Addex Therapeutics

Competitor setback in large Phase II study

Edison investment research

Lilly issues may give Addex a boost

Biotech & pharma

Addex has seen an unexpected boost to the prospects for its lead partnered product, JNJ-40411813, as a result of a trial setback reported recently with Lilly's pomaglumetad methionil, a mechanistically-close competitor. The news may allow Janssen Pharmaceuticals, Addex's partner, to catch up with a rival that had hitherto been several years ahead. Both products aim to up-regulate mGluR2, but Lilly's is an orthosteric mGluR2/3 agonist, while Addex's is a more selective mGluR2 PAM. Meanwhile J&J is completing its own Phase II study in schizophrenia and is starting a Phase II study in anxiety co-morbid with depression.

Year end	Revenue (CHFm)	PBT* (CHFm)	EPS* (CHF)	DPS (CHF)	P/E (x)	Yield (%)
12/10	4.0	(32.2)	(5.3)	0.0	N/A	N/A
12/11	3.7	(29.8)	(4.0)	0.0	N/A	N/A
12/12e	0.6	(22.7)	(2.9)	0.0	N/A	N/A
12/13e	0.6	(17.9)	(2.3)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation and exceptional items.

Lilly suffers setback with pomaglumetad methionil

Eli Lilly has reported a negative result in a pivotal 880-patient Phase II study of pomaglumetad methionil in acute exacerbations of schizophrenia. This was intended to be one of two trials designed to support a registration filing in acute schizophrenia. The result will inevitably delay this key competitor for Addex/J&J. Lilly intends to "review the future development" on the basis of data from this and other studies.

JNJ-40411813 data to come in Q4

Meanwhile J&J's Phase II study of JNJ-40411813 in schizophrenia remains on track to read out in Q4. J&J has also just started a separate Phase II trial of JNJ-40411813 as an add-on treatment in anxiety present with depression.

Plan to seek partnership in 2012

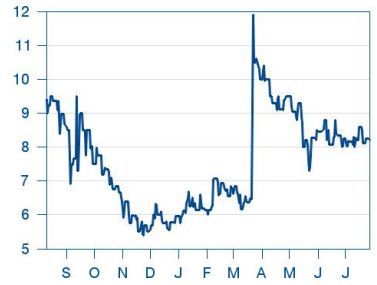
Addex continues its concerted campaign to secure a global licensing deal for dipraglurant, its internal lead molecule, following the recent positive results in Parkinson's disease levodopa-induced dyskinesia (PD-LID). These data were recently presented at the Movement Disorders Society. The drug also has wider potential in symptomatic PD and may allow earlier use of levodopa, which is currently limited by concerns of the development of dyskinesias.

Valuation: Risk-adjusted NPV of CHF227m

We maintain our risk-adjusted NPV of $232m/CHF227m, which when adjusted for forecast end 2012 cash is equivalent to CHF31.58/share. We assume industry-standard success probabilities for compounds based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813.

	30 July 2012
Price	CHF8.25
Market cap	CHF64m
	CHF0.986/US$
Shares in issue	7.7m
Free float	38%
Code	ADXN
Primary exchange	SIX
Other exchanges	N/A

Share price performance



%	1m	3m	12m
Abs	-10.4	25.3	-19.0
Rel (local)	-6.7	30.9	-9.3
52-week high/low	CHF11.9	CHF5.4	

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 (one partnered with J&J).

