Edison investment research

4 January 2012

Addex Pharmaceuticals

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
12/11e	3.7	(30.4)	(4.1)	0.0	N/A	N/A
12/12e	0.5	(17.8)	(2.3)	0.0	N/A	N/A
12/13e	0.5	(18.0)	(2.3)	0.0	N/A	N/A

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

Investment summary: Phase II data coming

Addex is approaching the read-out of two Phase II studies that represent significant catalysts in its investment case. These are the study of dipraglurant in Parkinson's disease levodopa-induced dyskinesia (PD-LID) and of ADX71149/JNJ-40411813 in schizophrenia. Positive results in either or both of these studies could catalyse a significant increase in value. Given its currently very depressed stock market valuation – Addex has an EV of just CHF12m based on forecast 2011 year-end cash – this could make for a very attractive investment scenario. We have revised our risk-adjusted NPV to CHF195m or c CHF29/share, some five times the share price.

Read-out from studies that define investment case

Addex is fast approaching the read-out from both of the Phase II studies of its lead products – a 72-patient study of dipraglurant in PD-LID and the 105-patient study of JNJ-40411813 in schizophrenia. The results from these two studies, which are due respectively in Q1 and Q3 2012, are critically important value drivers.

Positive results should be significant value-creating events

Addex could see a significant increase in value on the back of positive results in these studies. In both cases, there is validation from competing agents with similar mechanisms, so there should be relatively low risk. Nevertheless, a failure in one or both the studies would represent a significant setback.

R&D strategy focused on more early-stage deals

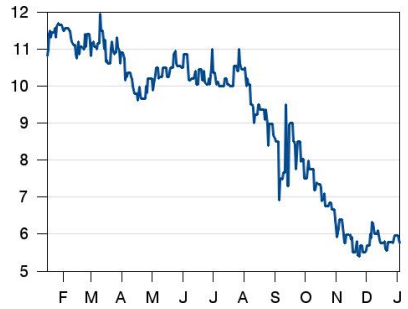
Addex has focused its efforts on fewer R&D projects following a pipeline review and is aiming to secure earlier-stage partnering deals for certain others than was previously the case. A licensing deal for one of its early-stage assets, especially if it were to come ahead of the read out from the Phase II studies, would mitigate risk.

Valuation: Risk-adjusted NPV of CHF195m

We have revised and updated our valuation model of Addex and this now yields a risk-adjusted NPV of $232m/CHF195m. This compares with an EV of CHF12m based on forecast year-end 2011 cash, and is equivalent to CHF29/share. We assume industry-standard probabilities for compounds based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813.

Price	CHF5.9
Market cap	CHF46m

Share price graph



Share details

Code	ADXN
Listing	SIX
Sector	Biotech
Shares in issue	7.83m

Price

52-week	High	Low
	CHF11.9	CHF5.4

Balance sheet as at 31 December 2011*

Debt/equity (%)	N/A
NAV per share (CHF)	4.27
Net cash (CHFm)	34.5

** Edison estimate*

Business

Addex Pharmaceuticals is a Swiss biotech company with 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).

Valuation

	2010	2011e	2012e
P/E relative	N/A	N/A	N/A
P/CF	N/A	N/A	N/A
EV/sales	N/A	N/A	N/A
ROE	N/A	N/A	N/A

Revenues by geography

UK	Europe	US	Other
0%	100%	0%	0%

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Investment summary: Phase II data coming

Company description: Leader in allosteric modulation

Addex Pharmaceuticals is a Swiss biotech company that has established a world-leading position in development of allosteric modulators. The company, which is based in Geneva with 82 employees, was founded in 2002 and has raised CHF263m in equity and c CHF47m from partnerships since its inception. Addex's R&D pipeline has two Phase II projects, JNJ-40411813 (which is partnered with J&J) and dipraglurant, together with five core preclinical programmes that are the focus of internal development efforts. It also has five other projects that have reached preclinical proof of concept. Key R&D programmes are summarised in Exhibit 1.

Exhibit 1: Addex core R&D programmes

Product	Indication	Stage	Notes
JNJ-40411813	Schizophrenia/ anxiety/other	Phase II	Partnered with **J&J**.
Dipraglurant	PD-LID/dystonia	Phase II	IR version for PD-LID; ER version for dystonia/other CNS indications.
$GABA_BR$ PAM	Pain/overactive bladder	Lead opt	Lead candidate selected, IND possible Q412.
mGluR4 PAM	Parkinson's disease	Lead opt	
GLP1R PAM	Type II diabetes	Lead opt	
TrkB PAM	Neurodegeneration		
TNFR1 NAM	Autoimmune	Hit to lead	

Source: Edison Investment Research

Valuation: Risk-adjusted NPV of CHF195m

We have revised and updated our valuation of Addex, based on a risk-adjusted NPV, to $232m/CHF195m (of which JNJ-40411813 contributes c CHF120m) which, if adjusted for forecast year-end 2011 cash, is equivalent to CHF29/share. This represents an unusually high multiple of the current share price. The valuation is based on the two clinical stage programmes and the $GABA_B$ PAM alone. We assume industry-standard probabilities for compounds based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813.

