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EDISON

Newron Pharmaceuticals

Initiation of coverage

Safinamide sets the stage

Pharma & biotech

Over the next 12-24 months, Newron could transition to a company with a marketed asset and a pipeline of orphan drugs in pivotal development, which it could commercialise alone. This will be dependent on gaining regulatory approvals and successfully sub-licensing safinamide, the lead product for all stages of Parkinson's disease, particularly in the key US market. Safinamide forms the bulk of our €253m/CHF317m valuation, and broadly underpins the current share price.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/12	8.9	(2.5)	(0.29)	0.0	N/A	N/A
12/13	3.5	(7.7)	(0.62)	0.0	N/A	N/A
12/14e	0.8	(12.1)	(1.04)	0.0	N/A	N/A
12/15e	0.0	(15.0)	(1.27)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items and share-based payments. We exclude safinamide royalties until formal approval.

Safinamide for all stages of Parkinson's disease

Safinamide has completed clinical development in both early and mid-late stage Parkinson's disease (PD). It was recently filed in Europe and US filing is expected in coming weeks. Safinamide could be the first add-on PD drug approved across all stages of disease, which combined with once-a-day dosing and a clean safety profile could position it uniquely in the growing PD market.

Sub-licensing is key for safinamide's success

Safinamide is partnered with Meiji Seika in Japan/Asia and with Zambon in the rest of the world. Zambon does not have a significant presence in certain regions, including the US, hence sub-licensing safinamide will be key to maximising its potential. Zambon, working together with Newron, is aiming to have a potential deal executed this year, ahead of safinamide US approval potentially in H115.

Orphan drugs could propel Newron to the next stage

The pipeline beyond safinamide consists of three Phase II orphan drugs, which Newron could potentially commercialise alone. These include sNN0031 for severe PD and sNN0029 for ALS/Lou Gehrig's disease, both from the NeuroNova acquisition, and sarizotan for Rett syndrome. If Newron has sufficient cash, pivotal trials for all three could start next year, which could allow for first launch from 2017.

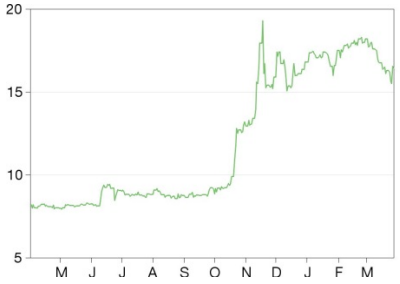
Valuation: Risk-adjusted NPV of €253m/CHF317m

We value Newron at €253m/CHF317m or CHF26.8/share based on a risk-adjusted NPV analysis, including current net cash, safinamide in PD, the portfolio of orphan drugs and NW-3509, which is being actively developed ahead of out-licensing. Current net cash of €23.8m, including a recent private placement and commitments from third parties, should be sufficient to fund operations to H215 beyond key value inflexion points, including safinamide regulatory approval decisions and potential sub-licensing.

31 March 2014

Price	**CHF16.4**
Market cap	**CHF194m**
	€0.8/CHF
Net cash (€m) at end December 2013	17
Shares in issue	11.8m
Free float	75%
Code	NWRN
Primary exchange	SIX
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(9.9)	(9.9)	100.2
Rel (local)	(8.8)	(1.5)	86.9
52-week high/low	CHF19.3		CHF7.9

Business description

Newron Pharmaceuticals is an Italian biotechnology company focused on CNS diseases. Its most advanced drug, safinamide, has completed Phase III trials for Parkinson's disease and has been filed in Europe. Safinamide is partnered with Zambon and Meiji Seika.

Next events

Safinamide US filing	End-April
Safinamide sub-licensing	2014
Safinamide EU approval	Q414
Safinamide US approval	H115

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Investment summary

Company description: CNS focus with late-stage PD asset

Newron is an Italian company that was spun of Pharmacia & Upjohn in 1999 around safinamide, which at the time was in preclinical development for epilepsy. Safinamide was originally partnered with Serono, which was then acquired by Merck KGaA, which returned rights in 2011. Since then Newron has successfully re-partnered safinamide with Meiji Seika in Japan/Asia and with Zambon in the rest of the world. Phase III development has been completed and safinamide has been filed in Europe, and US filing is anticipated in coming weeks. Safinamide could be the first add-on Parkinson's disease (PD) drug to work across all stages of disease, from first diagnosis through disease lifetime. Combined with once-a-day dosing and a clean safety profile, safinamide could have a unique profile in the growing PD market.

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 (now Newron Sweden). Newron is based in Bresso, Italy, and employs 23.

Exhibit 1: Newron pipeline

Product	Indication		Stage	Comments
Safinamide	Parkinson's disease		Filed	Filed in Europe 5 December 2013; US filing anticipated by end April
sNN0031	Treatment resistant PD	Orphan	Phase II	Phase II planned to start Q114
sNN0029	ALS	Orphan	Phase II	Phase II at higher dose planned to start Q114
Sarizotan	Rett syndrome	Orphan	Phase II	Start of pilot Phase II trial in Q314
NW-3509	Schizophrenia	Partnering	Phase I	Phase I ongoing; Newron plans to complete poc and then out-license
Ralfinamide	Neuropathic pain	Non-core	Phase II	Partnering candidate
HF0220	Alzheimer's disease	Non-core	On hold	Partnering candidate
HF0299	Neuropathic pain	Non-core	Phase I	Partnering candidate

Source: Edison Investment Research

Valuation: Risk-adjusted NPV of CHF317m or CHF26.8/share

We value Newron at €253m/CHF317m or CHF26.8/share, based on a risk-adjusted NPV analysis using a 12.5% discount rate. Our rNPV includes €23.8m net cash, safinamide for PD, the portfolio of orphan drugs and NW-3509, which Newron intends to out-license. We do not include non-core assets, which could all be partnering candidates. Safinamide is the most advanced product, having been filed in Europe, and constitutes the bulk of our valuation (65%). The current share price is more than underpinned by safinamide and current cash, with the portfolio of orphan drugs essentially a free option.

