Addex Therapeutics

Partnering update

Edison investment research

Targeting deals and data in 2013

Pharma & biotech

Buoyed by its recent fund-raising and pipeline progress, Addex is entering a critical period in which it hopes to secure a partnership for its lead programme, dipraglurant, for PD-LID and other CNS indications. Encouraging Phase II results for lead partnered drug, JNJ-40411813, being advanced for the treatment of negative symptoms in schizophrenia, raise the prospect of further positive clinical data in 2013 and/or initiation of new clinical studies by J&J. Addex's internal pipeline should also progress in 2013 with the initiation of Phase I trials for ADX71441.

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	0.4	(31.3)	(3.9)	0.0	N/A	N/A
12/13e	0.6	(23.0)	(2.7)	0.0	N/A	N/A

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

Dipraglurant deal closer, ADX71441 heads for Phase I

The recent CHF10m fund-raising means Addex is well financed as it continues partnership discussions for dipraglurant, its internal lead molecule for Parkinson's disease levodopa-induced dyskinesia (PD-LID). These discussions are supported by positive Phase IIa proof-of-concept data in PD-LID. Meanwhile, Addex also plans shortly to make a regulatory submission (CTA) to undertake the first-in-man studies with its $GABA_B$ receptor PAM, ADX71441. The intended initial focus of this programme will be spasticity associated with multiple sclerosis.

Encouraging '404 Phase II data, more in 2013?

Top-line results from the main (Part B) element of the Phase II study of JNJ-40411813 are reported to confirm safety and efficacy in schizophrenia patients with persistent negative symptoms, a group thought to comprise 20-40% of all schizophrenics. The study also identified the 50mg bid dose as having the optimal benefit/risk ratio. No specific safety or efficacy data were disclosed, in line with J&J's policy for early Phase II results. The Part B findings raise the prospect of further positive data in 2013 from the schizophrenia study (Part A) and, potentially, from the second Phase II study with this compound in anxious depression patients.

Financed to end-2013

The fund-raising has boosted Addex's cash reserves, which stood at CHF20m at the half year point, extending the runway to late 2013. Our updated model reflects new cash burn guidance of CHF20-21m/year (vs CHF25-27m/year); cash at the year end is projected to be CHF15m, exclusive of any revenues from new partnerships formed.

Valuation: Risk-adjusted NPV of CHF218m

We value Addex at $232m (CHF218m) 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.

4 December 2012

Price	CHF10.25
Market cap	CHF88m
	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	(3.3)	34.9	86.4
Rel (local)	(6.5)	26.3	54.4
52-week high/low	CHF12.4	CHF5.5	

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

Dipraglurant partnership	Q412/Q113
'404 Part A results	April 2013

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Addex datasheet

Exhibit 1: JNJ-40411813 schizophrenia study	
Design	105-pt two-part Phase II study. This consists of a 15-pt open-label, dose-escalation portion with the drug given as monotherapy to treatment naïve patients (Part A) and a 92 subject randomised element as adjunctive (add-on) therapy in pts who do not fully respond to antipsychotics (Part B). The two stages are run in parallel but analysed separately. Part A has a starting dose of 50mg bid, increasing in steps to 150mg bid over up to 12 wks. Part B has two dose levels: 50mg bid and 150mg bid. Results: Part B, top-line results reported Nov 2012; Part A (expected April 2013).
Subjects	Part A recruits treatment naïve pts with sub-acute psychosis. Part B recruited 92 pts with DSM IV diagnosis of schizophrenia >1 year with residual positive symptoms.[1] (n=25) or predominant negative symptoms.[2] (n=47) and/or an inadequate response to clozapine (n=20). Subjects were randomised (2:2:1).to receive either JNJ-40411813 at 50mg bid or 150mg bid or placebo, taken concomitantly with their currently prescribed antipsychotic medication.
Primary endpoints	Safety as measured by Udvalg for Kliniske Undersogelser (UKU) ratings, number of pts with abnormal clinical lab results, ECGs or physical exams, and AEs (Parts A and B). Part B reportedly showed that JNJ-40411813 met the primary objectives related to safety and tolerability (although no specific figures were disclosed).
Secondary endpoints	Efficacy as measured by positive and negative syndrome scale (PANSS), clinical global impression – schizophrenia (CGI-SCH) and subjective wellbeing under neuroleptics scale. Part B reportedly established efficacy that JNJ-40411814 was effective in pts with predominant negative symptoms. This suggests a separation vs placebo on PANSS score after 12 wks for JNJ-40411813 vs placebo. The implication is that there was no signal in the other two groups (residual positive symptoms and inadequate response to clozapine), but the small sample sizes may make these data difficult to interpret. 50mg bid was established as having optimal benefit/risk ratio, suggesting either there was no separation between 50mg and 150mg bid and/or tolerability issues at the higher dose.
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 generalised 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.
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 60-90 mins later), and evaluated at days 0, 1, 14 and 28.
Subjects	Male/females 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. 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 mGluR5-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 1 (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%). AUC_{0-3} showed c 20% difference on day 1 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 2-2.3hr vs 1.6hrs) and up to 70 mins. No increase in "off time" and a c 50 min/day reduction was seen at week 4.
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

