Addex Therapeutics

Phase II study

Edison investment research

J&J anxiety go-ahead

Biotech

J&J has recently disclosed plans to conduct a Phase II study on the Addex-licensed mGluR2 PAM, JNJ-40411813, in anxiety co-morbid with depression. J&J is concurrently completing its Phase II study of the compound in schizophrenia, with data expected in Q4. Meanwhile, Addex has cut back its workforce to extend its cash reach while it seeks a partner for dipraglurant, for which positive Phase II data in PD-LID were recently reported.

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

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

New study of JNJ-40411813 in anxiety with depression

J&J plans to conduct a 94-patient Phase II trial of JNJ-40411813 as an add-on treatment to antidepressants in adults where anxiety symptoms are present with depression. Moreover, the decision to move ahead with the study, ahead of the read out of the Phase II study in schizophrenia, is an indication of J&J's confidence in the programme.

Schizophrenia data to come in Q4

The Phase II study of JNJ-40411813 in schizophrenia is due to read out in Q4. It will provide randomised data on the drug as adjunctive (add-on) therapy in patients who do not respond fully to other antipsychotics.

Plan to seek partnership in 2012

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

Valuation: Risk-adjusted NPV of CHF214m

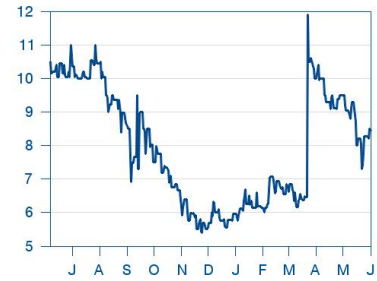
We maintain our risk-adjusted NPV of $232m/CHF214m, which when adjusted for forecast end 2012 cash is equivalent to CHF29.4/share. We assume industry-standard success probabilities for compounds based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813.

6 June 2012

Price	CHF8.5
Market cap	CHF65m

Shares in issue	7.7m
Free float	38%
Code	ADXN
Primary exchange	SIX
Other exchanges	N/A

Share price performance



%	1m	3m	12m
Abs	-10.4	25.3	-19.0
Rel (local)	-6.7	30.9	-9.3

52-week high/low	CHF11.9	CHF5.4

Business description

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

Next events

International Congress of Parkinson's Disease and Movement Disorders	17- 21 June
BIO International Convention	18-21 June

Analyst

Robin Davison +44(0)20 3077 5737

healthcare@edisoninvestmentresearch.co.uk

Edison profile page

Addex datasheet

Addex core R&D programmes			
Product	**Indication**	**Stage**	**Notes**
JNJ-40411813	Schizophrenia/ anxiety/other	Phase II	mGluR2 PAM. 105-pt Phase II study in schizophrenia and 94-pt Phase II study as adjunctive therapy for anxiety co-morbid with depression (see Exhibits 2 and 3). Partnered with **Johnson & Johnson**.
Dipraglurant	PD-LID/dystonia	Phase II	mGluR5 NAM. 72-pt, four wk Phase II study completed in PD-LID with positive results. IR version for PD-LID; ER version for dystonia/other CNS indications. See presentation and technical document.
ADX71441	OA Pain/overactive bladder	IND enabling studies	$GABA_BR$ PAM. IND planned for Q412. Study in female guinea pigs with bladder over-activity shows increase in inter contraction interval, a validated measure of bladder muscle control, in first 15 min post-admin vs vehicle. ADX71441 also decreased micturition frequency vs vehicle at 1mg/kg. Dose-dependent normalisation of urination latencies seen in a mouse diuretic stress-induced OAB and dose-dependent reduction of micturition frequency in furosemide-treated animals. Magnitude of effect similar to oxybutynin, without effects on body temperature, loco-motor activity or coordination.
mGluR4 PAM	Parkinson's disease	Lead opt	Clinical candidate selection H112. Lead candidate(s) have demonstrated efficacy in preclinical models of in various acute/chronic animal models of Parkinson's disease and anxiety. See presentation.
GLP1R PAM	Type II diabetes	Lead opt	Preclinical data from tool compound ADX91886 in the db/db model show an insulin response and better control over blood glucose than vehicle or sitagliptin (a DPP-4 inhibitor, as active control).
TrkB PAM	Neuro-degenerative disease	Hit to lead	Lead optimisation. Oral candidates identified against a target that has been otherwise intractable to conventional approaches.
TNFR1 NAM	Autoimmune	Hit to lead	Hit to lead. Oral products could be brain penetrant, hence possible development in indications characterised by neurological inflammation (Alzheimer's, MS, depression).

