sales* (€m)	Value (€m)	Value (CHFm)	Probability	rNPV (€m)	rNPV (CHFm)	rNPV/share (CHF/share)
Xadago	Parkinson's disease	2015	672	272.7	309.8	100%	272.7	309.8	17.4
	Dyskinesia	2021	354	80.9	91.9	50%	40.6	46.1	2.6
Sarizotan	RS	2021	574	527.7	599.4	30%	148.5	168.7	9.5
Evenamide	Schizophrenia	2022	937	266.6	302.9	50%	123.1	139.8	7.9
Net cash at 31 December 2018				43.9	49.8	100%	43.9	49.8	2.8
Valuation				**1,191.8**	**1,353.8**		**628.8**	**714.3**	**40.1**

Source: Edison Investment Research. Note: *FX changes have increased our forecasted peak sales slightly.

We have tweaked our royalty rate forecast for the US Xadago down to 8% from 12 % given Newron receives a portion of the royalties received by Zambon, we forecast this to increase to 10% on a broader dyskinesia label, reducing our valuation of Xadago to CHF17.4/share from CHF21.3/share.

We have pushed back sarizotan launch by two years to 2021, increasing our peak sales forecast slightly to €574m (from €566m), and changing the probability of success for Evenamide to 50% (from 25%) reflecting its transition to pivotal Phase IIb/III trials. Additionally we roll forward our model and update FX rates. Our valuation of Newron remains skewed to Xadago and sarizotan. It includes Xadago in PD and risk-adjusted contributions for the dyskinesia indication. Xadago is

making slow but steady progress, but a ramp-up in sales is required if it is to reach our global peak sales of €672m (in PD alone), which comprises Europe/ROW (ex-Japan) peak sales of €197m and US peak sales of €466m (based on launch pricing assumption of $21/day) Xadago for PD contribution to our valuation is CHF17.4/share (the US PD opportunity represents c 69% of our total Xadago peak sales estimate).

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 (25–30 medical liaison managers). Exhibit 7 shows the penetration and pricing sensitivity of sarizotan; at 25% penetration and pricing of €75,000 per year we attain an rNPV of CHF9.8/share. Our top-down analysis of the schizophrenia market highlights the large number of patients that could be eligible for Evenamide; and its valuation is proportionately risk adjusted, we believe peak sales of €0.9m as an add-on therapy in schizophrenia to be reasonable with further upside potential depending on the outcome of the Phase II/III clinical trials (likely 2020). In addition to updating for prevailing spot FX rates, our valuation has been rolled forward in time and includes 31 December 2018 net cash of €43.9m.

Exhibit 7: Sarizotan rNPV sensitivity to changes in pricing and penetration (CHF/share)

		Pricing per year				
		€60,000	€75,000	€100,000	€125,000	€150,000
Penetration	20.0%	3.3	6.7	10.6	14.5	18.4
	25.0%	5.4	**9.5**	14.3	19.1	23.9
	30.0%	7.6	12.2	17.9	23.6	29.4
	40.0%	12.0	17.7	25.2	32.8	40.3

Source: Edison Investment Research

Financials

At the FY18 results, Newron reported €4.0m in Xadago (safinamide) royalties in FY18 (vs €2.9m in FY17). Xadago is now available in 14 European countries as an add-on therapy to L-DOPA in mid- to late-stage PD and further worldwide launches as detailed above are expected over the next 12 months. The drug was launched in H217 into the US market for PD patients (as add-on therapy). In FY18, Newron reported an operating loss of €15.0m (vs a loss of €4.3m in FY17, which benefited from a €10.3m one-time milestone payment in the period).

We forecast FY19 and FY20 revenue of €8.5m and €21.6m respectively. Revenue forecasts are based on royalty income related to Xadago sales in Europe and the US, and a €4.0m milestone from Meija Seika for regulatory approval in Japan.

Reported R&D expenses in FY18 were €9.8m, compared to €8.6m FY17. We have increased R&D expenses in 2019 reflecting phasing of the two Evenamide Phase IIb/III studies, which are now expected to start in H119, and the ongoing pivotal sarizotan Phase II/III trial, which could conclude in Q419. Any further delays to pipeline development could result in phasing of R&D costs from 2019 to 2020.