Next events

H1 results	Late July

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Addex datasheet

Addex's core R&D programmes			
Product	**Indication**	**Stage**	**Notes**
JNJ-40411813	Schizophrenia/ anxiety/other	Phase II	mGluR2 PAM. 105-pt Phase II study in schizophrenia and 94-pt Phase II study as adjunctive therapy for anxiety co-morbid with depression (see below). Partnered with **Johnson & Johnson**.
Dipraglurant	PD-LID/dystonia	Phase II	mGluR5 NAM. 72-pt, four wk Phase II study completed in PD-LID with positive results. IR version for PD-LID; ER version for dystonia/other CNS indications. See presentation and technical document.
ADX71441	OA Pain/overactive bladder	IND enabling studies	$GABA_BR$ PAM. IND planned for Q412. Study in female guinea pigs with bladder over-activity shows increase in inter contraction interval, a validated measure of bladder muscle control, in first 15 min post-admin vs vehicle. ADX71441 also decreased micturition frequency vs vehicle at 1mg/kg. Dose-dependent normalisation of urination latencies seen in a mouse diuretic stress-induced OAB and dose-dependent reduction of micturition frequency in furosemide-treated animals. Magnitude of effect similar to oxybutynin, without effects on body temperature, loco-motor activity or coordination.
ADX88178 (mGluR4 PAM)	Parkinson's disease	Lead candidate	Clinical candidate selection. Efficacy demonstrated in two preclinical rodent models of anxiety: the marble burying test in mice and EPM in mice and rats. Lead candidate(s) have demonstrated efficacy in preclinical models of in various acute/chronic animal models of Parkinson's disease and anxiety. See presentation.
GLP1R PAM	Type II diabetes	Lead opt	Preclinical data from tool compound ADX91886 in the db/db model show an insulin response and better control over blood glucose than vehicle or sitagliptin (a DPP-4 inhibitor, as active control).
TrkB PAM	Neuro-degenerative disease	Hit to lead	Lead optimisation. Oral candidates identified against a target that has been otherwise intractable to conventional approaches.
TNFR1 NAM	Autoimmune	Hit to lead	Hit to lead. Oral products could be brain penetrant, hence possible development in indications characterised by neurological inflammation (Alzheimer's, MS, depression).

JNJ-40411813 schizophrenia study	
Design	105-pt, two-part Phase II study consisting of two components: a 15-pt open-label dose-escalation study (as monotherapy) and a randomised 90 subject (c 60 active, 30 placebo) study as adjunctive add-on therapy in patients who do not fully respond to other antipsychotics (with residual positive symptoms or predominant negative symptoms or an inadequate response to clozapine). The two stages run in parallel and will be analysed separately. Open-label phase: starting dose of 50mg bid, increasing in steps to 150mg bid over up to 12 wks. Randomised phase: two different dose levels of 50mg bid and up to 150mg bid. Results: Q4.
Subjects	DSM IV diagnosis of schizophrenia >1 year with residual positive symptoms or predominant negative symptoms. Patients with insufficient response to clozapine can be enrolled in the randomised phase.
Primary endpoints	Safety as measured by Udvalg for Klinische Undersogelser (UKU) ratings, number of patients with abnormal clinical lab results, ECGs or physical exams, and AEs.
Secondary endpoints	Efficacy as measured by positive and negative syndrome scale (PANSS), clinical global impression – schizophrenia (CGI-SCH) and subjective wellbeing under neuroleptics scale.

JNJ-40411813 anxiety/co-morbid with depression study	
Design	94-pt Phase II study as adjunctive (add-on) treatment to antidepressants in depression with anxiety symptoms. Study has an up to two-week screening phase, an eight-week double blind, placebo controlled, treatment phase, and a two-week post-treatment follow up. Patients will take the same daily dose of antidepressant throughout the study; JNJ-40411813 will be administered bid, following fixed and flexible schedules, at doses ranging from 25mg to 150mg. Results: Aug 2013.
Subjects	Major depressive disorder (MDD); pts with a diagnosis of co-morbid Generalized Anxiety Disorder, Social Anxiety Disorder, or Panic Disorder may be included, if MDD is considered the primary diagnosis. A 17-item Hamilton Depression Rating Scale (HDRS17) total score ≥18, a HDRS17 anxiety/somatisation factor score ≥7.
Primary endpoints	Change from baseline in the Hamilton Anxiety Rating scale (HAM-A6) score.
Secondary endpoints	Change from baseline HDRS17 total score; change from baseline in Structured Interview Guide of the Hamilton Anxiety Scale 14-item HAM-A (SIGH-A) total score; change in the Clinical Global Impression – Improvement (CGI-I) scale.