Sensitivities: Phase II study results are key catalysts

Addex is subject to the sensitivities typical of biotech drug development that include the unpredictable outcome of clinical trials, the success or failure of competitors and a high degree of reliance on its existing partner and on the formation of new partnerships. The investment case is highly sensitive to the outcome of Phase II studies of dipraglurant and JNJ-40411813, both believed due in H112. A significant increase in value could be expected on the back of positive results in these studies, although a failure in one or both would have significant negative implications. Addex is relatively well funded with cash to the end of 2013 (excluding any possible milestones from J&J). However, realistically it will have to sign one or more licensing deals from its early-stage assets to be in a stronger position to capitalise on a positive result from its Phase II study of dipraglurant. Biotechnology Value Fund holds a significant 30% equity stake.

Financials: CHF33m of cash at end FY11

We assume total revenues of CHF3.7m for 2011 (of which CHF3.2m was received in H1, principally reflecting a CHF2.6m milestone payment from J&J). We have modelled R&D expenses of CHF28m for 2011 (CHF14.6m in H1). This would be consistent with the planned CHF8m/year savings from 2012, with an assumed lower spending on trials, and the guided cash reach to the end of 2013. Our model suggests cash at the end of 2011 was CHF34.5m.

Outlook: Key Phase II trial read-outs approaching

Within just over the next six months, Addex should see the read-out of the two Phase II studies that largely define its investment case in the short/medium term. These are the 72-patient study of dipraglurant in PD-LID and the 105-patient study of ADX71149/JNJ-40411813 in schizophrenia, which is being conducted by Janssen Pharmaceuticals (a unit of Johnson & Johnson). Successful results in these studies – and both benefit from validation from compounds with similar mechanisms in the same indications – could therefore catalyse a significant increase in stock market value. This may offer an attractive investment scenario given Addex's current very depressed valuation – it trades at CHF12m above forecast 2011 year-end cash.

Addex has a pipeline that also consists of eight preclinical programmes (five of which are in active development and three targeted for early licensing), however, in investment terms, the substantial majority of its value currently rests in dipraglurant and JNJ-40411813, hence the near-term focus on the outcome of the studies of these compounds.

We believe the two studies are on track to render results in Q2 (possibly April) and Q312. We estimate completion of enrolment of JNJ-40411813 study in H112,[1] with results by the end of Q3. Both studies have safety as their primary endpoint, but examine their effect on disease through a number of secondary endpoints, which should be sufficient to provide a robust efficacy signal.

JNJ-40411813 schizophrenia study

JNJ-40411813 is a positive allosteric modulator of mGluR2. This mechanism is validated in schizophrenia to a degree by Lilly's mGluR 2/3 agonist, LY2140023/(pomaglu meth), and more specifically its now-discontinued parent compound LY404039, which has shown evidence of efficacy in Phase II trial.[2] LY2140023 is in Phase III studies for schizophrenia.

Although the Phase II results for JNJ-40411813 are important, evidence of J&J's continued commitment to the project is perhaps more so, and this may come in the form of initiation of further studies in schizophrenia or in the possible second indication of anxiety (in which J&J conducted a Phase I challenge study). J&J is unlikely, in our view, to initiate any further studies of JNJ-40411813 until after the outcome of the schizophrenia study is known and its decisions may be informed by competitive factors, including involving LY2140023. Lilly decided to go into Phase III studies with this compound despite an "inconclusive" Phase II study in acute exacerbations of schizophrenia. Results for this study were recently published,[3] which showed no effect on PANSS (positive and negative symptom scale) total score for either LY2140023 or olanzapine (the active control) with a higher-than-anticipated treatment effect seen on placebo.

The Phase IIb study of JNJ-40411813 would be a prelude to a Phase III registration programme, which in either schizophrenia or anxiety would involve a very substantial R&D investment. This is shown by the six Phase III studies (involving nearly 3,700 subjects) for Roche's RG1678 and three Phase III studies (involving c 2,300 patients) for Otsuka's OPC-34712 in schizophrenia.

[1] This is erroneously indicated to be earlier in the year on clinicatrials.gov.
[2] Grillon *et al.* Psychopharmacology (2003) 168: 446–454 and Patil ST, *et al.* Nat Med. 2007 Sep; 13 (9): 1,102-7. http://www.ncbi.nlm.nih.gov/pubmed/17767166.
[3] Kinnon *et al,* J Clin Psychopharmacol. 2011 Jun; 31 (3): 349-55.

Exhibit 2: JNJ-40411813 study details

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.
Dosing	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.
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.
Timelines	Primary completion: data expected in end Q312.

