EDISON

Newron Pharmaceuticals

R&D update

Evenamide down but not out

Pharma & biotech

Newron's plans for its novel mechanism of action drug, Evenamide, due to enter late-stage development for schizophrenia, have been delayed. Specifically, the FDA has requested that Newron carry out additional short-term safety studies before larger, pivotal-stage clinical trials can be undertaken. This has taken us and the market by surprise, as we had expected the two Phase II/III trials to start in Q219 as per guidance. The delay is a setback and we therefore push back our launch expectations by 18 months to 2024, erring on the side of caution. We now value Newron at CHF653m vs CHF714m previously.

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	8.6	(14.2)	(0.79)	0.0	N/A	N/A
12/20e	21.7	(3.5)	(0.20)	0.0	N/A	N/A

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

Regression to Phase I studies unexpected

The emergence of safety concerns from preclinical models is unexpected given that positive clinical safety data were reported from the Phase I/IIa proof-of-concept study of Evenamide (March 2017). The concerns raised by the FDA related specifically to a chronic toxicity study in rats and CNS events observed in dogs at higher doses, which could be related to a class effect for the drug. Management will meet with the FDA to discuss what is required in more detail, but has indicated that additional preclinical and clinical safety studies (presumably Phase I in healthy volunteers) are likely to be required before a Phase III study is cleared by the regulators. We now estimate that registrational studies will not start until late-2020/early-2021, pushing back a potential launch to early-2024 (from late-2022).

Sarizotan and Xadago development plans on track

Newron remains well funded through key near-term inflections, including top-line data from the pivotal study of sarizotan in Rett syndrome (Q419) and its subsequent regulatory filing (2020), and the start of a label extension study for its commercial Parkinson's disease (PD) drug Xadago for levodopa-induced dyskinesia (Q319). Newron reported net cash of €43.9m at end December 2018 and has access to an additional €40m loan facility through the European Investment Bank (EIB).

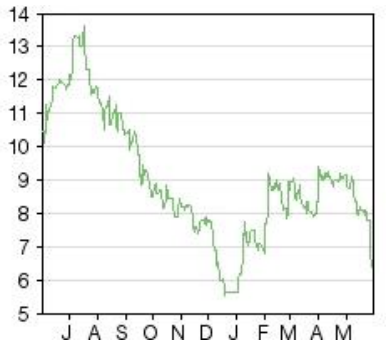
Valuation: CHF653m or CHF36.6/share

Our valuation of Newron has decreased to CHF653m from CHF714m. We have reduced the probability of success for Evenamide to 30% (from 50%), given that it is now likely to require an additional Phase I study, and pushed back its launch to 2024. Our valuation remains heavily skewed to Xadago and sarizotan, which represent 56% and 26% of our rNPV valuation, respectively. Sales of Xadago need to ramp up to reach our peak sales forecast of €679m.

31 May 2019

Price	**CHF6.37**
Market cap	**CHF113m**
	€0.89/CHF; $1.01/CHF; $1.12/€
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	(30.3)	(26.6)	(41.9)
Rel (local)	(28.7)	(27.8)	(47.1)
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

Additional FDA feedback on Evenamide Phase IIb/III trial	Mid-2019
Sarizotan Phase III STARS data	Q419
Sarizotan NDA filing	2020

