EDISON

Addex Therapeutics

Positive preclinical data

Dipraglurant data supports orphan disease focus

Pharma & biotech

Positive preclinical data for dipraglurant in dystonia supports progression into a Phase II study for rare dystonias in H113. Phase II results (Q413), if positive, could trigger a larger Phase IIb trial (2014). Addex continues to target a dipraglurant partnership for Parkinson's disease (PD), which may be informed by upcoming Phase II results (Q213) for Novartis's competing mGlu5 inhibitor (AFQ056). While Addex is currently financed to end-2013, potential deals and/or financings could extend the cash runway. A planned NASDAQ listing (timing tbc) in our view, could be a prelude to a financing.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
12/11	3.7	(29.8)	(4.0)	0.0	N/A	N/A
12/12	0.0	(26.7)	(3.4)	0.0	N/A	N/A
12/13e	0.0	(14.2)	(1.6)	0.0	N/A	N/A

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

Positive dipraglurant preclinical data in dystonia…

Addex has reported positive preclinical data for dipraglurant (an oral mGlu5 inhibitor) in a validated model of primary generalised tortional dystonia 1 (DYT1), a severe genetic form of dystonia (involuntary muscle spasms). The drug showed a dose-dependent normalisation of neuronal over-excitation in the brains of transgenic DYT1 mice. These results build on the existing body of supportive preclinical data (tottering mouse model, MPTP monkey) for dipraglurant in treating rare dystonia.

…supports progression into Phase II trial in H113

Positive preclinical data for dipraglurant in dystonia are supported by anecdotal findings in the Phase II study in Parkinson's disease levodopa-induced dyskinesia (PD-LID), where the drug reduced L-dopa-induced dystonia in four patients. We expect a pilot Phase II study in rare dystonia to start in Q213 and render data in Q413. In parallel, Addex continues to target a partnership for the PD indication. Separately, Novartis's Phase II study of the modified dose formulation of AFQ056 (oral mGlu5 inhibitor) in PD-LID is due to readout shortly (April 2013); this could determine the fate of this compound (a potential positive/negative catalyst for Addex), which has shown activity in PD-LID but with tolerability issues.

Financials: Cash runway into late 2013

Addex had cash of CHF15.3m at year-end 2012. We project operating expenditure of CH15m for 2013, including restructuring related costs. On these projections, and barring new partnerships and/or financing, Addex is financed to year-end 2013.

Valuation: Risk-adjusted NPV of CHF218m

We value Addex at CHF218m ($234m) or CHF25.40 per share. Our rNPV assumes industry-standard success rates for drugs based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813.

19 April 2013

Price	**CHF6.50**
Market cap	**CHF58.5m**
	CHF1.07/USD
Net cash (CHFm)	0.4
Shares in issue	9m
Free float	45.3%
Code	ADXN
Primary exchange	SIX
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(13.2)	(35.0)	(31.1)
Rel (local)	(10.3)	(36.8)	(43.9)
52-week high/low		CHF12.4	CHF6.3

Business description

Addex Therapeutics is a Swiss biotech company with a leading position in the identification of allosteric modulators with activity in CNS, inflammatory and metabolic disease. Its pipeline includes two Phase II compounds, with one partnered with J&J.

Next events

Start Dipraglurant Phase II in rare dystonia	Q213
Start ADX71441 Phase I in CMT1a	Q213
Results of Dipraglurant Phase II in rare dystonia	Q413
Results of ADX71441 Phase I in CMT1a	Q413

