Addex Therapeutics

Restructuring, refocusing, realigning

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New orphan disease focus

Pharma & biotech

Addex is now focused on developing its clinical pipeline for rare diseases and will significantly reduce discovery activities. In 2013 Addex will complete a pilot Phase II study of dipraglurant for rare dystonia and target a partnership for the Parkinson's disease (PD) indication. It will also complete a Phase I study of ADX71441 for Charcot-Marie-Tooth (CMT) disease, as well as select a clinical candidate for the mGlu4 PAM programme in multiple sclerosis. While Addex is currently financed to end-2013, potential licensing deals and/or financings could extend the cash runway.

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
12/12	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 and exceptional items.

Refocusing, restructuring and realigning

Following a strategic review, Addex will now focus on developing its clinical-stage pipeline in rare (orphan) disease indications. The restructuring of research operations (suspension of discovery activities) will free up financial resources to implement this new strategy. Finally, Addex has also announced plans to list on a US stock exchange (ADR on NASDAQ), which could broaden the potential US investor base.

Dipraglurant: Pilot Phase II in rare dystonias

The rationale for dipraglurant in dystonia is based on positive preclinical data and initial clinical findings in the Phase II study in PD, where the drug reduced levodopa-induced dystonia. We understand a Phase II trial in dystonia (start Q213) will readout in Q413. Addex will seek to partner the PD levodopa-induced dyskinesia (PD-LID) indication.

ADX71441: Advancing into Phase I for CMT1A

ADX71441 is being developed for CMT Type 1A (CMT1A) disease, a rare inherited neurological disease. A Phase I study in healthy volunteers (start Q213) will assess the safety, tolerability and initial biological activity of ADX71441. Provided results are positive in Q413, the drug could enter a Phase IIa study in CMT1A patients in 2014.

Cash runway to end-2013

Addex had cash of CHF15.3m at year-end 2012. We now model CH15m in operating expenditure for 2013, including restructuring related costs. On our revised 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 ($236m) 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.

	5 March 2013
Price	CHF7.65
Market cap	CHF66m
	CHF0.943/US$
Shares in issue	8.6m
Free float	70%
Code	ADXN
Primary exchange	SIX
Other exchanges	N/A

Share price performance

%	1m	3m	12m
Abs	(19.0)	(24.3)	11.7
Rel (local)	(21.5)	(31.6)	(9.5)
52-week high/low	CHF12.4		CHF6.2

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 dystonia	Q213
Initiate ADX71441 Phase I in CMT1A	Q213

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Investment summary

Company description: Allosteric modulators for orphan diseases

Addex Therapeutics is a Swiss-based biopharmaceutical company focused on the clinical development of novel oral therapies for rare disease indications. The company's R&D pipeline is based on its proprietary allosteric modulator discovery technology platform. Allosteric modulators may offer greater selectivity and better control of disease mediating receptors than traditional 'orthosteric' drugs. Following a strategic review, Addex has reduced its research operations and is refocusing its clinical pipeline – dipraglurant, ADX71441 – in orphan diseases. The scaling back of early-stage discovery efforts, with the exception of mGLu4 PAM, will reduce the overall cost structure and free up financial resources to advance the clinical-stage portfolio. In 2013, Addex should initiate (and complete) a pilot Phase II study of dipraglurant in dystonia and a Phase I trial of ADX71441 for Charcot-Marie-Tooth Type 1A (CMT1A) neuropathy. Addex's plans for a US listing on NASDAQ reflects its growing US shareholder base (c 45%) and could, in our view, be a prelude to an equity fund-raising.

Valuation: Risk-adjusted NPV of CHF218m

We value Addex at CHF218m ($236m), or CHF25.40 per share, based on a risk-adjusted NPV analysis. Our valuation remains unchanged following the restructuring and refocusing of the clinical pipeline. We forecast risk-adjusted cash flows for the company's internal and partnered clinical programmes and discount using a WACC of 12.5%. Our rNPV includes dipraglurant in both orphan (rare dystonias) and non-orphan (PD-LID) indications, along with partnered programme, JNJ-40411813, in schizophrenia and anxiety. We currently exclude ADX71441 (CMT1A) and mGlu4 PAM (multiple sclerosis) from our financial model, given their early stage of development. As such, these programmes represent pure upside to our forecasts and valuation.