Sensitivities: Safinamide sub-licensing and approvals

The main sensitivity for Newron in the next 12-18 months will be safinamide sub-licensing and regulatory approvals. Safinamide has been filed in Europe and US filing is planned by end April. To ensure successful commercialisation and to maximise safinamide's potential, Newron's partner Zambon will need to secure additional partners in regions where Zambon does not have a presence. These include the key US market. We have limited visibility on the timelines or terms of any potential sub-licensing deal terms.

Financials: Cash runway to H215

Newron reported FY13 net cash of €17m, which together with €2.9m from a private placement and €3.9m of commitments from third parties suggests post year-end net cash of €23.8m. This should be sufficient to fund operations to H215, taking Newron beyond key value inflexion points, including regulatory approval decisions and potential sub-licensing. Our forecasts only include a milestone for US filing and do not include any safinamide royalties, approval milestones or sub-licensing income.

Outlook: Safinamide sets the stage

Safinamide is Newron's lead drug candidate for the treatment of Parkinson's disease (PD). It has successfully completed four Phase III trials and was recently filed in Europe, with US filing anticipated by the end of April. This could allow for potential launches in early 2015. Newron is working with partner Zambon to sub-license safinamide in certain regions, including the US, which will be important for successful commercialisation. Safinamide could have a unique profile in the growing PD market, which we value at CHF16.3/share, based on peak sales potential of €500m. Newron also has a pipeline of orphan drugs, which we value at CHF7.3/share, which it could commercialise alone, in addition to a number of out-licensing opportunities.

Safinamide success

Safinamide has been filed in Europe as an add-on treatment for both early and mid-late stage PD and US filing is anticipated by end April, which could allow for launches in early 2015. Safinamide is partnered with Meiji Seika in Japan/Asia, and with Zambon in all other regions. Sub-licensing in territories where Zambon does not have a presence, such as the US, will be essential to maximise safinamide's potential. Safinamide could be the first add-on drug for all stages of PD, from first diagnosis through disease lifetime. Combined with once-a-day dosing and a clean safety profile safinamide is uniquely positioned in PD. In addition, data from Phase III studies suggest that safinamide could have a potential anti-dyskinetic effect in patients with baseline dyskinesia.

Orphan opportunity

Beyond safinamide is a pipeline of three orphan drugs that Newron could potentially commercialise alone. We value these at CHF7.3/share. If Newron has sufficient cash, all of these could enter pivotal trials in 2015. Newron also has a number of potential out-licensing candidates, including NW-3509 for schizophrenia, which Newron intends to partner once proof-of-concept data are available. A summary of Newron's pipeline is shown in Exhibit 1.

Key newsflow in the next 12-18 months

The key catalysts in the next 12-18 months will be safinamide related, with US filing in coming weeks. Sub-licensing will be crucial for maximising safinamide's sales potential, assuming regulatory decisions are positive. A summary of anticipated newsflow is shown in Exhibit 2.

Exhibit 2: Anticipated newsflow

News	Period	Comments
sNN0031 and sNN0029	Q114	Start of additional Phase II
Safinamide US filing	end-April	US filing will trigger milestone income from partner Zambon
NW-3509	Q214	Phase I data
Sarizotan start of Phase II	Q314	Small pilot trial prior to a pivotal trial in 2015
sNN0031 and sNN0029	H214	Data from Phase II
NW-3509	Q414	Start of Phase IIa
Safinamide EU approval	YE14	Assuming standard review timelines and filing on 5 December 2013; will trigger milestone income from Zambon
Safinamide sub-licensing	2014	Working to sub-license safinamide in regions where Zambon does not have a presence
sNN0031 & sNN0029	H115	Start of pivotal Phase III trial
Sarizotan	H115	Data from pilot Phase II trial
Safinamide US approval	Q215	Assuming standard review timelines and filing by end April 2014; will trigger milestone income from Zambon
Sarizotan	H215	Start of pivotal Phase III trial
NW-3509	2015	Phase IIa data which could trigger a partnership
sNN0031, sNN0029 and sarizotan	2016	Data from pivotal trials and decision on commercial strategy (alone or with a partner)

Source: Edison Investment Research

Exhibit 3: Overview of Parkinson's disease (PD)