1 Positive symptoms are symptoms such as hallucinations, delusions, disordered thoughts and speech that are not present in normal people.

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.

Update

Buoyed by its recent fund-raising and pipeline progress, Addex is entering a critical period in which it hopes to secure a partnership for its lead programme, dipraglurant, for PD-LID and other CNS indications. In addition, encouraging top-line results from the Phase II study of lead partnered drug JNJ-40411813 (ADX71149) raise the prospect of further positive clinical data and/or new clinical studies in 2013. Top-line results from the main portion (Part B) of the Phase II study of JNJ-40411813 in schizophrenia were reported as positive and to have established safety and efficacy in the sub-group of patients with residual negative symptoms, the principal target group for Addex's partner J&J. This study has also established the lower (50mg bid) of the two doses tested has the optimal benefit/risk ratio. The smaller, open-label portion of the study (Part A), in treatment-naïve schizophrenia patients, remains underway and is expected to render data in H113. Finally, headline results from a Phase II study of JNJ-40411813 in depression with anxiety symptoms might be available in H213.

No specific data were reported by J&J, which is in line with its normal policy for early Phase II results. However, J&J has allowed Addex to communicate sufficient qualitative information about the outcome in order to be compliant with stock market requirements. Hence, careful textual analysis of the press release does allow a number of inferences to be drawn.

Firstly, the study is 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 confirmed the 50mg bid dose as having the optimal benefit/risk ratio. These statements would suggest 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.

Secondly, efficacy has been established in patients with residual negative symptoms. We assume this would be measured by a separation vs placebo on PANSS[3] 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.

The Part B read-out from this study should be considered an important catalyst for Addex, especially given the recent failure of Phase III schizophrenia studies with Lilly's pomaglumetad methionil, a mechanistically-close mGluR2/3 agonist. Lilly conducted three pivotal studies with pomaglumetad methionil in schizophrenia, one of which was as adjunctive therapy (a 280-patient Phase II study, known as H8Y-MC-HBCO) in prominent negative symptoms.[4] None of the three studies met their primary or secondary endpoints or apparently showed any evidence of efficacy. Lilly did report that its decision to discontinue was not based on any safety signal.

This product's discontinuation leaves J&J with a virtually clear field for glutamate targeting agents in schizophrenia and anxiety (J&J is separately conducting a Phase II study with JNJ-40411813 in anxious depression with expected completion in H213). Furthermore, J&J's future investment decisions in relation to JNJ-40411813 can now be made in the context that it is no longer running behind a competitor with a closely-related mechanism. 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.

3 The Positive and Negative Syndrome Scale is a validated tool for measuring symptom severity in schizophrenia.
4 The other two were monotherapy: a 1,100 Phase III study (H8Y-MC-HBBN) for acute schizophrenia and an 880-patient pivotal Phase II study (H8Y-MC-HBBM) in acute exacerbations.