Sensitivities: Timely completion of orphan studies

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; absence of a deal in 2013 could raise questions on the drug's overall risk/benefit profile, in our view.

Financials: Cash runway to end-2013

Our updated financial model incorporates the recent FY12 results (year-end cash of CHF15.3m) and projected FY13 cash utilisation of CHF15m. 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 barring any new licensing agreements and/or equity fund-raisings, Addex is funded to year-end 2013.

Outlook: New orphan disease focus

Addex is to undergo a restructuring that will substantially reduce the size of its Swiss research operations in order to free up financial resources for the clinical development of two programmes – dipraglurant and ADX71441 – for orphan disease indications. The company has indicated it does not intend to invest further resources in its discovery portfolio, other than its mGlu4 PAM, although it will maintain its core competence and expertise in allosteric modulation. In 2013, the company will initiate (and complete) a pilot Phase II study of dipraglurant in rare dystonias and a Phase I trial of ADX71441 in healthy volunteers (but targeting Charcot-Marie-Tooth disease). In parallel, Addex aims to secure a licensing deal for dipraglurant in non-orphan indications: the company is using its positive Phase IIa data in Parkinson's disease levodopa-induced dyskinesia (PD-LID) as a basis for attracting a partner. The company's cash runway, in the absence of partnerships on dipraglurant and/or discovery assets, extends to end-2013. Finally, a listing on NASDAQ could broaden the potential US investor base.

Restructuring, refocusing, and realigning

Following a recent strategic review, Addex has outlined plans to restructure and refocus on its clinical-stage pipeline of rare disease indications. The key elements of this strategic shift are as follows:

- Develop the unpartnered clinical candidates for orphan disease indications. In 2013, Dipraglurant will advance into a Phase II proof-of-concept study in rare dystonias, while ADX71441 will complete Phase I testing for the target indication of Charcot-Marie-Tooth neuropathy (CMT1A).
- Continue partnering discussions for dipraglurant in Parkinson's disease levodopa-induced dyskinesia (PD-LID) following encouraging preliminary Phase IIa data in this indication.
- Complete preclinical development of an oral mGlu4 PAM for multiple sclerosis.
- Restructure to reduce Addex's research footprint (primarily in early-stage discovery) and reduce the overall cost base, thereby freeing up resources for the clinical pipeline. This should extend the company's cash runway to end-2013.
- List on a US exchange (ADR on NASDAQ) to improve visibility among US investors (now c 45% of Addex's shareholder base) and, potentially, provide access to additional capital.

Refocusing clinical pipeline on orphan indications

The central element of Addex's revised strategy is to advance its clinical-stage candidates – dipraglurant, ADX71441 – in rare disease indications. This is, in our view, sensible, as orphan drugs offer a potentially quicker (and less expensive) route to market and decent revenue-generating potential. Importantly, research supports the notion that orphan indications are more profitable (versus non-orphan indications) when considered in the context of development drivers including government financial incentives, smaller and shorter clinical trials, and higher rates of regulatory success..[1] As such, Addex has refocused its clinical pipeline on two orphan indications with high unmet medical need.

Dipraglurant for rare dystonias

During 2013, Addex plans to advance dipraglurant (mGlu5 NAM) into clinical development for certain rare types of dystonia, a movement disorder that causes involuntary muscle contractions and spasms. Estimates suggest that over 300,000 individuals in the US are affected by dystonia of various types[2]. Common forms of dystonia include focal (ie cervical dystonia, blepharospasm, hand dystonia), early-onset generalised, dopa-responsive and myoclonic. Existing medical treatments include oral medications (dopaminergic agents, anticholinergics, baclofen) and botox injections, which provide relatively modest symptomatic relief.