Source: Edison Investment Research

Exhibit 3: Schizophrenia – background

Description	Schizophrenia is a severe form of mental disorder characterised by a disintegration of thought processes and emotional response. Symptoms are divided into positive symptoms (auditory hallucinations, paranoid or bizarre delusions, disorganised speech and thinking) and negative symptoms (deficits of normal emotional responses).
Prevalence	Prevalence is estimated at 0.3-0.7% of the population worldwide, mostly in the age group 15-35 years. Though the incidence is low (3/10,000), the prevalence is high due to chronicity. Schizophrenia affects about 24 million people worldwide and more than 50% of people with schizophrenia are not receiving appropriate care (90% of people with untreated schizophrenia are in developing countries).
Current drug treatment	**Atypical antipsychotics:** quetiapine (Seroquel, AZ), olanzepine (Zyprexa, Lilly), aripiprazole (Abilify, BMS/Otsuka), resperidone (Risperdal, J&J), ziprasidone (Geodon, Pfizer) and clozapine. New agents include paliperidone (Invega, J&J), asenapine (Saphris, Merck & Co) and lloperidone (Fanapt, Vanda/Novartis). **Typical antipsychotics:** halperidone.
Unmet need	The unmet need in schizophrenia is for products that better control negative symptoms (withdrawal, blunted affect etc) and cognitive impairment associated with the condition and/or with fewer side effects (particularly weight gain). Currently available atypical antipsychotics are effective at controlling positive symptoms (delusions, hallucinations).
Market	Estimated at $23.1bn (+2%) in 2009.

Source: Edison Investment Research

Exhibit 4: Competing development programmes for schizophrenia (Phase II or later)

Drug	Company	Mechanism	Development status/notes
Cariprazine (RGH-188)	Forest/Richter/ M Tanabe	D_2/D_3 antagonist	450-pt and 600-pt Phase III studies (results: Dec/Jun 2011). 700-pt Phase III study in prevention of relapse (results: Jul 2013). Phase III for bipolar.
Pomaglu meth (LY2140023)	Eli Lilly	mGluR2/3 agonist	950-pt Phase III study (results: Feb 2013); 880-pt Phase II study (results: Dec 2011); 670-pt Phase III study vs aripiprazole (results: Aug 2012); 280-pt Phase II study (prominent negative symptoms (results: Oct 2011), 1,210-pt Phase II/III open label study (results: June 2015). 150-pt Phase III study to investigate physical dependence (results: Dec 2012).
OPC-34712	Otsuka/ Lundbeck	D_2 partial agonist	660-pt Phase III study (BEACON) and 630-pt Phase III study (VECTOR) (both results: Mar 2013), 1,000-pt Phase III study (ZENITH) (results: Jan 2016). Dose finding Phase II/III study. 450-pt Phase II study completed. (Also 3x Phase III trials in depression (>2,500 pts in total).
RG1678/ RO4917838	Roche	GlyT1 inhibitor	Three x 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 x 600-pt Phase III studies (NIGHTLYTE, MOONLYTE and TWILYTE) in pts with sub-optimally controlled symptoms (results: Aug 2015). 300-pt Phase II study for acute exacerbations (results: Oct 2012). 320-pt Phase II study showed improvement on negative symptoms and personal/social functioning.
Zicronapine (LU-31 030)	Lundbeck	MAOI	160-pt Phase III study vs risperidone on metabolic parameters (body weight, BMI etc) (results: July 2012). 40-pt Phase II study of once-weekly dosing (results: Apr 2012). Two Phase II studies completed (data not yet reported).
BL-1020	BioLineRx	$GABA_A$ agonist	435-pt Phase II/III study vs risperidone and placebo.
ALKS 9070	Alkermes	D_2 partial agonist	690-pt Phase III study in acute exacerbations (results: Apr 2013).
CYR-101/ MT-210	M Tanabe/ Cyrenaic	$5HT_{2a}$/sigma 2 antagonist	100-pt Phase II study completed, results apparently positive but no details.
AQW051	Novartis	α-7 nAChR inhibitor	132-pt Phase I/II study (results due: Oct 2011). 32-pt Phase II study on cognition in schizophrenia (results due: Sept 2011).
PF-02545920	Pfizer	PDE10 inhibitor	260-pt Phase II study for acute exacerbation (results due: Aug 2011).
TC-5619	Targacept	α-7 NNR r	456-pt Phase IIb study for negative symptoms/cognitive dysfunction.

Source: Edison Investment Research

Exhibit 5: 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

Dipraglurant PD-levodopa induced dyskinesia study

Dipraglurant is a negative allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), a mechanism that has clinical validation from Novartis's AFQ056, which is currently in Phase IIb for PD-LID and has shown significant reductions of LID in two Phase IIa trials and a Phase IIb trial. The rationale for down-regulating glutamate activity in PD stems from the hypothesis that the loss of dopamine-producing cells leads to an imbalance of neurotransmitters that causes excessive glutamatergic stimulation.

Addex believes that specifically targeting PD-LID offers a more rapid path to market than development for PD. However, there is a rationale for developing dipraglurant as an adjunctive (add-on) therapy with levodopa in both earlier stage PD patients (to allow earlier use of levodopa, without risking the development of LID) and later-stage patients with severe PD (to delay the need for deep brain stimulation or to treat breakthrough dyskinesias). Recent market research commissioned by Addex suggests a desire among physicians to use levodopa in earlier in PD and, when they do, at higher doses, if there was a way to do so that avoids the development of LID. Hence there may be a much larger potential market opportunity for dipraglurant than is currently modelled in our valuation. The initial target, however, remains PD-LID, where Addex believes dipraglurant could be given at the same time as (or co-formulated with) levodopa.