What is PD?	PD is a progressive, irreversible neurodegenerative disorder. It is arises by a lack of dopamine in the brain, owing to the death/damage of dopamine-generating cells in the substantia nigra. The cause of this cell death is unknown. Dopamine is a neurotransmitter used to control movement, and its loss leads to the main PD symptoms (described below).
How many people are affected by PD?	The American Parkinson Disease Association estimates there are around 1.5 million Americans affected by PD; the Parkinson's Disease Foundation estimates there are nearly one million US patients, with 60,000 diagnosed a year. The European Parkinson's Disease Association estimates there are around 1.2 million patients affected in Europe. Prevalence increases with age, with the typical age of onset >50 years old.
What are the symptoms of PD?	Dopamine is used to regulate and control movement; hence the lack of it in PD patients leads to movement disorders. The main motor symptoms associated with PD are: (1) tremors, often a resting tremor; (2) bradykinesia (slow movement); (3) rigidity; and (4) instability, especially when standing. Later on, cognitive and behavioural symptoms develop.
Treatment	There is no cure for PD, with treatment instead targeting the symptoms of PD. Drug treatment is usually effective for a period at managing motor symptoms, however, as the disease progresses and there is a greater loss of dopamine producing neurons, this becomes ineffective. There are a number of different classes of therapeutic molecules available: ■ **Levodopa:** standard treatment for PD, L-dopa is converted to dopamine in the brain; combined with carbidopa to prevent nausea and metabolism outside the brain; increasing dose and prolonged use of L-dopa is associated with development of dyskinesia (involuntary movement) known as levodopa-induced dyskinesia, or PD-LID. ■ **Dopamine agonists**: mimic the action of dopamine; often prescribed as early treatment. ■ **COMT inhibitors**: used in combination with L-dopa to prolong its effect by blocking its breakdown. ■ **MAO-B inhibitors:** prevent breakdown of dopamine in the brain by blocking monoamine oxidase type B; can be used in early PD as well as in combination with L-dopa.

Source: Edison Investment Research

Exhibit 4: Summary of safinamide Phase III data (primary endpoint in bold; mid-late stage PD shaded)

Trial	Design	Key efficacy and safety data
Study 015/017	n=269 50-100 or 100-200mg od 6 months ('015) with 12 month f/u ('017) Add-on to stable single DA dose Early PD patients	UPDRS III (mean change from baseline) ■ **6 months, placebo corrected: 50-100mg: -1.9 (p=0.0419); 100-200mg: -0.4 (p=ns)** ■ 18 months: pbo: -2.0; 50-100mg: -4.7 (p=0.019); 100-200mg: -1.3 (p=ns) Responder rate (defined as at least a 30% improvement in UPDRS III) ■ 6 months: pbo: 36.4%; 50-100mg: 50.6% (p=0.0447); 100-200mg: 54.3% (p=0.0183) ■ 18 months: pbo: 24%; 50-100mg: 43% (p=0.016); 100-200mg: 28% (p=ns) Safety and tolerability ■ Dropout rate (at 6 months): pbo: 10%; 50-100mg: 10%; 150-200mg 21% ■ Nausea most common AE but only 1-2% more common than pbo (ns) Note: '017 missed the primary endpoint of time to intervention
MOTION	n=679 50 or 100mg od 6 months with 18 month extension Add-on to stable single DA dose Early PD patients	UPDRS III (mean change from baseline, DA-ITT population only, placebo corrected) ■ **6 months: 50mg: -0.70 (p=ns); 100mg: -1.20 (p=0.04)** Quality of Life improvement at 6 months ■ EQ-5D: pbo: -0.04; 50mg: -0.01 (p=ns); 100mg: +0.01 (p=0.0051) ■ PDQ39: pbo: -0.12; 50mg: -1.19 (p=ns); 100mg: -1.81 (p=0.0389) Safety and tolerability ■ Dropout rate of c 11% across all treatment groups ■ Most common AEs: nausea, dizziness, somnolence, headache and back pain; ns differences Note: MOTION missed the primary endpoint in the ITT population
Study 016/018	n=669 50 or 100mg od 6 months ('016) with 18 month f/u ('018) Add-on to L-dopa Mid-late stage PD patients	Increase in mean daily "ON" time (ON time without dyskinesia + ON time with minor dyskinesia) ■ **6 months, pbo corrected: 50mg: +0.51 hours (p=0.008); 100mg: +0.55 hours (p=0.005)** ■ 24 months, pbo corrected: 50mg: +0.67 hours (p=0.003); 100mg: +0.83 hours (p=0.0002) Total daily "OFF" time (decrease in an improvement) ■ 6 months, pbo corrected: 50mg: -0.6 hours (p=0.002); 100mg: -0.6 hours (p=0.003) ■ 24 months, pbo corrected: 50mg: -0.62 hours (p<0.01); 100mg: -0.75 hours (p<0.01) Safety and tolerability ■ Dropout rate of c 11% across all treatment groups ■ No significant differences between groups in the incidence of withdrawals, SAEs or notable AEs Note: '018 missed the primary endpoint of decreased dyskinesia
SETTLE	n=549 50-100mg od 6 months Add-on to L-dopa and standard of care Mid-late stage PD patients	Increase in mean daily "ON" time (ON time without dyskinesia + ON time with minor dyskinesia) ■ **6 months, pbo corrected: 0.96 hours improvement (p<0.001)** Total daily "OFF" time (decrease is an improvement) ■ 6 months, pbo corrected: -1.03 hours (p<0.001) Change in UPDRS III during ON time ■ 6 months, pbo corrected: 1.82 point improvement (p=0.003) Quality of life improvement at 6 months ■ EQ-5D, pbo corrected: 0.038 index score improvement (p=0.019) ■ PDQ39, pbo corrected: 2.3 index score improvement (p=0.006) Safety and tolerability ■ Dropout rate of c 12% across both treatment groups ■ Most common AEs were nausea, urinary tract infections, falls, back pain and dyskinesia

Source: Edison Investment Research. Note: od=once daily; f/u= follow up; DA=dopamine agonist; pbo=placebo; ns=not significant; AE=adverse event; ITT=Intent to treat; EQ-5D=European Quality of Life; PDQ39=Parkinson's Disease Quality of Life.