Exhibit 2: Competing development programmes for PD-LID

Product	Company	Mechanism	Development stage/notes
Mavoglurant (AFQ056)	Novartis	mGluR5 NAM	140-pt Phase II study (150/200mg bid; results: Apr 2013); 108-pt open-label Phase II study (results: Nov 2015); 119-pt open-label extension (results: Dec 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: Dec 2012).
AQW051	Novartis	α-7 nAChR inhib	72-pt Phase II study (results: Jan 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

Exhibit 3: 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: Jul 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: 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	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: 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: Dec 2012).
Zicronapine	Lundbeck	D_1 antagonist; $5HT_{2A}$ antagonist	160-pt Phase III study vs risperidone, measuring efficacy and metabolic parameters (results due: Aug 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: Apr 2013).
PF-02545920	Pfizer	PDE10 inhibitor	260-pt Phase II study for acute exacerbation (completed).
TC-5619	Targacept	α7 nAChR partial agonist	456-pt Phase IIb study for negative symptoms/cognitive dysfunction (results: May 2013).

Source: Edison Investment Research

Exhibit 4: Addex's key preclinical programmes

Programme	Indication	Notes
ADX71441/ $GABA_BR$ PAM	MS spasticity/alcohol dependence	ADX71441 selected for development for MS spasticity. CTX submission expected Q412, with Phase I initiation planned in H113. ADX71441 has also shown activity in mouse model of alcohol binge drinking. Acute administration of ADX71441 (3, 10, 30mg/kg) resulted in a dose-dependent suppression of alcohol intake, achieving 80% reductions at higher doses (10, 30mg/kg) vs vehicle treatment. The effect of ADX71441 in this model was more robust and longer-lasting than with naltrexone, a positive control. Prior lead compounds have shown efficacy in models of anxiety, OAB and pain.
mGluR4 PAM	Parkinson's/anxiety	Tool compound ADX88178 has demonstrated efficacy in several rodent models of PD including reversal of haloperidol induced catalepsy (HIC) in rats, dose-dependent reversal of the forelimb akinesia deficit induced by bilateral 6-OHDA lesion in rats. Proof-of-concept in a validated model of multiple sclerosis, the mouse Relapsing-Remitting Experimental Allergic Encephalomyelitis (RR-EAE) model. Programme previously partnered with Merck & Co, but rights were returned in 2011.
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).

Source: Edison Investment Research

BD campaign for dipraglurant nears conclusion?

Addex is indicating that its campaign to secure a licensing deal for the lead internal product, dipraglurant, an mGluR5 NAM, is progressing well. The company is using the Phase IIa data in Parkinson's disease levodopa-induced dyskinesia (PD-LID) as a basis for attracting a partner.

Unlike the position with JNJ-40411813, dipraglurant is competing with a compound with an identical mechanism that is further ahead, namely Novartis's mavoglurant (AFQ056), which is in Phase II studies for PD-LID, as well as for Fragile X syndrome. Novartis has completed several Phase II studies of mavoglurant in PD-LID. However, it appears to have moved to a modified-release formulation and recently updated its filing target for PD-LID to 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.

Addex is targeting PD-LID as its initial indication because it offers a direct path to market and represents a large unmet medical need. However, dipraglurant has 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 non-motor 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. Addex has generated non-clinical data to suggest that dipraglurant could have benefit for treating non-parkinsonian dystonias, of which there are 16 subtypes (idiopathic generalised and focal dystonias).

$GABA_BR$ PAM programme heading for the clinic

Addex will shortly make a regulatory submission (CTX) to undertake the first-in-man studies with its $GABA_B$ receptor PAM, ADX71441. Addex has shown proof of concept with various $GABA_BR$ PAMs in preclinical models of pain, anxiety, obsessive-compulsive disorder and overactive bladder (OAB). $GABA_B$ agonists have shown activity in other indications, including gastroesophageal reflux disease..[5]

The intended initial focus of this programme will be multiple sclerosis spasticity. This will mean that ADX71441 will have to compete with Xenoport's $GABA_B$ agonist arbaclofen placarbil, which is in a 200-patient Phase III study for MS spasticity. Addex's programme is aimed at exploiting the allosteric binding mechanism to confer an improved profile versus baclofen, a widely used and now off-patent $GABA_B$ agonist. Baclofen is indicated for spasticity associated with spinal cord injuries and also used in other indications including overactive bladder (OAB). However, the drug has a number of limitations linked to its rapid clearance, development of tolerance, rebound and withdrawal syndrome.