1 Meekings et al, Drug Discovery Today 2012; 17(13/14):660-664.
2 Dystonia Medical Research Foundation.

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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/ **J&J**	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 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

The rationale for advancing dipraglurant in dystonia is based on recently-announced, positive preclinical data in this indication. Oral administration of dipraglurant (10, 30, 50mg/kg) showed a dose-dependent reduction in the severity of dystonia, induced by caffeine in the tottering mouse model. Moreover, the drug completely blocked the onset of dystonia in a sub-group of experimental animals. The preclinical data appears consistent with clinical findings in the PD-LID Phase II study, whereby a limited number of dipra-treated patients (n=4) with pure dystonia showed a reduction in peak dose dystonia scores.

Based on discussions with Addex, we believe dipraglurant will likely enter a pilot Phase II clinical pharmacology study in dystonia patients (precise subtype or subtypes still under discussion) in Q213 and deliver results by year-end 2013. We understand that the plan is for an acute dosing study in a limited number of patients; we believe that 5-7 day treatment duration in 10-20 dystonic patients could provide sufficient proof-of-concept data. Assuming the results are positive, the drug could be advanced into a larger Phase IIb trial in 2014. The latter could, in our view, comprise a randomised, placebo-controlled design in c 50 subjects with dystonia, similar to Medy-Tox's ongoing Phase II study of MT10109 in cervical dystonia.

ADX71441 for Charcot-Marie-Tooth disease

Around mid-2013, ADX71441 (a GABA-B PAM) will enter a Phase I study for the treatment of Charcot-Marie-Tooth disease Type 1A (CMT1A). CMT is the most common inherited neurological disorder, affecting around 125,000 people in the US, and characterised by progressive leg and arm weakness, numbness and pain..[3] We estimate that CMT1A accounts for 40% of all CMT cases or around 50,000 individuals in the US..[4] The underlying genetic abnormality in CMT1A is duplication of the PMP22 gene on chromosome 17, which encodes for a key protein in the myelin sheath covering around peripheral nerves. Over-expression of PMP22 protein triggers peripheral demyelination (possibly by interfering with Schwann Cell function), resulting in slowed nerve impulses and progressive loss of nerve fibres. There is no cure and pharmacotherapy provides limited relief of musculoskeletal and neuropathic pain; treatment options include anti-inflammatory drugs, tricyclic antidepressants and anticonvulsants.

The rationale for advancing ADX71441 in this orphan indication is based on positive data in a preclinical model of CMT1A, where the drug was administered for nine weeks to transgenic CMT rats. Results showed that ADX71441-treated animals had lower levels of PMP22 protein, increased peripheral nerve conduction, and fewer demyelinated nerves than placebo-treated CMT rats. ADX71441 also prevented grip strength loss in CMT rats versus controls. These preclinical results suggest that positive modulation of the GABA-B receptor might lower PMP22 overexpression, improve symptoms and, potentially, delay disease progression.

Addex expects to initiate a Phase I study of ADX71441 by mid-2013, with headline results in Q413. While the protocol is being finalised, we understand it will be a randomised, double-blind, placebo-controlled trial in healthy volunteers. The primary objective is safety and tolerability; however, the study will incorporate a number of pharmacodynamic endpoints (biomarkers) to demonstrate the biological activity of ADX71441. Provided data are positive, the drug could move into a Phase II proof-of-concept study in CMT1A patients in 2014.

Targeting partnerships for non-orphan indications…

Armed with positive results from a Phase IIa study in PD-LID, Addex is still targeting a licensing deal for dipraglurant in this non-orphan indication. In parallel with licensing discussions, the company will conduct additional clinical work to inform the design of a planned Phase IIb study in PD-LID in 2014.

3 Kedlaya et al, Charcot-Marie-Tooth Disease, Medscape September 2012.
4 Charcot-Marie-Tooth Association.

During 2013, Addex will complete several small clinical pharmacology studies to further characterise the dose response to dipraglurant. The aim is to optimise the dose, dosing regimen and formulation for the Phase IIb study in PD-LID. The first study will examine the mGLu5 receptor occupancy in the human brain following oral dipraglurant administration. The second trial will determine the bioavailability of the IR (immediate release) and ER (extended release) formulations as well as pharmacokinetics (absorption, distribution, metabolism and elimination).