Safinamide: Unique Parkinson's disease proposition

Safinamide has successfully completed four Phase III trials, two in early PD and two in mid-late stage PD. Overall, safinamide was well tolerated, with a c 11-12% dropout rate across all trials. In total, safinamide has been tested in over 1,500 patients, with around 1,000 treated for at least one year. The key Phase III safinamide data are shown in Exhibit 4 and summarised below.

Early-PD data

In the MOTION trial, high dose safinamide (100mg) in the modified ITT population (excludes 13 patients not on stable underlying dopamine agonists) showed a mild, but statistically significant, 1.2 placebo corrected point improvement (p=0.04) on the physician assessed UPDRS III[1] motor symptom score at six months. This translated into a more pronounced benefit in patient reported QoL (Quality of Life) outcomes, with high-dose safinamide demonstrating a significant improvement in both Parkinson's disease QoL (PDQ39, p=0.04) and European QoL (EQ-5D, p=0.005) at six months. In the unadjusted ITT population, safinamide did not hit the primary endpoint, with a 1.04 placebo corrected improvement in UPDRS III (p=0.073).

Mid-late stage PD data

In the SETTLE trial, 50-100mg of safinamide demonstrated a significant one hour improvement in daily "ON" time versus placebo (p<0.01). ON time is a measure of controlled symptoms, which was measured including time without dyskinesia and time with minor dyskinesia recorded over 18 hours per day in patient reported diaries. Safinamide also demonstrated significant improvement in daily OFF time (OFF time is when mobility is impaired), UPDRS III during ON time, and significant improvement at six months in PDQ39 (p=0.006) and EQ-5D (p<0.001). These data are consistent with and reinforce findings from the prior Phase III 016/018 trials where safinamide was associated with significant long-term QoL benefits out to 18-24 months.

There were significantly more 'responders' in the 50-100mg safinamide arm versus placebo; responders were defined as those with either a 20% or 30% improvement in motor symptoms as measured by UPDRS III. Within these responders, significantly more safinamide-treated patients did not experience worsening in activities of daily living. Safinamide also demonstrated a rapid onset of action, with significant improvements in ON and OFF-time observed from week two. Significantly more patients on safinamide who experienced at least a one-hour improvement in daily ON and OFF time were associated with at least a 30% improvement in motor symptoms (p=0.018).

Potential to improve dyskinesia and no dietary restrictions

Safinamide has multiple mechanisms of action, 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. Glutamate expression has been associated with dyskinesia, with blocking of glutamate potentially reducing dyskinesia. Hence, this glutamate inhibition could potentially improve dyskinesia. Although this has not been investigated in a prospective study, data from study 018 suggest that 100mg safinamide improves dyskinesia in patients with moderate dyskinesia at baseline (p=0.03). Further studies investigating this effect could be included as part of any potential sub-licensing deal(s). In contrast to other MAO-B inhibitors including rasagiline, safinamide does not appear to have a tyramine interaction, hence avoiding any dietary restrictions (such as cheese and red wine).

[1] UPDRS (Unified Parkinson's Disease Rating Scale) is a widely used scale to follow the course and progression of PD. UPDRS III is a physician assessed score of motor symptoms.

Safinamide could be an add-on for all stages of PD

In the US there are 1-1.5m PD patients; we estimate around 80% of PD patients receive treatment, suggesting a total treated PD patient population of around 1m (taking the mid-way point). There is a similar-sized market in Europe, and a smaller market of around 250k in Japan. Safinamide could be used to treat all stages of PD and we assume can reach peak penetration of 10% of treated PD patients six years post launch. We assume a price of $7/day in the US and €3.7/day in Europe and Japan (around a 20% discount to the US price), which compares favourably to other PD products, including rasagiline (which will go generic in 2017. Based on these assumptions, we arrive at peak sales of around €500m in the US, Europe and Japan.

An add-on to existing treatment

Safinamide is being positioned as an add-on rather than a monotherapy treatment in PD. It can be used in combination with DAs agonists in early PD and with L-dopa in mid-late stage patients. This means patients can remain on safinamide throughout their life, without physicians having to switch treatment with disease progression, which could facilitate use. Both DAs and L-dopa are now generic, hence expensive drug combinations should not be an issue or barrier to safinamide's use. Both DAs and L-dopa are well established in the treatment of PD, hence the biggest competition to safinamide, 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.

Partnered globally but seeking additional sub-licences

Safinamide was partnered with Meiji Seika in Japan/Asia, and with Zambon in all other regions during 2012. This followed partner Merck KGaA returning all rights to Newron in 2011. Serono originally in-licensed safinamide in 2006 and was subsequently acquired by Merck KGaA.