The drug may also have potential in non-Parkinsonian dystonia (which covers conditions such as idiopathic torsion dystonia, generalised or cervical dystonia) and Addex is planning to initiate preparatory Phase I studies with an extended-release formulation (allowing bid or daily administration), which would be more suitable for these indications in 2012. A proof-of-concept study (eg ~30 patients) in non-Parkinsonian dystonia would follow.

There is also potential for development (by a licensee) for a number of other indications where there is clinical validation. These include Fragile X syndrome, pain, anxiety, depression and gastro-esophageal reflux disease (GERD). Some of these conditions are co-morbid with PD (including anxiety/depression, addiction/compulsive behaviours) and it is therefore possible that dipraglurant may improve some non-motor symptoms of PD as well. Dipraglurant is believed to be the first drug candidate to have shown efficacy in both components of dyskinesia, specifically the dystonia element, and Addex believes this may become a key differentiating factor over AFQ056. Addex envisages the development of an immediate-release version of dipraglurant (possibly in a co-formulation with levodopa) for the PD-LID indication, while an extended-release formulation for non-Parkinsonian dystonia.

Dipraglurant has been running 18 months behind AFQ056, although it is looking increasingly possible that Addex can catch up with Novartis in the PD-LID indication. Novartis has recently initiated two new Phase II studies (including one at higher doses, 150/200mg bid), after an underwhelming result in a dose-ranging Phase II study. Currently, it is targeting a 2014 filing for AFQ056 in PD-LID, which would require it to initiate a Phase III study in 2012. This, however, looks unlikely as these new studies do not report until H212. This will also mean a Phase III decision will be made after the outcome of Addex's study is known. Furthermore, if Addex is able to partner dipraglurant on the back of its Phase II data and the partner was to run an expanded Phase IIb/III study, it could potentially match the Novartis timeline. Details on the dipraglurant study, a backgrounder on PD-LID and competing PD-LID and mGluR5 NAM/antagonist programmes are shown in Exhibits 6-9 (overleaf). A presentation and document are also available on dipraglurant.

Exhibit 6: Dipraglurant Phase II study details

Design	72-pt, four wk Phase II study in moderate to severe PD-LID.
Dosing	Dose titration from 50mg daily to 100mg tid taken with levodopa.
Subjects	Male/female with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria 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.
Primary endpoints	Safety/tolerability, physical and neurological examination, heart rate and blood pressure, 12-lead ECG, haematology and biochemistry assessments, use of concomitant medications, AEs/SAEs.
Secondary endpoints	Exploratory efficacy (trained observer scores LID severity – Abnormal Involuntary Movement Score, patient diaries, PD rating scales (including dystonia), evaluation of mood, objective evaluation (at baseline, wks 2 and 4).
Timelines	Primary completion: Jan 2012; completion Feb 2012.

Source: Edison Investment Research

Exhibit 7: PD/PD-LID – background

Parkinson's disease	Parkinson's disease is a degenerative disorder of the central nervous system that results from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain. Early in the course of the disease, the most obvious symptoms are movement related, including shaking, rigidity, slowness of movement and difficulty with walking and gait. Later, cognitive and behavioural problems may arise, with dementia commonly occurring in the advanced stages of the disease. Other symptoms include sensory, sleep and emotional problems. PD is more common in the elderly with most cases occurring after the age of 50.
Current approach to management	Levodopa, usually given in combination with carbidopa, is considered the gold-standard treatment for PD, but its use is limited by the development of dyskinesias. Hence, physicians usually try to delay the introduction of levodopa in mild PD and/or younger patients in favour of dopamine agonists and MAO-B inhibitors. However, these drugs are considered less effective and have CNS and other side effects. In particular, dopamine agonists have profound dis-inhibitory effects that can lead to impulse control disorders (eg pathological gambling) and/or disturbing hyper-sexual behaviour (thought to be around 6%). The strategy of delaying levodopa use also has the drawback it is when the drug is finally introduced patients are less able to respond.
PD-LID	Dyskinesia (abnormal movements) that develop as a result of a sensitisation of dopamine receptors to repeated cycles of stimulation by dopamine as well as exposure to higher doses that are required as dopaminergic cells are progressively lost as a result of the disease. PD-LID has two components chorea (rapid uncontrolled movements) and dystonia (writhing and cramping movements). Some 50% of PD patients develop LID after five years of levodopa treatment and 90% within 10 years of treatment.
Drug treatment	Amantadine is used off-label, although its use is controversial.
Prevalence	~ 200,000 pts in US/EU suffer from severe dyskinesia. PD affects around 4m worldwide (1.5m in the US, Japan, EU5). Prevalence is 0.3% in the population, rising to 1% >60 years of age and to 4% of > 80 years.
Current market	Negligible, but potential >$1bn/year.