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

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

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

Source: Edison Investment Research

Update J&J boldly goes into anxiety

Janssen Pharmaceuticals (J&J) will initiate a Phase II study of the Addex-licensed mGluR2 PAM, JNJ-40411813 (ADX71149), in anxiety co-morbid with depression. The move comes a few months ahead of the read out of a Phase II study of the compound in schizophrenia, itself a major stock catalyst for Addex, hence the move can be seen as a vote of confidence in the programme.

J&J will conduct a 94-patient Phase II trial of JNJ-40411813 as add-on treatment to antidepressants in adults where anxiety symptoms are present with depression. The study will be similar in size to the randomised phase of the schizophrenia study and has an efficacy measure (Hamilton Anxiety Rating Scale) as its primary endpoint. In the schizophrenia study, efficacy is measured by secondary endpoints (with a primary endpoint of safety).

The study will look for evidence of efficacy in treating anxiety when present with depression, presumably without adversely affecting the treatment of the depression component (Roche is studying an mGluR2 antagonist, RG1578[1], as an add-on therapy to antidepressants in major depression). A Lilly mGluR2/3 agonist LY-404039 is believed to have shown efficacy in a Phase II trial for anxiety (although was discontinued because of issues believed unrelated to the mechanism). Anxiety is frequently present with depression and certain classes of anti-psychotics commonly seen as antidepressants (notably selective serotonin reuptake inhibitors) are also indicated for treatment of various anxiety disorders. However, the market has seen little innovation in recent years and is now virtually entirely served by generics (backgrounds on anxiety and competitive programmes are shown in Exhibits 1 and 2 overleaf).

Meanwhile, the Phase II study of JNJ-40411813 in schizophrenia is expected to complete recruitment in H112 and render results in Q4. If this study is successful, J&J will presumably look to conduct a larger Phase IIb (including possibly as monotherapy) to prepare for the Phase III registration programme. Up-regulation of glutaminergic activity via mGluR2 receptor appears to offer an alternative way treat the positive[2] and the harder-to-treat negative[3] symptoms of schizophrenia, without the side effects such as weight gain, hyperprolactinemia or extrapyramidal symptoms associated with dopamine antagonists.

J&J has one of two approaches that up-regulate the mGluR2 receptor; Lilly has a more advanced, but orthosteric, mGluR 2/3 agonist, pomaglumetad methionil (formerly LY2140023). Addex believes that there are advantages conferred by the greater sub-type selectivity of its molecule (ie for mGluR2) as well as from its allosteric mechanism. Lilly's pomaglumetad methionil is in five[4] Phase III studies for schizophrenia, all as monotherapy. A number of these studies are scheduled to read out over the next year so their outcome may influence J&J's plans for JNJ-40411813. It is possible that J&J may develop JNJ-40411813 initially as an add-on therapy with risperidone[5].

[1] We believe this to be RO4995819, which is in a 480-pt Phase II study as an adjunctive therapy in patients with major depressive disorder with inadequate response to on-going antidepressant treatment.
[2] Positive symptoms are those that normal individuals do not normally experience, but are present in people with schizophrenia. They are typically regarded as manifestations of psychosis and can include paranoid or bizarre delusions, disordered thoughts and speech, auditory or visual hallucinations, delusions etc.
[3] Negative symptoms are deficits of normal emotional responses or of other thought processes, and commonly include flat or blunted affect and emotion, poverty of speech, inability to experience pleasure, lack of desire to form relationships, and lack of motivation. They respond less well to medication.
[4] Two pivotal efficacy studies (one versus aripiprazole and one placebo), two long-term safety studies and a large Phase II/III study versus standards of care (olanzapine, aripiprazole, risperidone, quetiapine).
[5] J&J was the originator of risperidone, which as Risperdal, was a blockbuster, although is now off-patent. The long-acting depot formulation Risperdal Consta is, nevertheless, an important product for J&J.