Zambon is a private Italian company with 2012 revenues of €550m, with the pharmaceutical division contributing 84% and the chemicals division 16%. The main focus of the pharma division is respiratory, pain management and women's health. Zambon does not have a significant pharmaceutical sales presence in the US and hence sub-licensing in this and certain regions will be central to maximising safinamide's potential. Newron is eligible for regulatory related milestone payments from Zambon (we assume US and EU filing and approval) and to 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.

Orphan drug portfolio could shape Newron's future

Following the end 2012 acquisition of NeuroNova, the pipeline consists of three Phase II compounds targeting orphan indications. Newron is actively developing these compounds, which it could potentially commercialise alone. We value the orphan drug portfolio, including sNN0031 for severe PD, sNN0029 for Lou Gehrig's disease and sarizotan for Rett syndrome, at CHF7.3/share, based on a risk-adjusted NPV analysis.

sNN0031 for advanced treatment resistant PD

sNN0031 is a potential treatment for severe PD that is infused into the brain via an implanted catheter. It has completed a Phase I/II study where it was well-tolerated. A further Phase II study is planned this year, prior to starting a potentially pivotal Phase II/III global study in 2015. sNN0031 is based around platelet-derived growth factor (PDGF), a naturally occurring protein that can stimulate cell division. Newron has received a €6m grant from the European Commission to support additional studies.

sNN0031 is thought to act on stem and progenitor cells in the brain and preclinical studies in rats demonstrated nerve cell restoration and reduced PD-like behaviour. In the most recent Phase I/II study, sNN0031 administration was well tolerated with no dropouts (n=12) and no severe side effects, with patients followed for more than two years. Motor symptoms improved in most patients, and a dose response in dopamine activity in areas of the brain damaged by PD was observed. A further Phase II will be initiated to gain additional experience and data with the dose and device.

Once additional data are available, Newron could start a pivotal Phase II/III trial during 2015 in around 180 patients, which could potentially allow for data in 2016. Newron estimates there are around 180,000 patients in the US and Europe who could be eligible for treatment with sNN0031, consistent with estimates from the European Medicines Agency of around 90,000 patients with advanced idiopathic Parkinson's disease with severe motor fluctuations and not responding to oral treatment in Europe alone.[2]

Based on this market, and assuming pricing of €30,000 (similar to Duodopa, an intestinal gel that is administered via an external pump and tube inserted directly into the duodenum), we arrive at peak sales in the US and Europe of €200m by 2024. As comparison, Duodopa generated 9m13 sales of $129m (c €100m) in Europe alone where it has been approved for nearly 10 years (it is not yet approved in the US). We assume sNN0031 penetration will be slightly lower than the implied 4-5% achieved by Duodopa, given administration into the brain rather than the stomach.

sNN0029 for ALS (Lou Gehrig's disease)

sNN0029 is a potential treatment for amyotrophic lateral sclerosis (ALS). In common with sNN0031, it is administrated into the brain via an implanted catheter. It has completed an initial Phase I/II study and a higher dose will be studied in a further Phase II study due to start in coming months. sNN0029 is based around vascular endothelial growth factor (VEGF), a protein used in blood vessel formation.

ALS, or Lou Gehrig's disease, is a progressive neurodegenerative disorder affecting both upper (in the brain) and lower (in the spinal cord) motor neurons. Patients lose the ability to control muscle movement, leading to atrophy (muscle wasting). Early symptoms include muscle weakening, often in the arms and legs, with death generally due to respiratory failure. Average survival is two to three years, with a 20% five-year survival rate and 10% surviving for longer than 10 years. US prevalence is around 25,000 patients, with c 5,000 diagnosed each year. The only approved treatment for ALS is Rilutek (riluzole), which has modest efficacy; a Cochrane review[3] concluded that it is "reasonably safe and probably prolongs median survival by about two to three months".

In mice models, reduced VEGF has been associated with neuron degeneration, potentially suggesting that VEGF could be used to improve motor neuron survival. In preclinical ALS models sNN0029 has shown slowing disease progression and increased life-span. An 18 patient Phase I/II has been completed with a dose response observed on a number of efficacy parameters.

Following data from the higher dose study later this year, Newron could initiate a potentially pivotal Phase II/III in 2015, if the trial design can be agreed by health authorities, with data in 2016, suggesting potential launch in 2018. Peak sales of €200-300m could be possible with even a relatively conservative 10% penetration of the c 50,000 US/EU ALS patient market, based on pricing of around €40,000 per year.

NeuroNova concluded a licensing deal with Genentech/Roche in 2009 allowing development of VEGF in ALS; Genentech has an opt-in in certain regions, including the US. In 2013 Newron was awarded a €2.5m grant from the Wellcome Trust to support further trials examining higher doses.

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2 www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500006499.pdf

3 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001447.pub3/abstract

Sarizotan for Rett syndrome

Sarizotan is a potential treatment for life-threatening breathing disorders associated with Rett syndrome (RS). RS is a genetic neurodevelopmental disorder that generally affects girls, arising from a spontaneous genetic mutation. RS affects between one in every 10,000 to 15,000 female births (source: US NIH). According to the IRSF (International Rett Syndrome Foundation) sudden death occurs in around 25% of RS patients, with studies speculating that possible causes could include respiratory failure and apnoea, owing to an underlying disorder in the heart's electrical activity. Research suggests that RS is associated with a prolonged QT interval[4] (a measure of the heart's electrical activity).