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Edison profile page

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Safety first, safety second

Following the initial announcement, management followed up with an analyst call during which it highlighted that the concerns raised by the US FDA related to recently completed preclinical studies, including recent (undisclosed) findings from a long-term (26-week) toxicology study in rats and undisclosed CNS events observed in dogs on higher doses of Evenamide. These specifically related to Evenamide, as the studies did not relate to any combinations with atypical antipsychotics. Management has guided that these could be associated with commonly observed class effects related to the mechanism of action through which Evenamide works (inhibition of voltage-gated sodium channels). Management has guided that long-term preclinical toxic studies (26 to 52 weeks) are unlikely to be required and that sufficient preclinical safety data can be generated from short-term studies (four to eight weeks). However, the likely requirement to conduct another Phase I clinical study (50–60 healthy volunteers), even in parallel to preclinical work, will significantly affect development timelines; we note that the original Phase I study for Evenamide (conducted in 54 healthy volunteers) took 18 months to complete. With this in mind, we do not anticipate that Newron will be able start the originally proposed registrational studies for 18 months, which takes into account time frames to interact with the FDA, agree an appropriate study plan, analyse data and present the findings. Following receipt of further guidance from the FDA, we will revise these assumptions.

Cross-supportive studies remain the most likely path

Newron had been in active discussions with several regulatory bodies, including an end of Phase II meeting with the US FDA in Q218, to design two cross-supportive Phase IIb/III clinical trials for Evenamide in two schizophrenia patient populations, which Newron had previously expected to start in Q219 and complete in H220.

- **Study 003/005 for non-treatment resistant patients**: chronic schizophrenic patients inadequately responding to atypical antipsychotic monotherapy (risperidone, aripiprazole, paliperidone, olanzapine or quetiapine). This trial will evaluate the efficacy, safety and tolerability of three fixed doses of Evenamide (or placebo) as an **add-on to the patient's current atypical antipsychotic medication.**
- **Study 004/006 for treatment-resistant patients**: defined as treatment-resistant schizophrenia (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 the efficacy, safety and tolerability of two fixed doses of Evenamide (or placebo) as **add-on to clozapine.**

We expect that Newron should be back on track to start these pivotal studies once the supportive explanatory studies have been completed. Regulators had indicated that 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 alone is positive, another confirmatory Phase III trial would be needed for this larger patient subset. We note that this scenario would require us to revisit our forecasts.

Exhibit 1: Likely approval pathways following Phase IIb/III studies

		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. Note: APD – antipsychotic drug.

As an add-on to atypical antipsychotic drugs (APD) in the wider schizophrenia patient population, the scope for Evenamide is potentially huge and Newron would need to partner for the wider schizophrenia indication (add-on to any APD). However, Newron could elect to market the smaller indication of TRS as defined by resistance to clozapine by itself, and could rapidly capture this smaller subset of patients if breakthrough designation was granted.

Valuation

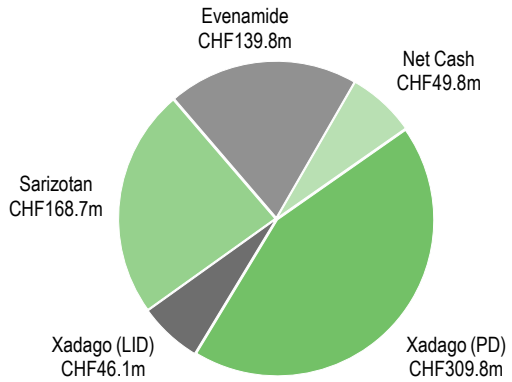
Our revised valuation of Newron is CHF653m (CHF36.6/share), down 8.5% from our previous valuation of CHF714m (CHF40.1/share) (Exhibits 3 and 4). This downgrade stems from reducing our probability of success for Evenamide to 30% from 50% to reflect the need for additional preclinical and Phase I studies, and delaying potential launch from late-2022 to early-2024. We have pushed back Evenamide-associated R&D to reflect the timing of the start of the larger, more costly Phase II/III programme. Additionally, we have rolled forward our model and updated FX rates. Our valuation includes Xadago peak sales in Parkinson's disease, in addition to risk-adjusted contributions from Xadago for PD-related levodopa-induced dyskinesia (LID), sarizotan in Rett syndrome (RS) and Evenamide in schizophrenia. The breakdown of our rNPV valuation, using a 12.5% discount rate for clinical-stage assets and a 10% discount rate for commercially available asset Xadago, is shown in Exhibit 2.