Source: Edison Investment Research

Exhibit 8: Competing development programmes for PD-LID

Product	Company	Mechanism	Development stage/notes
AFQ056	Novartis	mGluR5 NAM	92-pt Phase II study (150/200mg bid; results: Nov 2012). 63-pt Phase II study (results: June 2012). 244-pt open-label extension (results: Dec 2014).
Safinamide	Newron	MAO-B inhibitor	36-pt Phase II trial in PD-LID (results: Dec 2011).
Amantadine	Adamas	NMDA antag.	80-pt Phase II/III study (results: Apr 2012).
AQW051	Novartis	α-7 nAChR inhib.	72-pt Phase II study (results: Jun 2012).
Fipamezole	Santhera/Ipsen	A_{2A} antagonist.	Pre-specified secondary analysis (116-pts) of Phase II FJORD study showed reduced PD-LID for the highest tested dose (p=0.047, n=29). On hold.
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 receptor modulator	20-pt Phase I/II study completed.
Ordopidine	Neurosearch	full D_2 antagonist	Phase Ib study. Completed. On hold.

Source: Edison Investment Research

Exhibit 9: Competing mGluR5 NAMs/antagonist programmes (clinical only)

Product	Company	Indication(s)	Trials/mechanism/notes
AFQ056	Novartis	Fragile X	160-pt Phase II/III study (adults) (results: Aug 2012); 160-pt Phase II/III study (adolescents) (results: Apr 2012) and 200-pt long-term safety study (results: Sept 2012). 24-pt Phase I PK study (results: Dec 2012).
		PD-LID	Four Phase II studies (see above).
RO4917523	Roche	Tx–resistant depression	315-pt Phase IIb study as adjunctive therapy major depressive disorder and inadequate response to ongoing anti-depressant therapy (results: Oct 2103). 34-pt Phase IIa study (treatment-resistant pts) (completed, no results published).
		Fragile X	60-pt Phase II study (results: Aug 2012).
STX107	Seaside Therapeutics	Fragile X syndrome	16-pt Phase II study (SAD in adults) (results due: Sep 2011).
AZD2066	AstraZeneca	Chronic neuropathic pain	Continues to be listed in AZ pipeline, despite 385-pt Phase II study being listed as terminated on clinicaltrials.gov. Two Phase II studies completed.

Source: Edison Investment Research

Preclinical pipeline

Addex has recently completed an R&D review and, as a result, has decided to focus resources on five of its nine preclinical programmes (shown in Exhibit 10) in addition to dipraglurant. The remaining four preclinical programmes are being held for early-stage partnering deals (Exhibit 11). This review was prompted by the management change earlier in the year (and was largely complete before the appointment of the new CEO in September). It also occurred at the same time as the return of rights to two programmes (mGluR4 PAM and mGluR5 PAM) that were previously the subject of separate research partnerships with Merck & Co. These decisions appear to have been the result of R&D cutbacks and portfolio reviews by the US group.

Addex has prioritised one of the former Merck programmes, mGluR4 PAM, for further internal development, holding the mGluR5 PAM assets for potential partnering. It is aiming to select an mGluR4 PAM clinical candidate in early 2012. This target is under investigation by several other companies including Lundbeck[4] and Merck KGaA.

$GABA_BR$ PAM

The $GABA_BR$ PAM is the most advanced of the core preclinical programmes and Addex hopes to select a clinical candidate by the end of this year. It aims to conduct GLP/tox studies year to have an IND-ready candidate in Q412. Addex previously conducted some animal studies with a prior lead $GABA_B$ PAM, ADX71943, which demonstrated superior tolerability and analgesic-like effects in various preclinical pain models after both acute and sub-chronic dosing.

The hypothesis of the project is that the allosteric binding mechanism can confer an improved profile over baclofen, an orthosteric $GABA_B$ agonist, which is used for treating spasticity. Baclofen is effective but its use is limited by induction of tolerance and other side effects (sedation, hypothermia, memory impairment etc). Addex believes the profile could provide an alternative to opioids for certain pain indications (eg osteoarthritis) and to anti-muscarinic drugs for over-active bladder, which in both cases have limiting side effects. There are just two $GABA_B$ agonists in active clinical, both formulations of arbaclofen and both in Phase III studies: Xenoport's XP19986 (for spasticity due to multiple sclerosis) and Seaside Therapeutics' STX209 (autism). AstraZeneca discontinued development of its $GABA_B$ agonist, lesogaberan/AZD3355, which had been in Phase II studies for gastro-oesophageal reflux disease.

GLP-1R PAM

Addex is generating lead molecules with activity as PAMs of the GLP-1 receptor (GLP-1R), which would have potential in treating type 2 diabetes. The desired profile is to have no or reduced propensity for nausea/vomiting versus existing agents and be suitable for combination with other therapies. This target has not proved readily tractable to conventional small molecule drug discovery approaches and all of the currently approved agents and most of the developmental GLP-1 agonists are proteins or peptides and therefore given as injections. Two GLP-1 agonists are currently approved: Byetta (exenatide, Amylin) and Victoza (liraglutide, Novo Nordisk); with Lyxumia (lixisenatide, Sanofi) recently filed and Syncria (albiglutide, GSK) and dulaglutide (Lilly) mid-way or completing Phase III studies. Roche has an oral dual GLP-1/GIP agonist, RG7685, in Phase I studies and Novo Nordisk, an orally delivered peptide GLP-1, NNC 0113-0987.