Exhibit 1: Anxiety - background		
Description	An exaggerated response to a natural fear or an excessive fear in a normal situation. Comprises various disorders including panic disorder, social phobia, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and generalised anxiety disorder (GAD). Often co-morbid with other psychiatric conditions such as depression, schizophrenia and addiction.	
Incidence/ prevalence	Prevalence is c.20% of the population, including >40m persons in US (6.8m with GAD, c.6m with panic disorder, 15m with social phobia, 2.2m with OCD and 7.7m with PTSD. Pharmaceutical market has historically been large, but is now largely served by generic products and has contracted significantly to around $5bn/year.	
Current drug treatment	**Class**	**Use/limitations**
	Benzodiazapines	Rapid acting but with problems of sedation, memory impairment/confusion and reduced muscle coordination/balance. Risk of tolerance and habit formation.
	SSRI	Approved for panic, social anxiety and GAD in adults (paroxetine is contraindicated for children). Lack of sedation or cognitive impairment but slow onset of action, with sexual dysfunction/weight gain. Discontinuation syndrome and drug-drug interactions.
	Azapirones	Lack of addiction/dependence/tolerance issues but slow onset of action.
	SNRI	Lack of addiction/dependence/tolerance issues. Venlafaxine has withdrawal symptoms and is contraindicated in children and adolescents because of risk of suicidal ideation.

Exhibit 2: Competing development programmes in anxiety (Phase II or later)		
Class	**Company**	**Notes**
Cymbalta (duloxetine)	Lilly	260-pt Phase III study in paediatric patients with GAD (results: Aug 2013).
Vortioxetine Lu AA21004	Lundbeck/ Takeda	48-pt Phase II study in child/adolescents with depressive or anxiety disorder (results: Sept 2013). Two Phase III studies completed in GAD (no results yet). Eight Phase III trials underway and 10 completed in depression.
MN-305/ MKC-242	MediciNova/ Mit. Tanabe	416-pt Phase II study in GAD showed trends in all efficacy outcome measures and significant improvements in HAM-A total score and item 1 of HAM-A (anxious mood).
ABIO 0801	Abiogen	Phase II studies (no details disclosed).
Nepicastat	Biotie	120-pt Phase II study for PTSD (results: Jun 12).
SPD-503/ Intuniv	Shire	80-pt Phase II study of guanfacine in subjects (aged 6-17 yrs) with GAD, separation anxiety disorder (SAD), or social phobia (results due: Feb 2012).
GSK	Neurocrine Biosciences	150-pt Phase II study in women with PTSD (results: Dec 2012).

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 24m people worldwide and more than 50% of people with schizophrenia are not receiving appropriate therapy.
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	Antipsychotic market is estimated at $25.4bn (+9%) in 2010, split c 70:30 between schizophrenia: bipolar disorder. Market is likely to contract due to generic erosion.