Addex also believes that dipraglurant has the potential as a symptomatic treatment of PD in mid-to-late stage patients (ie in those who have not developed LID). Specifically, dipraglurant could be given with levodopa to allow earlier use of this gold standard therapy (levodopa use is currently limited by the concern about development of LID and hence, it is reserved for older patients and/or those with more severe disease). Dipraglurant is thought to be suited to co-formulation with levodopa, as its release profile following oral administration is similar so that maximum plasma concentration would occur at the point when dyskinesia is most likely. Dipraglurant is one of perhaps four programmes in active development for PD-LID.

In addition to dyskinesia, there is clinical and non-clinical evidence that dipraglurant may improve nonmotor symptoms of PD, including anxiety, depression and impulse control disorders (this can be a side-effect of dopamine agonists), as well as provide benefits on the PD motor symptoms when given as an adjunct to dopamine replacement. As noted above, Addex has generated non-clinical data to suggest that dipraglurant could have benefit for treating non-parkinsonian dystonias.

As a reminder, dipraglurant is effectively competing with a compound (Novartis's mavoglurant/AFQ056) that has an identical mechanism and is further ahead in development, with several larger Phase II studies already undertaken in PD-LID, as well as for Fragile X syndrome. Novartis maintains a filing target for PD-LID of 2015 (from 2014). Development of mavoglurant in Fragile X is a year ahead of PD-LID (its filing target is 2014), potentially presenting a commercial differentiation challenge if it is successful in both indications (as an orphan indication, Fragile X, would be expected to be priced higher than the more mainstream Parkinson's disease indication). Both indications appear likely to use broadly similar doses.

Exhibit 4: Competing development programmes for PD-LID

Product	Company	Mechanism	Development stage/notes
Mavoglurant (AFQ056)	Novartis	mGlu5 NAM	140-pt Phase II study (150/200mg bid; results: April 2013); 108-pt open-label Phase II study (results: November 2015); 119-pt open-label extension (results: December 2014). Also in development for Fragile X syndrome.
Safinamide	Newron/Zambon /Meiji	MAO-B inhibitor	36-pt Phase II trial (completed, no results yet).
Amantadine	Adamas	NMDA antag.	80-pt Phase II/III study (results: December 2012).
AQW051	Novartis	α-7 nAChR inhib	72-pt Phase II study (results: January 2013).
AVP-923	Avanir	NMDA antagonist	Planned crossover study will compare AVP-923 (45mg dextromethorphan/10mg of quinidine) vs pbo in LID. (Fixed dose combination of dextromethorphan and quinidine sulphate).
NP002	Neuraltus	nicotine receptor agonist	65-pt Phase II trial showed clinically relevant trends and/or statistical superiority of NP002.
ND0611 (carbidopa)	NeuroDerm	DDC inhibitor	24-pt Phase I/II study of ND0611 with levodopa/carbidopa in PD-LID met all PK endpoints.
Neu-120	Neurim	NMDA mod	20-pt Phase I/II study completed.

Source: Edison Investment Research

Advancing mGlu4 PAM in multiple sclerosis…

Despite scaling back its early-stage discovery assets, Addex will continue to advance its oral mGlu4 PAM programme in multiple sclerosis (MS). During 2013, the company expects to complete pre-IND studies and select a clinical candidate for Phase I development.

The rationale for selecting and advancing mGlu4 PAM is based on encouraging preclinical data in a validated rodent model of MS. In Q312, the company reported that its lead chemical series, a highly-

selective and orally available mGlu4 PAM, showed good pharmacokinetic properties and initial efficacy in the standard neuroinflammation model of MS (RR-EAE model). Following daily administration for three weeks at ascending doses (10, 30 and 60mg/kg), the oral mGlu4 PAM showed a dose-dependent, statistically significant reduction in paralysis and relapse rates.

… And seeking partnerships on other discovery assets

With the exception of mGlu4 PAM, Addex will seek to monetise its non-core discovery programmes and allosteric platform through licensing agreements. Potential partnerships on these assets and technologies could provide additional sources of non-dilutive financing and extend the company's cash runway into 2014.