[4] Lundbeck recently published a paper on the work J Med Chem. 2011 Jul 28; 54 (14): 5,070-5,081.

Exhibit 10: Core preclinical pipeline

Programme	Indication	Notes
$GABA_B$ PAM	Pain/overactive bladder	Lead candidate selected. In vivo efficacy and superior tolerability established in models of anxiety, inflammatory pain and osteoarthritis pain. Former lead candidate ADX71943, showed analgesic-like effects in various preclinical models (CFA-induced inflammatory pain, Formalin-induced pain, acetic acid-induced writhing [a model of visceral pain] and the MIA model of osteoarthritis.
mGluR4 PAM	Parkinson's/ anxiety	Clinical candidate selection H112. First oral nanomolar mGluR4 PAM to achieve preclinical PoC. Novel mGluR4 PAM chemical scaffold recently disclosed with a pharmacophore and structure activity relationship that is completely different from existing molecules in the field. Lead candidate(s) have demonstrated efficacy in preclinical models of in various acute/chronic animal models of Parkinson's disease and anxiety. Presentation. Preclinical data presented on ADX88178 in anxiety models (elevated plus maze, marble burying). Previously partnered with Merck & Co.
GLP1R PAM	Type II diabetes	Lead generation/optimisation. Profile is for an orally available agent (current GLP-1 agonists are all injectable). 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	Neurodegeneration	Hit to lead – lead optimisation expected 1Q12. 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).

Source: Edison Investment Research

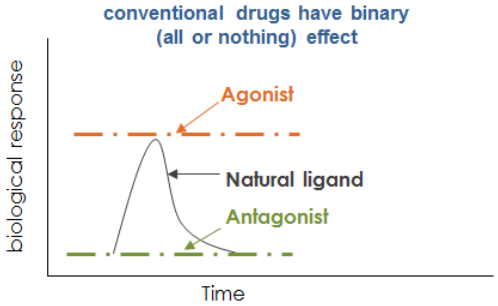
Exhibit 11: Partnering targets

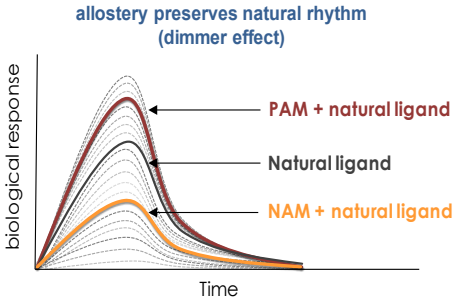
Programme	Indication	Notes
FSH R/LHR NAM	Hormone dependent tumours/ reproductive system disorders	Previously considered for endometriosis and benigh prostatic hyperplasia. Possible use in controlled ovarian stimulation for *in vitro* fertilisation.
mGluR2 NAM	Alzheimer's disease/ depression	Lead compound 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.
mGluR5 PAM	Schizophrenia	Rights to joint research programme returned by Merck & Co in 2011.
mGluR7 NAM	Depression/anxiety	Presentation.

Source: Edison Investment Research

Exhibit 12: Factsheet on allosteric modulators

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 are 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 GLP-1 receptor, the FSH receptor and TNF receptor, for which only peptide or hormonal therapies are currently available.
Approved drugs	To date, two drugs with a known allosteric mechanism have been approved: Sensipar/Minpara (cinacalcet, Amgen), which is a PAM of Ca^{2+}-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.

Source: Edison Investment Research

TrkB PAM

Addex has identified several compounds with TrkB PAM activity. This is a receptor that has been not been readily tractable to conventional small molecule drug discovery approaches. TrKB is a receptor for several neurotrophic factors including BDNF (brain derived neurotrophic factor) and as such, compounds with this activity should have potential in the treatment of neurodegenerative disease (such as Parkinson's, Alzheimer's and Huntington's).

TNF-R1 NAM

Addex is also screening for compounds with TNF-R1 (CD120a) NAM activity. This is receptor for TNF, which is targeted by anti-TNF drugs that are approved in rheumatoid arthritis, psoriasis and other autoimmune indications. Although there a number of new oral drugs approaching the market for rheumatoid arthritis (eg Pfizer's tofacitinib), which may make this a challenging indication commercially, Addex believes a compound with this mechanism may have wider use in conditions characterised by neurological inflammation (such as Alzheimer's disease, multiple sclerosis or depression).

Partnering targets

Addex has four programmes for which it is primarily seeking licensing partners only, and hence not advancing them internally at this time, to conserve financial resources (Exhibit 11). However, if Addex can secure one or more partnerships for the mGluR2 NAM, mGluR5 PAM or mGluR7 NAM projects, it would probably advance the FSHR NAM programme further internally.

The FSHR NAM has potential in a variety of indications, including sex hormone-related tumours, endometriosis and in *in vitro* fertilisation. Follicle-stimulating hormone (FSH) is produced by the pituitary gland and works synergistically with luteinizing hormone (LH) to control reproductive function. In women, FSH stimulates oogenesis as well as release of estradiol during the first half of the menstrual cycle. LH triggers ovulation and production of progesterone. In men, FSH facilitates spermatogenesis while LH stimulates testosterone production.