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Edison profile page

Addex datasheet

Exhibit 1: Addex clinical/late-preclinical R&D pipeline

Programme	Mechanism	Indication	Notes
Dipraglurant	mGlu5 NAM	PD-LID	76-pt Phase II study completed. Intention to partner for further development.
		Dystonia	Small proof-of-principle Phase II study with IR formulation planned. Subsequent studies with ER formulation.
ADX71149/ JNJ-40411813	mGlu2 PAM	Schizophrenia	105-pt Phase II study completing. 92-subject part as adjunctive (add-on) therapy in pts who do not fully respond to antipsychotics, reported in November 2012 as positive (no specific results disclosed, as per normal J&J policy).Small part as monotherapy in sub-acute psychosis (treatment-naïve pts) terminated.
		Anxiety (co-morbid with major depression)	94-pt Phase II study as adjunctive (add-on) treatment in depression with anxiety symptoms. JNJ-40411813 will be an administered bid, following fixed and flexible schedules, at doses ranging from 25mg to 150mg. Patients will take the same daily dose of antidepressant throughout the study. Results: August 2013.
ADX71441	$GABA_BR$ PAM	Charcot-Marie-Tooth neuropathy; spasticity in MS	Phase I study in healthy volunteers to start H113 – will assess safety, tolerability and initial biological activity via biomarker pharmacology (results: H213). Plan for Phase II in Charcot-Marie-Tooth neuropathy (CMT1A) in 2014.
N/D	mGlu4 PAM	MS	Clinical candidate selection targeted this year, with IND-enabling studies possible in 2014. Proof-of-concept in a validated model of multiple sclerosis (RR-EAE).

Source: Edison Investment Research

Exhibit 2: Addex's preclinical assets

Programme	Indication(s)	Notes
ADX71441	alcohol dependence/OAB/OA pain	Activity shown in mouse model of alcohol binge drinking. Acute administration of ADX71441 resulted in a dose-dependent suppression of alcohol intake, achieving 80% reductions at higher doses (10, 30mg/kg) vs vehicle treatment. Effect of more robust and longer-lasting than with naltrexone, a positive control. Prior lead compounds have shown activity in models of anxiety, OAB and OA pain. Tool compounds have shown efficacy in rodent models of PD including reversal of haloperidol induced catalepsy (HIC) in rats. Previously partnered with Merck & Co, but rights were returned in 2011.
mGlu7 NAM	Depression/anxiety	Lead compound ADX71743 showed potential in treatment of anxiety. Presentation.
mGlu2 NAM	Alzheimer's disease/ depression	Lead compound ADX92639 showed significant, dose-dependent reversal of memory deficit in Alzheimer's model. Preclinical data presented on tool compound RO4491533 on novel object recognition model and in a genetic model of depression.
TrkB PAM	Neurodegeneration	Oral candidates identified against a target that has been intractable to conventional approaches. Potential for treating various neurodegenerative diseases.
TNF R1 NAM	Autoimmune disease	Oral products could be brain penetrant, hence possible development in indications characterised by neurological inflammation (Alzheimer's, MS, depression).
GLP1 PAM	Type II diabetes	Identified tractable GLP1 PAM compounds with increased insulin secretion in presence of suboptimal GLP1 concentrations. These compounds are progressing through lead generation.
A2AR PAM	Inflammation	Partnership with Viva Biotech to advance oral small molecule compounds targeting A2AR activation for the treatment of inflammatory diseases. Viva is providing fully-integrated structural biology discovery services for A2AR PAMs identified using Addex's HTS technologies.