Sarizotan modulates activity of serotonin and dopamine receptors in the brain. It was in-licensed from Merck KGaA in 2011, having previously been discontinued in PD following the failure of two Phase III trials in 2006. Merck has a buy-back option that can be executed upon completion of proof-of-concept trials; if executed, this triggers a co-development option for Newron.

In preclinical studies sarizotan has demonstrated reduced apnoea and corrected irregular breathing in RS mouse models. There is already a substantial safety database accumulated with prior development in PD. Hence, a small pilot trial could start this year, followed by a pivotal trial next year to secure regulatory approval, which could be as early as 2017. Newron estimates there is a potential market of around 30,000-40,000 RS patients in the US and Europe, of which around 25% are affected by life-threatening breathing disorders. We assume pricing of €60,000k a year, higher than '029 and '031, reflecting the ultra-orphan indication. As no treatment options currently exist, we forecast 40% penetration of the targeted patients, representing 10% penetration of the overall RS population, suggesting potential peak sales of around €260m. Pricing and penetration will ultimately depend on sarizotan's magnitude of benefit; if sarizotan can command pricing of €80,000k a year with 70% penetration, this would suggest peak sales of around €600m.

Out-licensing opportunities

Newron has a number of assets, both from internal development and from acquisitions, which could all be candidates for partnering. NW-3509 is in active development as a potential treatment for schizophrenia and Newron intends to complete the ongoing Phase I and subsequent proof-of-concept development prior to seeking a partner. In addition, there are a number of non-core assets we do not include in our valuation (including ralfinamide and other compounds in various stages of early clinical development acquired with Hunter-Fleming), where investment is limited but all could be candidates for partnering.

NW-3509 for schizophrenia

NW-3509 could be used in schizophrenia as an add-on treatment to antipsychotics. It has shown benefits in preclinical models of psychosis, mania, depression, anxiety and cognition and is currently in Phase I development in the US in healthy volunteers to assess safety and tolerability. Prior to partnering, Newron intends to conduct a proof-of-concept trial in patients with schizophrenia who are experiencing breakthrough symptoms despite being on standard of care.

The antipsychotic market is worth around $23bn. However, until proof-of-concept data are available, estimating NW-3509's peak sales potential is challenging. For the purposes of our valuation, we conservatively assume that NW-3509 could achieve peak sales of c $500m, representing c 2% of the current market. We include spend for the ongoing Phase I and planned proof-of-concept trial and then assume a partnership in exchange for royalties and milestones.

[4] Ellaway C J, Sholler G, Leonard H. et al Prolonged QT interval in Rett syndrome. Arch Dis Child 1999. 80470–472.472.

Sensitivities

Newron is subject to the usual biotech risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, financing and commercial risks. Safinamide has already completed Phase III development and data have been reported. Hence, the main sensitivity for Newron in the next 12-18 months will be regulatory approval in both Europe and the US, in addition to commercial execution risk, including sub-licensing in regions such as the US.

Safinamide has been filed in Europe in two indications; as an add-on to dopamine agonists in early PD and as an add-on to L-dopa in mid-late stage PD. Approvals could therefore be granted in either, both, or neither indications. We believe the safety database should be sufficient for regulators. However, the MOTION trial in early-stage PD did not hit the primary endpoint (mean change in UPDRS III from baseline), although when 13 patients who were not on stable underlying dopamine agonists (one of the key inclusion criteria) were excluded from the analysis, safinamide did hit the primary endpoint. Although we are not aware that regulators have defined the boundaries for clinically relevant changes in UPDRS III, research suggests[5] that the minimal clinically important difference in UPDRS III is around 2.3-2.7 points; in the high dose safinamide group, the mean change from baseline in UPDRS III was around 2 points (1.2 placebo corrected).

Newron is working with partner Zambon to sub-license safinamide in certain key regions, including the US. We have limited visibility on the potential timing and terms of any sub-licences. A lack of US partner prior to US approval could delay launch beyond our current forecasts.

Newron has sufficient cash and cash commitments to fund operations into H215 according to our model. This does not factor in any milestone income on safinamide approvals, nor any income from sub-licensing in the US, which could extend the cash runway.

Valuation

We value Newron at €253m/CHF317m or CHF26.8/share (shown in Exhibit 5), based on a risk-adjusted NPV analysis, which includes €23.8m net cash (see the Financials section for details on the cash position) and uses at 12.5% discount rate. Our valuation includes forecasts for safinamide in PD, in addition to contributions from the orphan drug pipeline and NW-3509, which Newron plans to out-license. We do not include any contributions from non-core assets.

Exhibit 5: Newron rNPV valuation

Product	Indication	Launch	Peak sales (€m)	NPV (€m)	Probability	rNPV (€m)	rNPV (CHFm)	NPV/share (CHF/share)
Safinamide	Parkinson's disease	2015	500	171.2	90%	154.7	193.4	16.3
sNN0031	Severe PD	2018	200	87.5	25%	16.2	20.2	1.7
sNN0029	ALS	2018	250	117.5	25%	23.8	29.7	2.5
Sarizotan	Rett syndrome	2017	260	166.5	20%	29.3	36.7	3.1
NW-3509	Schizophrenia	2019	380	54.5	15%	5.6	6.9	0.6
Net cash/(debt)				23.8	100%	23.8	29.7	2.5
Valuation				**621.1**		**253.3**	**316.7**	**26.8**

Source: Edison Investment Research

For safinamide we assume Newron will receive a 10% royalty from partner Meiji Seika in Japan and could receive royalties starting at 11% in the US and Europe. As part of the deal with Zambon Newron receives a double-digit undisclosed royalty on sales made by Zambon, and will receive 50% of royalties from any sub-licensing. Hence the royalty rate will be dependent on the precise deal terms that Newron and partner Zambon can negotiate in the US. We assign a 90% probability

[5] Shulman LM et al. The clinically important difference on the unified Parkinson's disease rating scale. Arch Neurol. 2010 Jan;67(1):64-70.

of success, reflecting that safinamide has been filed in Europe and filing is anticipated in the US, with safinamide contributing CHF16.3/share (65%) to our valuation, largely underpinning the current share price.