Baclofen has shown clinical relevance in a number of other indications, which interestingly include alcohol dependence, where there are a number of investigator-sponsored studies underway. This in fact may become a second indication for ADX71441, since Addex has just presented data showing reduction of alcohol intake for its compound in a preclinical model of alcohol binge drinking. Clinical and preclinical data suggest that activation of the $GABA_B$ receptor offers a way to address various

5 This was the target indication for AstraZeneca's now-discontinued lesogaberan.

components of alcohol and drug addiction, including the physical symptoms (pain, gastrointestinal/urinary disturbances) and emotional symptoms (anxiety) associated with withdrawal; as well as reducing craving.

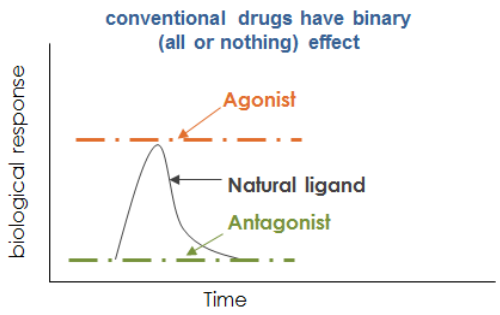
Exhibit 5: Competing programmes targeting mGluRs (clinical only)

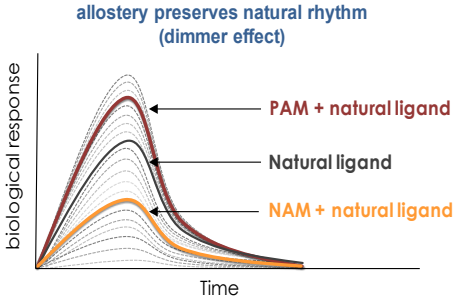
Product	Mechanism	Indication(s)	Trials
Mavoglurant/ **Novartis**	mGluR5 NAM	Fragile X	160-pt Phase II/III study in adults (results: Dec 2013).
			160-pt Phase II/III study in adolescents (results: Dec 2013).
			200-pt long-term safety study (results: Sept 2015).
		PD-LID	Four Phase II studies (see Exhibit 2).
RO4917523/ RG70980 **Roche**	mGluR5 NAM[6]	Tx–resistant depression	300-pt Phase IIb study (MARIGOLD) (results: Nov 2013).
		Fragile X syndrome	180-pt Phase II study (results: Nov 2013).
RG1578/ RO4995819 **Roche**	mGluR2/3 NAM[5]	Major depression	480-pt Phase II study (results: Dec 2013).

Source: Edison Investment Research.

Exhibit 6: 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 These are now described by Roche as "negative modulators".

Metabolotropic glutamate universe

The discontinuation of Lilly's pomeglumetad has left five different compounds targeting metabolotropic glutamate receptors currently in active clinical development[7], all of which are allosteric modulators. Addex is responsible for two of these (the other three are shown in Exhibit 5). Addex also has three preclinical programmes targeting mGluRs and was recently awarded a CHF0.7m grant from the Swiss Commission for Technology and Innovation to fund work, in collaboration with the University of Lausanne and the Ecole Polytechnique Fédérale de Lausanne, on mGluR4 and mGluR7.

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. The failure of pomaglumetad should create a larger opportunity for JNJ-40411813. The 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 7: 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
$GABA_B$ PAM	MS spasticity	Preclinical	2016	5%	2%	10.0

Source: Edison Investment Research

Sensitivities

Addex is relatively well funded with cash, following the fund-raising, sufficient to late 2013. Thus, it has a relatively low risk profile for a biotech company. With the positive result in the Phase II study of JNJ-40411813 in schizophrenia, the key risks to the investment case relate to Addex's ability to form an economically attractive partnership for dipraglurant. Longer-term sensitivities include the success or failure of competitors (now principally Novartis's mavoglurant) and its reliance on J&J as a partner for JNJ-40411813. Addex has a single substantial shareholder, Biotech Value Fund, which owns a~30% stake. Visium Asset Management has taken a 5% stake in the recent fund-raising.

Financials

Edison's updated financial model is shown in Exhibit 8. This is in line with recent financial guidance principally suggesting year-end cash of c CHF15m, exclusive of any revenues from new partnerships formed. We presume that R&D expenditure will be c CHF 23m in 2012, with G&A costs of CHF6.6m with CHF4m of exceptional costs incurred in connection with the restructuring (termination benefits, leasehold surrender etc). Assuming R&D expenditure of CHF20m in 2013 and G&A spending of CHF5m, Addex is funded to Q313.