Exhibit 5: Addex's non-core preclinical programmes

Programme	Indication	Notes
mGluR7 NAM	Depression/anxiety/PTSD	Lead compound ADX71743 showed potential in treatment of anxiety. Presentation.
mGluR2 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	Hit to lead. Oral candidates identified against a target that has been intractable to conventional approaches. Potential for treating various neurodegenerative diseases (Parkinson's, Alzheimer's and Huntington's).
TNF R1 NAM	Autoimmune disease.	Hit to lead. 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. Compounds 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.

Source: Edison Investment Research

Targeting Phase IIa completion for JNJ-40411813

Lead partnered drug JNJ-40411813 remains in Phase II development with Janssen Pharmaceuticals Inc. In November 2012, top-line results from the main portion (Part B) of the Phase II study of JNJ-40411813 (ADX71149) in schizophrenia were claimed to have established safety and efficacy in patients with persistent negative symptoms, a group thought to comprise 20-40% of all schizophrenics. Further details on the study may come out this year, possibly at AAN.

The study was reported to have met its objectives of demonstrating good safety and tolerability and identifying the population of schizophrenia patients most likely to benefit from adjunctive treatment and established the 50mg bid dose as having the optimal benefit/risk ratio. This suggests that there were no specific safety concerns related to the use of the drug and that any tolerability issues were either associated with the 150mg bid dose or there was little or no additional efficacy benefit associated with the higher dose relative to the lower 50mg bid dose.

Efficacy was established in patients with residual negative symptoms. We assume this was determined by a separation vs placebo on PANSS[5] score after 12 weeks, a secondary endpoint. This group was the largest of the three subgroups targeted in the study (n=47). By inference, it would suggest the separation was less clear (or not evident at all) in the other two smaller subgroups (residual positive symptoms and inadequate response to clozapine). However, the small sample sizes of these two groups may make these data more difficult to interpret.

J&J is separately conducting a Phase II study with JNJ-40411813 in patients with anxiety and major depression with expected completion in H213. As the next step, we would expect J&J to conduct a larger Phase IIb study (or studies) in preparation for the Phase III registration programme.

5 The Positive and Negative Syndrome Scale is a validated tool for measuring symptom severity in schizophrenia.

Exhibit 6: Competing development programmes for schizophrenia (Phase II or later)

Drug	Company	Mechanism	Trial status/notes
Cariprazine (RGH-188)	Forest/Richter/ Mitsubishi Tanabe	D_2/D_3 antagonist	450-pt and 600-pt Phase III studies completed with positive results. US filing in November 2012. 700-pt Phase III study in prevention of relapse (results: July 2013). Separately in Phase III studies for bipolar disorder.
Brexpiprazole (OPC-34712)	Otsuka/ Lundbeck	D_2 partial agonist	660-pt Phase III study (BEACON) and 630-pt Phase III study (VECTOR) (results: March 2013), 1,000-pt Phase III study (ZENITH) (results: January 2016). Dose finding Phase II/III study. Also 3x Phase III trials in depression (>2,500-pts in total).
Bitopertin/(RG1678/RO4917838)	Roche	GlyT1 inhibitor	Three 630-pt Phase III studies (SUNLYTE, DAYLYTE and FLASHLYTE) in pts with persistent, predominant negative symptoms as add-on to antipsychotics (results: July 2015). Three 600-pt Phase III studies (NIGHTLYTE, MOONLYTE and TWILYTE) in pts with sub-optimal symptom control (results: August 2015). 300-pt Phase II study for acute exacerbations (results: December 2012).
Zicronapine	Lundbeck	D_1 antagonist; $5HT_{2A}$ antagonist	160-pt Phase III study vs risperidone, measuring efficacy and metabolic parameters (results due: August 2012).
BL-1020	BioLineRx	D_2 antagonist, GABA agonist	435-pt Phase II/III study vs risperidone and placebo (results: H113).
ALKS 9072	Alkermes	D_2 partial agonist	690-pt Phase III study in acute exacerbations (results: April 2013).
TC-5619	Targacept	α7 nAChR partial agonist	456-pt Phase IIb study for negative symptoms/cognitive dysfunction (results: May 2013).
AMG-747	Amgen	GlyT1 inhibitor	Two 270-pt Phase II study as add-on for negative symptoms (results: Dec 2013).