Partnership terms for JNJ-40411813	
Upfront	€3m received on signing in December 2004.
Research	€4.2m in research funding was received during the research phase of the collaboration, which concluded in 2007.
Milestones	€112m in milestones are tied to clinical and regulatory events of which €3m have been received to date: €1m on Phase I initiation (June 2009), €2m on Phase II initiation (2011).
Royalties	Low double-digit royalties on worldwide sales.
Other	J&J is responsible for all costs of preclinical and clinical development.

Source: Edison Investment Research

Update: Competitive boost for JNJ-40411813

Addex has seen an unexpected boost to the prospects for its lead partnered product, JNJ-40411813, as a result of a trial failure with Lilly's pomaglumetad methionil, a mechanistically-close competitor. The news may allow Janssen Pharmaceuticals, Addex's partner, to catch up with a direct rival that has hitherto been several years ahead. Lilly's product is an orthosteric mGluR2/3 agonist, while the Addex licensed compound is a more selective, mGluR2 positive allosteric modulator.

Eli Lilly reported a negative result in its 880-pt Phase II study (known as H8Y-MC-HBBM) of pomaglumetad methionil in acute exacerbations of schizophrenia. It stated that there was no separation of pomaglumetad methionil from placebo in the primary efficacy endpoint (PANSS) in the overall or an (undisclosed) predefined genetic subpopulation for either of the two doses tested (40mg and 80mg BID), while the active control, risperidone, showed a separation from placebo in both of these populations.

The HBBM study was intended to be the first of two trials designed to support a registration filing for monotherapy use in acute schizophrenia. A second pivotal Phase III study, enrolling 1,100-patients (known as H8Y-MC-HBBN) is underway and scheduled to undergo an interim analysis later this year, with full results expected in February 2013. Results are also thought imminent from a 280-patient Phase II study (known as H8Y-MC-HBCO) of pomaglumetad methionil as an adjunctive (add-on) treatment with atypical antipsychotics in patients with prominent negative symptoms. Lilly is also conducting a 670-patient Phase III study directly comparing pomaglumetad with aripiprazole (results due October 2012).

Lilly states that data from the HBBN and HBCO studies will inform its decisions on the future development of pomaglumetad methionil. Although it is not unusual for studies to fail in CNS indications (for ultimately successful products), pomeglumetad methionil has now failed in two Phase II studies. An earlier Phase II study was reported to be "inconclusive" because of an unusually high placebo response. Lilly started its Phase III programme ahead of obtaining this result, which was presumably to short cut the development timeline.

Pomeglumetad methionil is a pro drug version of an earlier, now discontinued, mGluR2/3 agonist, LY404039, which reported some positive results in Phase II studies. The switch to the pro drug suggests LY404039 may have had PK or dosing limitations, and it is possible that pomeglumetad methionil, at the doses tested, may also have still had these (eg. inadequate penetration of the blood brain barrier).

Furthermore, Addex speculates that specific issues in the HBBM study design may have contributed to its failure, particularly its broad patient inclusion criteria and poorly-suited outcome measures. It believes that adjunctive (add on) therapy in patients who do not respond adequately to conventional anti-psychotics, is a more appropriate target for an mGluR2-targeted agent. If this is the case, it may become apparent if the outcome of the HBCO study (in this setting) is positive.