7 Seaside Therapeutics has an mGluR5 NAM that is ostensibly ready to enter Phase II for Fragile X syndrome, but no activity appears to be underway.

Exhibit 8: Financial summary

Year ending 31 Dec	CHF'000s	2009	2010	2011	2012e	2013e
PROFIT & LOSS						
Revenue		**4,503**	**4,000**	**3,743**	**442**	**600**
Gross profit		4,503	4,000	3,743	442	600
EBITDA		**(39,044)**	**(29,353)**	**(27,163)**	**(30,211)**	**(22,322)**
Operating profit (before GW and except.)		(41,758)	(32,178)	(29,607)	(31,393)	(23,035)
Amortisation		(121)	(116)	(63)	(40)	(20)
Share-based payments/other		(1,175)	(1,304)	(1,304)	(1,859)	(1,304)
Exceptionals		0	0	0	(4,000)	0
Operating profit		(43,054)	(33,598)	(30,974)	(37,292)	(24,359)
Net interest		362	(48)	(167)	90	0
Profit before tax (norm)		**(41,396)**	**(32,225)**	**(29,774)**	**(31,303)**	**(23,035)**
Profit before tax (FRS 3)		**(42,692)**	**(33,645)**	**(31,141)**	**(37,202)**	**(24,359)**
Tax		0	0	0	0	0
Profit after tax (norm)		(41,396)	(32,225)	(29,774)	(31,303)	(23,035)
Profit after tax (FRS3)		(42,692)	(33,645)	(31,141)	(37,202)	(24,359)
Ave no of shares out (m)		5.7	6.1	7.5	8.0	8.6
EPS - normalised (CHF)		(7.2)	(5.3)	(4.0)	(3.9)	(2.7)
EPS - FRS 3 (CHF)		(7.4)	(5.6)	(4.2)	(4.6)	(2.8)
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**	**5,548**	**4,531**	**4,002**
Intangible assets		182	84	32	7	2
Tangible assets		9,568	6,568	3,964	2,972	2,449
Other		405	1,037	1,551	1,551	1,551
Current assets		**78,399**	**66,495**	**38,068**	**18,079**	**553**
Stocks		0	0	0	0	0
Debtors		737	1,199	667	667	667
Cash		76,560	63,797	36,065	15,221	694
Other		1,102	1,499	1,336	2,192	2,192
Current liabilities		**(10,890)**	**(9,277)**	**(8,728)**	**(9,617)**	**(9,617)**
Trade payables		(4,524)	(3,147)	(1,686)	(1,686)	(1,686)
Provisions		0	0	(215)	(1,123)	(1,123)
Other current liabilities		(5,679)	(5,835)	(6,828)	(6,809)	(6,809)
Current deferred income		(687)	(295)	0	0	0
Long Term Liabilities		**(83)**	**(592)**	**(1,052)**	**(732)**	**(5,732)**
Long-term borrowings		0	0	0	0	(8,000)
Provisions		(83)	(592)	(1,052)	(732)	(732)
Other long-term liabilities		0	0	0	0	0
Net assets		**77,581**	**64,314**	**33,836**	**12,261**	**(10,794)**
CASH FLOW						
Operating cash flow		**(39,376)**	**(31,341)**	**(26,551)**	**(30,229)**	**(17,322)**
Net interest		315	(48)	(167)	90	0
Tax		0	0	0	0	0
Capex		(4,137)	(408)	(167)	(190)	(190)
Acquisitions/disposals		0	0	0	0	0
Financing		315	19,851	(183)	9,500	0
Dividends		0	0	0	0	0
Other		(73)	(452)	(15)	(15)	(15)
Net cash flow		(42,957)	(12,397)	(27,083)	(20,845)	(17,527)
Opening net debt/(cash)		**(119,471)**	**(76,560)**	**(63,797)**	**(36,065)**	**(15,221)**
HP finance leases initiated/other		46	(366)	(649)	0	0
Closing net debt/(cash)		**(76,560)**	**(63,797)**	**(36,065)**	**(15,221)**	**2,306**

Source: Edison Investment Research, Addex accounts

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