Source: Edison Investment Research

Planned NASDAQ listing – could broaden US investor base

As a component of its revised strategy, Addex is planning to list its shares on the US NASDAQ exchange (as an ADR). There are, in our view, two interrelated elements to this plan:

- Increase visibility among US investors – we see a good rationale for a NASDAQ listing given Addex's growing US shareholder base (c 45% currently) and potential for greater visibility among specialist US healthcare funds.
- Access to capital – Addex is funded to end-2013 and, provided clinical data is positive, would require additional financing to advance both orphan indications into larger Phase II studies. As evidenced by the recent surge in US biotech fundraisings (over $1bn year-to-date), and the relative absence of EU financings, Addex may find it easier to access capital in the US market.

Background: Metabolotropic glutamate universe

The discontinuation of Lilly's pomeglumetad in 2012 has left five different compounds targeting metabolotropic glutamate receptors currently in active clinical development[6], all of which are allosteric modulators. Addex is responsible for two of these (the other three are shown in Exhibit 7).

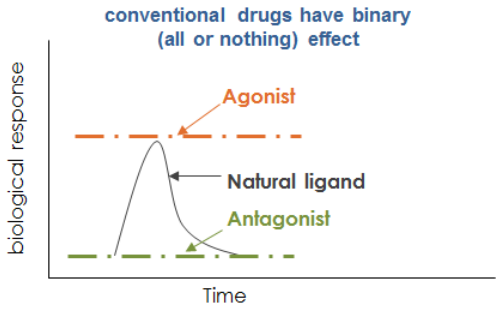
Exhibit 7: Competing programmes targeting mGlu Receptors (clinical only)

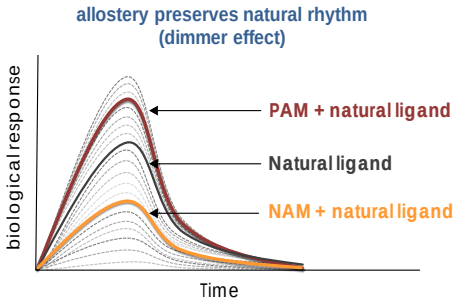
Product	Mechanism	Indication(s)	Trials
Mavoglurant/ Novartis	mGlu5 NAM	Fragile X	160-pt Phase II/III study in adults (results: December 2013).
			160-pt Phase II/III study in adolescents (results: December 2013).
			200-pt long-term safety study (results: September 2015).
		PD-LID	Four Phase II studies (see Exhibit 2).
RO4917523/ RG70980 Roche	mGlu5 NAM.[7]	Tx–resistant depression	300-pt Phase IIb study (MARIGOLD) (results: November 2013).
		Fragile X syndrome	180-pt Phase II study (results: November 2013).
RG1578/ RO4995819 Roche	mGlu2/3 NAM[5]	Major depression	480-pt Phase II study (results: December 2013).

Source: Edison Investment Research.

Exhibit 8: Factsheet on allosteric modulation

What are they?	Allosteric modulators are small molecule drugs that exert their activity without binding to the active site of a receptor. Allosteric modulators usually exert an effect only when the endogenous ligand is bound to the receptor, while classical orthosteric drugs compete for the active site with endogenous ligands. As a result, lower affinity allosteric modulators may be effective where a similar affinity orthosteric modulator is not. Allosteric modulators are usually devoid of activity in the absence of endogenous ligands. Because of this, they preserve the natural biological rhythms compared to orthosteric approaches.
Positive allosteric modulator (PAM)	PAMs potentiate the activity of a receptor. They are analogous to agonists as they contribute to overall receptor activation, but the signal is up-regulated only in the presence of the natural (endogenous) ligand. PAMs can be used to "turn up" a signal, while preserving the natural ligands' ability to turn it on/off.
Negative allosteric modulator (NAM)	Attenuates activity of a receptor via binding to a separate (topographically distinct) binding site, usually on the cell membrane. NAMs down-regulate activity but are also non-competitive with the natural ligand (in contrast to antagonists or inverse agonists). NAMs "turn down" a signal, while preserving the natural ligands' ability to turn it on and off.