The nGluR2 programme targets the cognitive deficit associated with Alzheimer's and depression. There is evidence that down-regulation of mGluR2 inhibition could reverse cognitive deficit associated with Alzheimer's disease. Addex has shown with an mGluR2 NAM compound dose-dependent reversal of memory deficit exhibited after beta-amyloid protein administration without any locomotor activity compared to vehicle.

Last year, Addex received the rights back to a joint research programme it had conducted with Merck & Co in mGluR5 PAMs, directed at schizophrenia, particularly addressing the cognitive impairment associated with the disease. Published research suggests mGluR5 PAMs can reverse schizophrenia-like brain activity induced in animals by NMDA receptor antagonists (which in humans are known to impair brain activity associated with cognitive functions including learning, attention and memory).

Valuation

We have revised our valuation of Addex to $232m/CHF195m, which if adjusted for cash, is equivalent to CHF29/share. This is an unusually high multiple (5x) of the current share price, which has been under particular pressure in H211. The valuation is based on the risk-adjusted net present value of the two lead clinical stage programmes and the $GABA_B$ PAM (since this is approaching the IND stage). Hence, all Addex's other assets represent pure upside. We assume

industry-standard 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).

The valuation includes 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. Since J&J is bearing all the costs of JNJ-40411813 this contributes the largest share of the valuation, c CHF120m. Importantly, the model assumes a 25% share of a hypothetical $2bn potential market in PD-LID (ie $500m peak sales), largely on the basis that there are four or five active programmes in this indication. Dipraglurant is one of the leading programmes in this indication. Hence, if its competitive position were to improve (eg if Novartis were to discontinue AFQ056 in LID for commercial reasons) it would significantly enhance the valuation. Inputs used in the valuation are tabulated in Exhibit 13.

Exhibit 13: Edison risk-adjusted NPV inputs

Product	Indication	Stage	Year of launch	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 I	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
$GABA_B$ PAM	OA pain/other	Preclinical	2016	5%	2%	10.0

Source: Edison Investment Research

Sensitivities

Addex is exposed in the short term to the outcome of two clinical studies. In the longer term, other sensitivities include the success or failure of competitors (particularly Novartis's AFQ056 and Lilly's LY2140023), and a reliance on its Johnson & Johnson as a partner. The company relies on the formation of new partnerships, especially the dipraglurant. The investment case currently is highly sensitive to the outcome of Phase II studies of Addex's two lead products, due in H112. A significant increase in value could be expected on the back of positive results in these studies back, although a failure in one or both the studies would have significant negative implications.

Addex is relatively well funded, with cash to the end of 2013 (excluding any possible milestones from J&J). However, realistically the company needs to sign one or more licensing deals from early-stage assets to be in a strong position to capitalise on a positive result from its Phase II study of dipraglurant.

Biotechnology Value Fund (BVF), a US investment fund, holds a 30% equity stake, and two other investors hold 10% and 9% respectively, hence a near 50% shareholding is held by three parties. Addex has a seven-person board of directors (which excludes executive management), one of which, Oleg Nodelman, is a BVF nominee/employee.

Financials

Our financial model is shown in Exhibit 14. We assume total revenues of CHF3.7m in 2011 (CHF3.2m in H1, principally reflecting a CHF2.6m milestone payment from J&J on the Phase II start of JNJ40411814) and R&D expenses of CHF28m (CHF14.6m in H1). This would be consistent with the planned CHF8m/year savings from 2012, with an assumed lower spending on trials, and the guided cash reach to the end of 2013. Our model suggests cash at the end of 2011 was CHF34.5m.

Exhibit 14: Addex financial model

Notes: No assumption of future milestones from collaborations is made. Expenditure is consistent with the guided cash reach to the end of 2013. Revenue includes some deferred recognition of previously received up-front and milestone payments.