Source: Edison Investment Research

Exhibit 3: Dipraglurant Phase II study results

Study	76-pt pts (dipraglurant, n=52; pbo, n=24) with moderate or severe PD-LID. Pts followed a dose-titration regimen, receiving 50mg, initially 1/day rising to 3/day, from days 1-14 and then 100mg, up to 3/day, from days 14-28. 47-pts completed dosing regimen per protocol. Dyskinesia was provoked by taking peak levodopa dose (LID occurs 60-90mins later), and evaluated at days 0, 1, 14 and 28.
Subjects	Male/females with idiopathic PD and experiencing moderately disabling dyskinesia (screening visit UPDRS 33 score≥2) and an mAIMS score at baseline ≥7 with a score ≥3 in at least one body area. Deep brain stimulation pts were included in the covariate analysis and did not affect the outcome.
Safety/tolerability (primary endpoint)	The 50mg and 100mg doses were both well tolerated, with incidence of adverse events similar in active and placebo (88.5% vs 75%). Typical mGlu5-type AEs (vertigo, visual disturbance, feeling drunk) were seen in <10% of pts on dipraglurant but were not severe or dose limiting. There were no significant changes in any safety monitoring parameters, and in particular, no changes in liver function tests were seen in either treatment group.
Modified Abnormal Involuntary Movement Scale (mAIMS).	Peak mAIMS reduction. Statistically significant on day one (19% vs 4.1% at 50mg; p=0.042) and day 14 (32.3% vs pbo 12.6% 100mg; p=0.038), non-significant at day 28 (31.1% vs pbo 21%, 100mg, NS), because of higher placebo response. Targeted magnitude of effect (defined as either a 30% reduction or a 20% separation from pbo) achieved at day 14 (32.7%) and day 28 (27.5%). AUC0-3 showed c 20% difference on day one and c 30% reductions at days 14 (p=0.042) and 28 (NS).
Patient-reported LID diaries.	Showed increase in "on-time, without dyskinesia" averaging c 30-45 mins (eg 2-2.3hrs vs 1.6hrs) and up to 70 mins. No increase in "off-time" and a c 50 min/day reduction was seen at week four.
PD rating scales (UPDRS part III, CGIC & PGIC)	UPDRS Part III (motor scores) unchanged at all time points, indicating that dipraglurant did not interfere with levodopa efficacy. Dipraglurant also shown to reduce dystonia severity in addition to chorea. In patients with levodopa-induced dystonia, dipraglurant reduced dystonia severity. PGIC and CGIC scales show higher percentages reporting improvement for dipraglurant.

Source: Edison Investment Research

Sensitivities

Addex has a cash runway with cash to the end of 2013. With the new focus on orphan diseases, the key risks to the investment case relate to successful completion of clinical studies for ADX71441 and dipraglurant by year-end 2013. While preclinical and limited clinical data are supportive, the outcome of these studies is difficult to call. Another key sensitivity is Addex's ability to secure an economically attractive partnership for dipraglurant in PD-LID; in our view, absence of a deal in 2013 could raise questions on the drug's overall risk/benefit profile.

Longer-term sensitivities include the success or failure of competitors (now principally Novartis's mavoglurant) and Addex's reliance on J&J as a partner for JNJ-40411813. Addex has a single substantial shareholder, Biotech Value Fund, which owns a ~27% stake. Visium Asset Management has taken a 5% stake in the recent fund-raising.

Valuation

Our current valuation of Addex is $234m (CHF218m), equivalent to CHF25.40 per share. The valuation is based on the risk-adjusted net present value of Addex's lead programmes and market dynamics are reflected in the peak sales projections. Our rNPV includes dipraglurant in both orphan (dystonia) and non-orphan (PD-LID) indications, along with JNJ-40411813 in schizophrenia and anxiety. We do not currently include ADX71441 (CMT1A) or mGlu4 PAM (multiple sclerosis) in our financial model, given their early stage of development, so they represent pure upside to our forecasts and valuation.

Our rNPV model assumes industry-standard success probabilities (eg 35% for a Phase II compound) based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813 (in line with the terms of the licensing deal). It also assumes estimated costs of development up to the point of expected licensing, and in the case of JNJ-40411813 a probability-adjusted contribution from known milestones.

Exhibit 4: Edison risk-adjusted NPV inputs

Product	Indication	Stage	Launch year	Probability	Peak market share	Potential market size ($bn)
Dipraglurant IR	PD-LID	Phase II	2016	35%	25%	2.0
Dipraglurant ER	Non-PD dystonia	Phase II	2016	35%	15%	0.5
JNJ-40411813	Schizophrenia	Phase II	2015	35%	3%	16.0
JNJ-40411813	Anxiety/other	Phase II	2015	35%	5%	4.0

Source: Edison Investment Research

Financials

Edison's financial model is shown in Exhibit 5. This incorporates the recent financial FY12 results (year-end cash of CHF15.3m) and projected cash burn of CHF15-16m for FY13.

For FY13, we assume a significant reduction in R&D to CHF12m (previously CHF23m) and G&A to CHF2.5m (previously CHF7m). We also assume c CHF2m of exceptional costs related to the restructuring (ie termination benefits). On these projections, and in the absence of licensing agreements, Addex is funded to year-end 2013. Thus, our revised financial model no longer assumes a CHF8m financing during this period.