Advantages	Allosteric modulators can sometimes be identified for targets where it has been difficult to make selective orthosteric small molecule drugs. Examples include the FSH receptor and TNF receptor, for which only peptide or hormonal therapies are currently available.
Approved drugs	Two drugs with a known allosteric mechanism have been approved: Sensipar/Minpara (cinacalcet, Amgen), which is a PAM of Ca2+-sensing receptors and is indicated for secondary hyperparathyroidism, and Selzentry/Celsentry (maraviroc, Pfizer), an NAM of chemokine receptor CCR5, indicated for HIV infection. Other compounds, including benzodiazepines, are thought to have a partial allosteric mechanism.
Addex's technology	Addex has developed a variety of high throughput assays for various targets including GPCRs, receptor tyrosine kinases, and certain single-pass transmembrane receptors. Addex believes its technology can be used to identify modulators of target enzymes, including epigenetic enzymes, kinases and bacterial enzymes that could have application in other therapeutic areas including inflammation, metabolic disease and oncology.

Source: Edison Investment Research

6 Seaside Therapeutics has an mGlu5 NAM that is ostensibly ready to enter Phase II for Fragile X syndrome, but no activity appears to be underway.
7 These are now described by Roche as "negative modulators".

Valuation

Our current valuation of Addex is $232m (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 9: 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

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; absence of a deal in 2013 could raise questions on the drug's overall risk/benefit profile, in our view.

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.

Financials

Edison's updated financial model is shown in Exhibit 10. 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 10: 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

Edison investment research

Contact details	Revenue by geography
12, chemin des Aulx 1228 Plan-les-Ouates Geneva Switzerland +41 22 884 1555 www.addextherapeutics.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2010-14e	N/A	ROCE 2013e	N/A	Gearing 13e	N/A	Litigation/regulatory	●
EPS 2012-14e	N/A	Avg ROCE 2010-14e	N/A	Interest cover 13e	N/A	Pensions	○
EBITDA 2010-14e	N/A	ROE 13e	N/A	CA/CL 13e	N/A	Currency	○
EBITDA 2012-14e	N/A	Gross margin 13e	N/A	Stock days 13e	N/A	Stock overhang	○
Sales 2010-14e	N/A	Operating margin 13e	N/A	Debtor days 13e	N/A	Interest rates	○
Sales 2012-14e	N/A	Gr mgn / Op mgn 13e	N/A	Creditor days 13e	N/A	Oil/commodity prices	○

Management team

CEO: Dr Bharrat Chowrira

Appointed in August 2011. Formerly SVP and COO of Nektar Therapeutics (May 2008 to January 2011), executive director, worldwide licensing and external research at Merck & Co (2007-08) and VP, legal affairs at Sirna Therapeutics (1993-2006). He holds JD and PhD in microbiology and molecular genetics and is a registered US patent attorney.

CFO: Tim Dyer

Co-founder of Addex and CFO since 2002. Before joining Addex he spent 10 years with Price Waterhouse (later PricewaterhouseCoopers) in the UK, Russia and the CIS and Switzerland. He is a chartered accountant and has a degree in biochemistry and pharmacology.

Chief scientific officer: Dr Graham Dixon

Joined in July 2012. Previously he was CSO, SVP R&D at Galapagos NV, CSO of two biotech companies, and had senior management positions in both research and development at AstraZeneca. He holds PhD in biochemistry and an honours degree in biology.

Principal shareholders	(%)
Biotech Value Fund	26.1%
Sofinnova Partners	8.9%
TVM Capital	7.8%
Visium Asset Management	5.4%

Companies named in this report

Adamas, Avanir, Alkermes (ALKS), BioLineRx (BLRX), J&J (JNJ), Lundbeck (LUN) Medy-Tox, Newron (NWRN), Neuraltus, NeuroDerm, Novartis (NVS), Pfizer (PFE), Roche (ROG), Targacept (TRGT).

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