If a US sub-licensing deal cannot be secured prior to US safinamide approval, this could delay US launch beyond our current forecasts. A 12-month delay to US launch could have an adverse impact on our safinamide valuation of around CHF2/share. If safinamide is approved and pricing is double our current forecast in the US/Europe/Japan, then peak sales would be closer to €1bn, suggesting a safinamide valuation of around CHF33/share. Conversely, if penetration of safinamide is around half of our current expectation, then based on our current pricing assumptions, safinamide would be worth around CHF10/share.

For the orphan drug portfolio of sNN0031, sNN0029 and sarizotan, our valuation currently assumes that Newron will commercialise these alone, rather than with a partner. Hence our valuation is based on our estimates for potential sales (discussed earlier in this report), in addition to the R&D and S&M spend needed to secure regulatory approval and to market the products in Europe and the US. We assign a 25% probability of success to both '031 and '029, both of which have already completed initial Phase II development, with higher doses planned to be investigated prior to commencing pivotal trials. We assign a slightly lower 20% probability to sarizotan and 15% to NW-3509, reflecting the earlier stage of development, and execution risk around partnering NW-3509.

Financials

Newron reported cash at end December of €18.4m, which together with debt of €1.4m, relating to an Italian government grant of €5m awarded in 2008 that is repayable over 10 years, suggests net cash at end 2013 of €17m. In January, Newron raised a further €2.9m from issuing 211k shares as part of a private placement to JPMorgan at CHF17/share. In addition, Newron has €3.9m of cash commitments from third parties (EU grant, Wellcome trust grant and money from Zambon towards the completion of safinamide filing). This suggests post year-end net cash of €23.8m.

We estimate cash should be sufficient to fund operations to H215. This should take Newron beyond regulatory approval decisions anticipated by YE14 in Europe, where it was filed in December, and during H115 in the US, assuming filing in coming weeks. We do not include any royalty income for safinamide in our revenue forecasts until formal approval. In addition, our estimates only include a milestone payment (<€1m) from partner Zambon for US filing. We do not include any milestone payments for regulatory approvals in the US or Europe, which we estimate together could be around €11m. We do not include any potential milestone income from safinamide sub-licensing.

If approved, safinamide could launch in early 2015, which would lead to royalty income, which we do not include in our revenue forecasts until formal approval. Our revenue forecast in 2014 includes €0.3m licensing income, which represents the remaining deferred income as part of the €5m upfront received from Zambon on licensing safinamide, which is being recognised over the period to completion of safinamide filing. We also include €0.8m milestone income for safinamide US filing.

Our future R&D forecasts include spend to complete the planned further Phase II trials for both '029 and '031, in addition to a pilot study with sarizotan and completion of NW-3509 proof-of-concept development. Beyond these, we include R&D spend for a pivotal trial for one of the orphan drugs.

Our forecasts include €6.5m and €14.4m illustrative financing in 2015 and 2016, respectively, which we class as a long-term liability for the purposes of our model. Safinamide approval milestones, royalties and sub-licensing income could extend the cash runway beyond our current forecast.

Newron is based in Italy and reports financials 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 €0.8/CHF.