Exhibit 5: Financial summary

Year ending 31 December	CHF'000s	2009	2010	2011	2012	2013e
PROFIT & LOSS						
Revenue		4,503	4,000	3,743	121	0
Cost of sales		0	0	0	0	0
Gross profit		4,503	4,000	3,743	121	0
EBITDA		(39,044)	(29,353)	(27,163)	(24,661)	(12,643)
Operating profit (before GW and except.)		(41,758)	(32,178)	(29,607)	(26,719)	(14,229)
Amortisation		(121)	(116)	(63)	(40)	(20)
Share-based payments/other		(1,175)	(1,304)	(1,304)	(251)	(251)
Exceptionals		0	0	0	0	(2,000)
Operating profit		(43,054)	(33,598)	(30,974)	(27,010)	(16,500)
Net interest		362	(48)	(167)	(8)	0
Profit before tax (norm)		(41,396)	(32,225)	(29,774)	(26,727)	(14,229)
Profit before tax (FRS 3)		(42,692)	(33,645)	(31,141)	(27,018)	(16,500)
Tax		0	0	0	0	0
Profit after tax (norm)		(41,396)	(32,225)	(29,774)	(26,727)	(14,229)
Profit after tax (FRS3)		(42,692)	(33,645)	(31,141)	(27,018)	(16,500)
Average number of shares outstanding (m)		5.7	6.1	7.5	7.9	8.6
EPS - normalised (CHF)		(7.2)	(5.3)	(4.0)	(3.4)	(1.7)
EPS - FRS 3 (CHF)		(7.4)	(5.6)	(4.2)	(3.4)	(1.9)
Gross margin (%)		100.0%	100.0%	100.0%	100.0%	N/A
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		10,155	7,689	5,548	4,714	3,313
Intangible assets		182	84	32	98	93
Tangible assets		9,568	6,568	3,964	2,089	693
Refund from assumption of dev costs		0	0	0	0	0
Other		405	1,037	1,551	2,527	2,527
Current assets		78,399	66,495	38,068	17,020	2,172
Stocks		0	0	0	0	0
Debtors		737	1,199	667	906	906
Cash		76,560	63,797	36,065	15,256	408
Other		1,102	1,499	1,336	858	858
Current liabilities		(10,890)	(9,277)	(8,728)	(4,655)	(4,655)
Trade payables		(4,524)	(3,147)	(1,686)	(709)	(709)
Short term borrowings		0	0	0	0	0
Provisions		0	0	(215)	(65)	(65)
Finance lease liabilities		0	0	0	0	0
Other current liabilities		(5,679)	(5,835)	(6,828)	(3,881)	(3,881)
Current portion deferred income		(687)	(295)	0	0	0
Long Term Liabilities		(83)	(592)	(1,052)	(789)	(789)
Long-term borrowings		0	0	0	0	0
Provisions		(83)	(592)	(1,052)	(789)	(789)
Deferred income		0	0	0	0	0
Deferred taxes		0	0	0	0	0
Other long-term liabilities		0	0	0	0	0
Net assets		77,581	64,314	33,836	16,290	41
CASH FLOW						
Operating cash flow		(39,376)	(31,341)	(26,551)	(28,824)	(12,643)
Net interest		315	(48)	(167)	(8)	0
Tax		0	0	0	0	0
Capex		(4,137)	(408)	(167)	(219)	(190)
Acquisitions/disposals		0	0	0	0	0
Financing		315	19,851	(183)	9,639	0
Dividends		0	0	0	0	0
Other		(73)	(452)	(15)	(1,398)	(2,015)
Net cash flow		(42,957)	(12,397)	(27,083)	(20,809)	(14,848)
Opening net debt/(cash)		(119,471)	(76,560)	(63,797)	(36,065)	(15,256)
HP finance leases initiated		46	(366)	(649)	0	0
Other		(0)	0	0	0	0
Closing net debt/(cash)		(76,560)	(63,797)	(36,065)	(15,256)	(408)

Source: Edison Investment Research, Addex Therapeutics

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