Up-regulation of glutaminergic activity via mGluR2 receptor, may offer an alternative way treat the positive[1] and the harder-to-treat negative[2] symptoms of schizophrenia, without the side effects such as weight gain, hyperprolactinemia or extrapyramidal symptoms associated with dopamine antagonists. Lilly's earlier mGluR2/3 agonist, LY404039, had shown efficacy in the control of schizophrenia symptoms without the side-effects of weight gain or extrapyramidal symptoms (movement disorders). The drug also showed activity in a Phase II study for anxiety. However, Addex

[1] Positive symptoms are those that normal individuals do not normally experience, but are present in people with schizophrenia. They are typically regarded as manifestations of psychosis and can include paranoid or bizarre delusions, disordered thoughts and speech, auditory or visual hallucinations, delusions etc.
[2] Negative symptoms are deficits of normal emotional responses or of other thought processes, and commonly include flat or blunted affect and emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships and lack of motivation. They respond less well to medication.

believes its product's specificity for mGluR2 receptor (which appears to be possible only as a result of allosteric binding mechanism) may confer advantages.

Nevertheless, the negative outcome in the HBBM study will certainly delay the product's timeline to registration (by perhaps 18 months or more) and if subsequent studies are also negative, it might prompt the termination of the programme altogether. Even if pomeglumetad is only delayed, the change in timelines will be valuable for J&J and its partner commercially, and we speculate that it could obviate the need for J&J to conduct a risky head-to-head study vs pomaglumetad to establish superiority.

JNJ-40411813 read out approaching

J&J-40411813 is in a Phase II study for schizophrenia (which has competed recruitment, and is due to read out in Q4) and has also just started a Phase II for anxiety co-morbid with depression. If the schizophrenia study is successful, J&J will presumably look to conduct a larger Phase IIb (including possibly as monotherapy) to prepare for a Phase III registration programme.

Typically, schizophrenia requires very large Phase III programmes (>2,000 patients) to achieve registration. In addition to cariprazine, which we expect will be filed shortly, there are four Phase III stage programmes (including pomaglumetad methionil) and five in Phase II (including JNJ-40411813). Competing programmes are shown in Exhibit 1.

Exhibit 1: Competing development programmes for schizophrenia (Phase II or later)

Drug	Company	Trial status/notes
cariprazine (RGH-188)	Forest/Richter/ Mitsubishi Tanabe	450-pt and 600-pt Phase III studies completed with positive results. Expected to be filed shortly. 700-pt Phase III study in prevention of relapse (results: Jul 2013). Separately in Phase III studies for bipolar disorder.
pomaglumetad methionil (LY2140023)	Eli Lilly	Failed 880-pt Phase II study. 1,100-pt Phase III study results: Feb 2013); 670-pt Phase III study vs aripiprazole (results: Oct 2012); 280-pt Phase II study (prominent negative symptoms (results: Jun 2012), 1,210-pt open label Phase II/III study (results: June 2015). 150-pt Phase III study to investigate physical dependence (results: Dec 2012).
OPC-34712	Otsuka/ Lundbeck	660-pt Phase III study (BEACON) and 630-pt Phase III study (VECTOR) (results: Mar 2013), 1,000-pt Phase III study (ZENITH) (results: Jan 2016). Dose finding Phase II/III study. Also 3x Phase III trials in depression (>2,500 pts in total).
bitopertin/ (RG1678/ RO4917838)	Roche	Three 630-pt Phase III studies (SUNLYTE, DAYLYTE and FLASHLYTE) in pts with persistent, predominant negative symptoms as add-on to antipsychotics (results: Jul 2015). Three 600-pt Phase III studies (NIGHTLYTE, MOONLYTE and TWILYTE) in pts with sub-optimal symptom control (results: Aug 2015). 300-pt Phase II study for acute exacerbations (results: Oct 2012).
Zicronapine	Lundbeck	160-pt Phase III study vs risperidone on metabolic parameters (results: Aug 2012).
BL-1020	BioLineRx	435-pt Phase II/III study vs risperidone and placebo (results: H1 13).
ALKS 9070	Alkermes	690-pt Phase III study in acute exacerbations (results: Apr 2013).
PF-02545920	Pfizer	260-pt Phase II study for acute exacerbation (completed)
TC-5619	Targacept	456-pt Phase IIb study for negative symptoms/cognitive dysfunction (results: May 2013).