Exhibit 6: Financial summary

€000s	2010	2011	2012	2013	2014e	2015e	2016e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS							
Revenue	806	4,289	8,924	3,539	800	0	0
Cost of Sales	0	0	0	0	0	0	0
Gross Profit	806	4,289	8,924	3,539	800	0	0
Research and development	(15,922)	(3,822)	(3,534)	(4,537)	(6,000)	(7,500)	(7,000)
EBITDA	(21,789)	(6,570)	(2,760)	(7,815)	(12,372)	(15,028)	(14,901)
Operating Profit (before amort. and except.)	(21,667)	(6,499)	(2,710)	(7,786)	(12,340)	(14,995)	(14,868)
Intangible Amortisation	27	17	13	10	24	24	24
Exceptionals	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Operating Profit	(21,640)	(6,482)	(2,697)	(7,776)	(12,316)	(14,971)	(14,844)
Net Interest	(33)	45	200	63	191	(14)	(14)
Profit Before Tax (norm)	(21,700)	(6,454)	(2,510)	(7,723)	(12,149)	(15,009)	(14,882)
Profit Before Tax (FRS 3)	(21,673)	(6,437)	(2,497)	(7,713)	(12,126)	(14,986)	(14,858)
Tax	1,128	(8)	122	615	0	0	0
Profit After Tax (norm)	(20,572)	(6,462)	(2,388)	(7,108)	(12,149)	(15,009)	(14,882)
Profit After Tax (FRS 3)	(20,545)	(6,445)	(2,375)	(7,098)	(12,126)	(14,986)	(14,858)
Average Number of Shares Outstanding (m)	6.6	7.3	8.2	11.5	11.7	11.8	11.8
EPS - normalised (€)	(3.11)	(0.89)	(0.29)	(0.62)	(1.04)	(1.27)	(1.26)
EPS - normalised and fully diluted (€)	(3.11)	(0.89)	(0.29)	(0.62)	(1.04)	(1.27)	(1.26)
EPS - (IFRS) (€)	(3.11)	(0.89)	(0.29)	(0.62)	(1.03)	(1.27)	(1.26)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0	N/A	N/A
EBITDA Margin (%)	N/A	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	N/A
BALANCE SHEET							
Fixed Assets	6,026	5,937	11,900	9,821	9,826	9,831	9,835
Intangible Assets	5,188	5,171	11,199	9,125	9,122	9,119	9,116
Tangible Assets	128	56	72	79	87	95	102
Investments	710	710	629	617	617	617	617
Current Assets	13,106	7,629	32,747	21,797	12,039	4,658	4,645
Stocks	396	246	233	301	301	301	301
Debtors	2,557	1,469	2,811	2,088	2,088	2,088	2,088
Cash	8,087	5,367	29,243	18,426	8,873	1,491	1,479
Other	2,066	547	460	982	777	777	777
Current Liabilities	(4,635)	(2,827)	(11,585)	(6,070)	(4,791)	(5,387)	(5,330)
Creditors	(4,635)	(2,472)	(11,230)	(5,712)	(4,433)	(5,029)	(4,972)
Short term borrowings	0	(355)	(355)	(358)	(358)	(358)	(358)
Long Term Liabilities	(2,306)	(4,154)	(5,454)	(4,458)	(4,400)	(10,581)	(24,654)
Long term borrowings	0	(1,802)	(1,447)	(1,087)	(729)	(6,910)*	(20,983)*
Other long term liabilities	(2,306)	(2,352)	(4,007)	(3,371)	(3,671)	(3,671)	(3,671)
Net Assets	12,191	6,585	27,608	21,090	12,674	(1,479)	(15,504)
CASH FLOW							
Operating Cash Flow	(17,973)	(4,884)	6,015	(10,071)	(12,355)	(13,486)	(14,010)
Net Interest	0	0	0	1	191	(14)	(14)
Tax	(1,128)	8	(122)	(615)	154	0	0
Capex	(7)	(1)	(11)	(56)	(40)	(40)	(40)
Acquisitions/disposals	0	0	9,971	301	0	0	0
Financing	4,787	0	8,378	(20)	2,855	(21)	(21)
Dividends	0	0	0	0	0	0	0
Net Cash Flow	(14,321)	(4,877)	24,231	(10,460)	(9,195)	(13,562)	(14,086)
Opening net debt/(cash)	(22,408)	(8,087)	(3,210)	(27,441)	(16,981)	(7,786)	5,776
HP finance leases initiated	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Closing net debt/(cash)	(8,087)	(3,210)	(27,441)	(16,981)	(7,786)	5,776	19,862

Source: Edison Investment Research, Newron Pharmaceuticals accounts. Note: *Includes €6.5m and €14.4m illustrative financing as long-term debt in 2015 and 2016, respectively.

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

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2010-14e	N/A	ROCE 2013	N/A	Gearing 2013	N/A	Litigation/regulatory	●
EPS 2012-14e	N/A	Avg ROCE 2010-14e	N/A	Interest cover 2013	N/A	Pensions	○
EBITDA 2010-14e	N/A	ROE 2013	N/A	CA/CL 2013	N/A	Currency	◖
EBITDA 2012-14e	N/A	Gross margin 2013	N/A	Stock days 2013	N/A	Stock overhang	◖
Sales 2010-14e	N/A	Operating margin 2013	N/A	Debtor days 2013	N/A	Interest rates	○
Sales 2012-14e	N/A	Gr mgn / Op mgn 2013	N/A	Creditor days 2013	N/A	Oil/commodity prices	○

Management team

CEO: Stefan Weber

Mr Weber was appointed CEO in 2012, having been CFO since 2005 and having successfully executed 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

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. Mr Anand completed his medical training in the US, specialising in psychiatry and neurology.

VP Business Development: Marco Caremi

Mr Caremi has held senior positions at Newron since 2002. He has more than 30 years of experience in the pharmaceutical industry, including business development at both Schwarz Pharma and Schering-Plough. He holds a degree in natural sciences from the University of Milan and the Advanced Development Programme from the London Business School.

General Manager Newron Sweden: Anders Haegerstrand

Mr Haegerstrand joined Newron through its acquisition of NeuroNova, where he was CSO since 2004, having previously been CEO since 2000. Prior to this, he was at both Astra and then AstraZeneca involved in the CNS and pain teams. He has a medical degree from the Karolinska Institute in Stockholm, where he also completed a PhD and became associate professor in Neuroscience.

VP Finance: Roberto Galli

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 he is a chartered auditor.

Principal shareholders	(%)
Investor AB	12.8%
Zambon Group	12.5%
Aviva	6.0%
Omega	2.9%
TVM	2.5%
Abingworth	1.8%
JPMorgan	1.8%

Companies named in this report

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

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