Exhibit 2: Newron sum-of-the-parts valuation

Product	Indication	Launch	Peak sales* (€m)	NPV (€m)	NPV (CHFm)	Probability	rNPV (€m)	rNPV (CHFm)	rNPV/share (CHF/share)
Xadago	Parkinson's disease	2015	679	280.6	314.9	100%	280.6	314.9	17.6
	Dyskinesia	2021	358	84.1	94.3	50%	42.2	47.4	2.7
Sarizotan	RS	2021	574	540.8	606.9	30%	152.2	170.8	9.6
Evenamide	Schizophrenia	2024	960	245.3	275.3	30%	62.9	70.5	4.0
Net cash at 31 December 2018				43.9	49.2	100%	43.9	49.2	2.8
Valuation				**1,194.6**	**1,340.6**		**581.7**	**652.8**	**36.6**

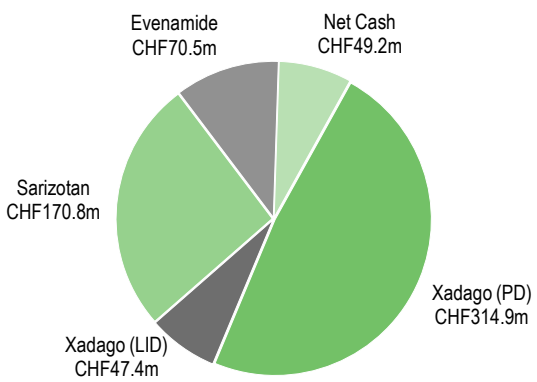
Source: Edison Investment Research. Note: *FX changes have increased our forecast peak sales slightly.

Exhibit 3: Previous rNPV split



Source: Edison Investment Research

Exhibit 4: Revised rNPV split



Source: Edison Investment Research

Exhibit 5: Financial summary

€000s	2016	2017	2018	2019e	2020e
Year-end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	6,726	13,428	4,025	8,559	21,689
Cost of Sales	0	0	0	0	0
Gross Profit	6,726	13,428	4,025	8,559	21,689
Research and development (net)	(12,398)	(8,596)	(9,835)	(13,160)	(15,620)
EBITDA	(15,290)	(4,298)	(14,931)	(14,255)	(3,603)
Operating Profit (before amort. and except.)	(15,318)	(4,332)	(14,967)	(14,277)	(3,626)
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)	(14,301)	(3,644)
Net Interest	121	(955)	(41)	111	93
Profit Before Tax (norm)	(15,197)	(5,287)	(15,008)	(14,166)	(3,533)
Profit Before Tax (reported)	(15,204)	(5,301)	(15,019)	(14,190)	(3,551)
Tax	(33)	19	(16)	0	0
Profit After Tax (norm)	(15,230)	(5,268)	(15,024)	(14,166)	(3,533)
Profit After Tax (reported)	(15,237)	(5,282)	(15,035)	(14,190)	(3,551)
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)	(79.39)	(19.80)
EPS - (reported) (€)	(1.04)	(0.32)	(0.84)	(0.80)	(0.20)
Dividend per share (c)	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	48,154	47,255
Stocks	5	5	0	0	0
Debtors	9,667	12,714	15,659	15,000	15,000
Cash	46,468	60,081	43,853	33,154	32,255
Other	0	0	0	0	0
Current Liabilities	(6,645)	(4,727)	(4,281)	(5,000)	(5,544)
Creditors	(6,281)	(4,727)	(4,281)	(5,000)	(5,544)
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	42,760	41,317
CASH FLOW					
Operating Cash Flow	(19,616)	(8,404)	(16,108)	(10,770)	(953)
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)	(10,699)	(900)
Opening net debt/(cash)	(40,205)	(46,104)	(60,081)	(43,853)	(33,154)
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)	(33,154)	(32,255)

Source: Company accounts, Edison Investment Research

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