Source: Edison Investment Research

BD campaign for dipraglurant continues

Addex continues its campaign to secure a licensing deal for the lead internal product, dipraglurant, following the positive Phase IIa data in Parkinson's disease levodopa-induced dyskinesia (PD-LID) reported earlier this year. These data were recently presented at the Movement Disorders Society.

Dipraglurant has to compete with a compound with the exact same mGluR5 NAM mechanism: the Novartis product, mavoglurant (AFQ056), which is in several Phase IIb studies for PD-LID, as well as for Fragile X syndrome (results of which are due in August). Novartis has conducted several Phase II studies of mavoglurant in PD-LID, including a dose-ranging Phase II study, although this suggested it been under-dosed. Novartis has initiated new Phase II studies involving higher doses (100mg/150mg bid) and with a modified release formulation that read out later this year.

Novartis continues to target a 2014 filing for mavoglurant in PD-LID, although this looks ambitious as its current Phase II studies do not report until H212 and this would certainly require a Phase III start

this year. Thus, in our view, if Addex is able to partner dipraglurant quickly, it could potentially match the hypothetical Novartis timeline. Results from the study can be found here.

Addex believes dipraglurant can be used in combination with levodopa or dopamine agonists or as a standalone treatment for PD-LID, PD-related motor symptoms, non-motor symptoms of PD and other movement disorders. It may also be effective in non-Parkinsonian dystonia (which covers conditions such as idiopathic torsion dystonia, generalised or cervical dystonia).

mGlur4 PAM preclinical data published

Addex separately announced the publication[3] of preclinical data on ADX88178, the lead compound in its mGluR4 PAM programme. The paper reports that ADX88178 has the potential to ameliorate the Parkinsonian symptoms as shown in two rodent models of dopamine depletion (haloperidol-induced catalepsy and induced forelimb akinesia). ADX88178 was shown to reverse haloperidol-induced catalepsy in rats at 3 and 10mg/kg and at forelimb akinesia at doses of 3, 10 and 30mg/kg when combined with L-DOPA.

Valuation

We maintain our valuation of Addex at $232m (CHF227m), which if adjusted for forecast end FY12 cash is equivalent to CHF31.58/share. The valuation is based on the risk-adjusted net present value of the two lead clinical stage programmes and the $GABA_B$ PAM (which is approaching the IND stage). Hence, all Addex's other assets represent pure upside. We assume 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). Market dynamics are reflected in the peak sales potential of products, hence if Lilly were to discontinue pomaglumetad methionil as a result of its setback, it should in principal result in a larger opportunity for JNJ40411813 (which would boost the value). The valuation assumes estimated costs of development up to the point of expected licensing, and in the case of JNJ-40411813, a probability-adjusted contribution from the known milestones.

Sensitivities

The recent positive result in the dipraglurant PD-LID study has significantly improved Addex's risk profile, although it still remains exposed in the short term to the outcome of the Phase II study of JNJ-40411813 in schizophrenia. Longer-term sensitivities (both on the upside and downside) include the success or failure of competitors (particularly Novartis's mavoglurant and Lilly's pomaglumetad methionil), and a reliance on its J&J as a partner. The investment case relies on the formation of an economically attractive partnership for dipraglurant, although investors should not be overly concerned about this given the strength of the data. Addex is relatively well funded, with cash to the end of 2013 (excluding any possible milestones from J&J).

Financials

Our financial model (shown in Exhibit 2) is unchanged, and shows a cash reach to the end of 2013. This shows R&D expenditure of CHF20m in 2012 and CHF15m in 2013. Addex has recently undergone a reorganisation that reduced its headcount by one-third that we estimate could save CHF2m in 2012 (net of one-off costs) and some CHF4-6m in 2013. A CHF5m financing requirement for 2013 is currently shown in the model as long-term debt.