Year ending 31 December	CHF'000s	2009	2010	2011e	2012e	2013e
PROFIT & LOSS						
Revenue		**4,503**	**4,000**	**3,693**	**500**	**500**
Cost of sales		0	0	0	0	0
Gross profit		4,503	4,000	3,693	500	500
EBITDA		**(39,044)**	**(29,353)**	**(29,169)**	**(16,774)**	**(17,048)**
Operating profit (before GW and except.)		**(41,758)**	**(32,178)**	**(30,891)**	**(17,956)**	**(17,956)**
Amortisation		(121)	(116)	(80)	(40)	(40)
Share-based payments/other		(1,175)	(1,304)	(1,304)	(1,304)	(1,304)
Exceptionals		0	0	0	0	0
Operating profit		**(43,054)**	**(33,598)**	**(32,275)**	**(19,300)**	**(19,300)**
Net interest		362	(48)	500	200	0
Profit before tax (norm)		**(41,396)**	**(32,225)**	**(30,391)**	**(17,756)**	**(17,956)**
Profit before tax (FRS 3)		**(42,692)**	**(33,645)**	**(31,775)**	**(19,100)**	**(19,300)**
Tax		0	0	0	0	0
Profit after tax (norm)		**(41,396)**	**(32,225)**	**(30,391)**	**(17,756)**	**(17,956)**
Profit after tax (FRS3)		**(42,692)**	**(33,645)**	**(31,775)**	**(19,100)**	**(19,300)**
Average number of shares outstanding (m)		5.7	6.1	7.5	7.8	7.8
EPS - normalised (CHF)		(7.2)	(5.3)	(4.1)	(2.3)	(2.3)
EPS - FRS 3 (CHF)		(7.4)	(5.6)	(4.2)	(2.4)	(2.5)
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		**10,155**	**7,689**	**6,132**	**5,155**	**4,451**
Intangible assets		182	84	49	54	59
Tangible assets		9,568	6,568	5,046	4,064	3,355
Refund from assumption of dev costs		0	0	0	0	0
Other		405	1,037	1,037	1,037	1,037
Current assets		**78,399**	**66,495**	**37,228**	**20,409**	**3,116**
Stocks		0	0	0	0	0
Debtors		737	1,199	1,199	1,199	1,199
Cash		76,560	63,797	34,530	17,711	418
Other		1,102	1,499	1,499	1,499	1,499
Current liabilities		**(10,890)**	**(9,277)**	**(9,335)**	**(9,335)**	**(9,335)**
Trade payables		(4,524)	(3,147)	(3,500)	(3,500)	(3,500)
Short term borrowings		0	0	0	0	0
Provisions		0	0	0	0	0
Finance lease liabilities		0	0	0	0	0
Other current liabilities		(5,679)	(5,835)	(5,835)	(5,835)	(5,835)
Current portion deferred income		(687)	(295)	0	0	0
Long Term Liabilities		**(83)**	**(592)**	**(592)**	**(592)**	**(592)**
Long-term borrowings		0	0	0	0	0
Provisions		(83)	(592)	(592)	(592)	(592)
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**	**33,432**	**15,635**	**-2,361**
CASH FLOW						
Operating cash flow		**(39,376)**	**(31,341)**	**(29,522)**	**(16,774)**	**(17,048)**
Net interest		315	(48)	500	200	0
Tax		0	0	0	0	0
Capex		(4,137)	(408)	(200)	(200)	(200)
Acquisitions/disposals		0	0	0	0	0
Financing		315	19,851	0	0	0
Dividends		0	0	0	0	0
Other		(73)	(452)	(45)	(45)	(45)
Net cash flow		(42,957)	(12,397)	(29,267)	(16,819)	(17,293)
Opening net debt/(cash)		**(119,471)**	**(76,560)**	**(63,797)**	**(34,530)**	**(17,711)**
HP finance leases initiated		46	(366)	0	0	0
Other		(0)	0	0	0	0
Closing net debt/(cash)		**(76,560)**	**(63,797)**	**(34,530)**	**(17,711)**	**(418)**

Source: Edison Investment Research

Growth	Profitability	Balance sheet strength	Sensitivities evaluation	
N/A	N/A	N/A	Litigation/regulatory	●
			Pensions	○
			Currency	◖
			Stock overhang	○
			Interest rates	◖
			Oil/commodity prices	○

Growth metrics	%	Profitability metrics	%	Balance sheet metrics		Company details	
EPS CAGR 08-12e	N/A	ROCE 11e	N/A	Gearing 11e	N/A	Address:	
EPS CAGR 09-11e	N/A	Avg ROCE 09-11e	N/A	Interest cover 11e	N/A	12 Chemin des Aulx, 1228 Plan-les-Ouates, Geneva, Switzerland	
EBITDA CAGR 07-11e	N/A	ROE 11e	N/A	CA/CL 11e	4.0		
EBITDA CAGR 09-11e	N/A	Gross margin 11e	N/A	Stock turn 11e	0.0	Phone	41 22 884 1555
Sales CAGR 07-11e	N/A	Operating margin 11e	N/A	Debtor days 11e	118	Fax	41 22 884 1556
Sales CAGR 09-11e	N/A	Gr mgn / Op mgn 11e	N/A	Creditor days 11e	346	www.addexpharma.com	

Principal shareholders	%	Management team
Biotech Value Fund	30.0	**CEO: Dr Bharrat Chowrira**
Sofinnova Capital	10.3	Appointed in August 2011. Formerly SVP and COO of Nektar Therapeutics (May 2008-January 2011), executive director, worldwide licensing and external research at Merck & Co (2007-08) and VP, legal affairs at Sirna Therapeutics (1993-2006). Holds JD and PhD in microbiology and molecular genetics and is a registered US patent attorney.
TVM V Life Science Ventures	9.0	
Hottinger Capital	4.5	
SR One (GSK)	3.2	
		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.

Forthcoming announcements/catalysts	Date *	
Results of dipraglurant PD-LID study	Q212	
FY11 financial results	23 February 2012	**Chairman: André Mueller**
Results of JNJ-40411813 studies	Q312	Chairman since 2002. Board member of Synthes. Formerly vice chairman of Actelion, vice-president finance at Biogen (now Biogen Idec) and founding partner and director of investments at Genevest.
*Note: * = estimated*		
Companies mentioned in this report:	J&J, Merck & Co, GSK, Roche, Lilly, Novartis, AstraZeneca, Lundbeck, Neurosearch, Newron, Xenoport.	