Newron reported cash and equivalents of €43.9m at end December 2018. We continue to expect that current cash resources should be sufficient to fund operations well into FY20 through key inflection points. Newron also has access to a further €40m from the EIB through a loan.

Exhibit 8: Financial summary

€000s	2016	2017	2018	2019e	2020e
Year end December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	6,726	13,428	4,025	8,493	21,553
Cost of Sales	0	0	0	0	0
Gross Profit	6,726	13,428	4,025	8,493	21,553
Research and development (net)	(12,398)	(8,596)	(9,835)	(29,160)	(20,620)
EBITDA	(15,290)	(4,298)	(14,931)	(30,321)	(8,740)
Operating Profit (before amort. and except.)	(15,318)	(4,332)	(14,967)	(30,344)	(8,762)
Intangible Amortisation	(7)	(14)	(11)	(24)	(18)
Exceptionals	0	0	0	0	0
Other	0	0	0	0	0
Operating Profit	(15,325)	(4,346)	(14,978)	(30,367)	(8,780)
Net Interest	121	(955)	(41)	111	93
Profit Before Tax (norm)	(15,197)	(5,287)	(15,008)	(30,233)	(8,669)
Profit Before Tax (reported)	(15,204)	(5,301)	(15,019)	(30,256)	(8,687)
Tax	(33)	19	(16)	0	0
Profit After Tax (norm)	(15,230)	(5,268)	(15,024)	(30,233)	(8,669)
Profit After Tax (reported)	(15,237)	(5,282)	(15,035)	(30,256)	(8,687)
Average Number of Shares Outstanding (m)	14.7	16.3	17.8	17.8	17.8
EPS - normalised (c)	(103.69)	(32.32)	(84.20)	(169.43)	(48.58)
EPS - (reported) (€)	(1.04)	(0.32)	(0.84)	(1.70)	(0.49)
Dividend per share	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	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
BALANCE SHEET					
Fixed Assets	451	224	218	212	211
Intangible Assets	261	35	30	12	0
Tangible Assets	120	107	106	118	129
Investments	70	82	82	82	82
Current Assets	56,140	72,800	59,512	35,595	27,148
Stocks	5	5	0	0	0
Debtors	9,667	12,714	15,659	3,883	3,883
Cash	46,468	60,081	43,853	31,712	23,265
Other	0	0	0	0	0
Current Liabilities	(6,645)	(4,727)	(4,281)	(8,507)	(6,639)
Creditors	(6,281)	(4,727)	(4,281)	(8,507)	(6,639)
Short term borrowings	(364)	0	0	0	0
Long Term Liabilities	(199)	(576)	(606)	(606)	(606)
Long term borrowings	0	0	0	0	0
Other long term liabilities	(199)	(576)	(606)	(606)	(606)
Net Assets	49,747	67,721	54,843	26,694	20,114
CASH FLOW					
Operating Cash Flow	(19,616)	(8,404)	(16,108)	(12,212)	(8,501)
Net Interest	102	388	(3,120)	111	93
Tax	33	0	0	0	0
Capex	(69)	(24)	(34)	(34)	(34)
Acquisitions/disposals	0	0	0	0	0
Financing	25,448	22,324	51	0	0
Other	(3)	(300)	2,983	(6)	(6)
Dividends	0	0	0	0	0
Net Cash Flow	5,895	13,984	(16,228)	(12,141)	(8,447)
Opening net debt/(cash)	(40,205)	(46,104)	(60,081)	(43,853)	(31,712)
HP finance leases initiated	0	0	0	0	0
Other	4	(7)	0	0	(0)
Closing net debt/(cash)	(46,104)	(60,081)	(43,853)	(31,712)	(23,265)

Source: Company accounts, Edison Investment Research

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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: Dr Ravi Anand	**VP finance: Roberto Galli**
Dr 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%
AXA	3.3%
Polar	3.1%

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