[3] A potent and selective mGluR4 positive allosteric modulator improves movement in rodent models of Parkinson's disease. Journal of Pharmacology and Experimental Therapeutics, DOI:10.1124/jpet.112.196063.

Exhibit 2: Financial summary

Year ending 31 December	CHF'000s	2010	2011	2012e	2013e
PROFIT & LOSS					
Revenue		**4,000**	**3,743**	**600**	**600**
Cost of sales		0	0	0	0
Gross profit		4,000	3,743	600	600
EBITDA		**(29,353)**	**(27,163)**	**(21,674)**	**(17,163)**
Operating profit (before GW and except)		(32,178)	(29,607)	(22,856)	(17,876)
Amortisation		(116)	(63)	(40)	(20)
Share-based payments/other		(1,304)	(1,304)	(1,304)	(1,304)
Exceptionals		0	0	0	0
Operating profit		(33,598)	(30,974)	(24,200)	(19,200)
Net interest		(48)	(167)	200	0
Profit before tax (norm)		**(32,225)**	**(29,774)**	**(22,656)**	**(17,876)**
Profit before tax (FRS 3)		**(33,645)**	**(31,141)**	**(24,000)**	**(19,200)**
Tax		0	0	0	0
Profit after tax (norm)		(32,225)	(29,774)	(22,656)	(17,876)
Profit after tax (FRS3)		(33,645)	(31,141)	(24,000)	(19,200)
Ave no of shares out (m)		6.1	7.5	7.8	7.8
EPS - normalised (CHFc)		(5.3)	(4.0)	(2.9)	(2.3)
EPS - FRS 3 (CHFc)		(5.6)	(4.2)	(3.1)	(2.5)
Gross margin (%)		100.0%	100.0%	100.0%	100.0%
EBITDA margin (%)		N/A	N/A	N/A	N/A
Operating margin (before GW and except) (%)		N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed assets		**7,689**	**5,548**	**4,531**	**4,002**
Intangible assets		84	32	7	2
Tangible assets		6,568	3,964	2,972	2,449
Other		1,037	1,551	1,551	1,551
Current assets		**66,495**	**38,068**	**16,389**	**4,021**
Stocks		0	0	0	0
Debtors		1,199	667	667	667
Cash		63,797	36,065	14,386	2,019
Other		1,499	1,336	1,336	1,336
Current liabilities		**(9,277)**	**(8,728)**	**(8,728)**	**(8,728)**
Trade payables		(3,147)	(1,686)	(1,686)	(1,686)
Short term borrowings		0	0	0	0
Provisions		0	(215)	(215)	(215)
Other current liabilities		(5,835)	(6,828)	(6,828)	(6,828)
Current portion deferred income		(295)	0	0	0
Long Term Liabilities		**(592)**	**(1,052)**	**(1,052)**	**(6,052)**
Long-term borrowings		0	0	0	(5,000)
Provisions		(592)	(1,052)	(1,052)	(1,052)
Net assets		**64,314**	**33,836**	**11,140**	**(6,757)**
CASH FLOW					
Operating cash flow		**(31,341)**	**(26,551)**	**(21,674)**	**(12,163)**
Net interest		(48)	(167)	200	0
Capex		(408)	(167)	(190)	(190)
Financing		19,851	(183)	0	0
Dividends		0	0	0	0
Other		(452)	(15)	(15)	(15)
Net cash flow		(12,397)	(27,083)	(21,679)	(12,368)
Opening net debt/(cash)		**(76,560)**	**(63,797)**	**(36,065)**	**(14,386)**
HP finance leases initiated		(366)	(649)	0	0
Other		0	0	0	0
Closing net debt/(cash)		**(63,797)**	**(36,065)**	**(14,386)**	**(2,019)**

Source: Edison Investment Research