Exhibit 4: Competing development programmes for schizophrenia (Phase II or later)		
Drug	**Company**	**Development status/notes**
Cariprazine (RGH-188)	Forest/Richter /M Tanabe	450-pt and 600-pt Phase III studies completed with positive results. 700-pt Phase III study in prevention of relapse (results: Jul 2013). Separately in Phase III for bipolar disorder.
Pomaglu meth (LY2140023)	Eli Lilly	950-pt Phase III study (results: Feb 2013); 880-pt Phase II study (results: May 2012); 670-pt Phase III study vs aripiprazole (results: Oct 2012); 280-pt Phase II study (prominent negative symptoms (results: Jun 2012), 1,210-pt open label Phase II/III study (results: June 2015). 150-pt Phase III study to investigate physical dependence (results: Dec 2012).
OPC-34712	Otsuka/ Lundbeck	660-pt Phase III study (BEACON) and 630-pt Phase III study (VECTOR) (results: Mar 2013), 1,000-pt Phase III study (ZENITH) (results: Jan 2016). Dose finding Phase II/III study. (Also 3x Phase III trials in depression (>2,500 pts in total).
RG1678/ RO4917838	Roche	Three 630-pt Phase III studies (SUNLYTE, DAYLYTE and FLASHLYTE) in pts with persistent, predominant negative symptoms as add-on to antipsychotics (results: Jul 2015). Three 600-pt Phase III studies (NIGHTLYTE, MOONLYTE and TWILYTE) in pts with sub-optimal symptom control (results: Aug 2015). 300-pt Phase II study for acute exacerbations (results: Oct 2012).
Zicronapine	Lundbeck	160-pt Phase III study vs risperidone on metabolic parameters (results: Jul 2012).
BL-1020	BioLineRx	435-pt Phase II/III study vs risperidone and placebo.
ALKS 9070	Alkermes	690-pt Phase III study in acute exacerbations (results: Apr 2013).
CYR-101/ MT-210	M Tanabe/ Cyrenaic	100-pt Phase II study completed, results apparently positive but no details.
PF-02545920	Pfizer	260-pt Phase II study for acute exacerbation (completed)
TC-5619	Targacept	456-pt Phase IIb study for negative symptoms/cognitive dysfunction (results: May 2013).

Source: Edison Investment Research

If the drug shows potential, it may be developed subsequently as monotherapy, which would require a more substantial undertaking in terms of registration studies, including probably comparative studies against atypical antipsychotics and possibly pomaglumetad methionil (if the Lilly product is successful).

Schizoprenia is a much larger market than anxiety, although it is also seeing the patent expiries of leading products. There is, however, more competitive activity with five compounds in Phase III studies (including Forest's caripazine, which has reported positive results and will presumably shortly be filed). A further six compounds in active Phase II studies (including JNJ-40411813). Backgrounds on schizophrenia and competitive developments are shown opposite in Exhibits 3 and 4.

BD campaign for dipraglurant

Addex is currently seeking a licensing deal or partnership for its lead product, the mGluR5 NAM dipraglurant, on the back of the recent positive Phase IIa data in Parkinson's disease levodopa-induced dyskinesia (see Exhibit 5, overleaf). Dipraglurant competes with a Novartis product with the same mechanism, mavoglurant (AFQ056), which is in several Phase IIb studies for PD-LID (as well as for treatment of Fragile X syndrome). Novartis has conducted several Phase II studies of mavoglurant in PD-LID, including a dose-ranging Phase II study that suggested it been under-dosed. Novartis has initiated new Phase II studies involving higher doses (100mg/150mg bid) and with a modified release formulation that read out later this year.

Novartis continues to target a 2014 filing for mavoglurant in PD-LID, although this looks ambitious as its current Phase II studies do not report until H212 and it would certainly require it to start Phase III this year. It will also have to make a Phase III decision in the light of the dipraglurant data. Furthermore, if Addex is able to partner dipraglurant quickly, it could potentially match the hypothetical Novartis timeline. Backgrounds on PD-LID and competing PD-LID programmes are shown in Exhibits 6 and 7 (overleaf).

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

Valuation

We maintain our valuation of Addex at $232m (CHF214m at current FX rates), which if adjusted for forecast end FY12 cash is equivalent to CHF29.4/share. The valuation is based on the risk-adjusted net present value of the two lead clinical stage programmes and the $GABA_B$ PAM (which is approaching the IND stage). Hence, all Addex's other assets represent pure upside. We assume industry-standard success probabilities (eg 35% for a Phase II compound) based on their development stage and a hypothetical 18% royalty on dipraglurant and 12% on JNJ-40411813 (in line with the terms of the licensing deal).

The valuation assumes estimated costs of development up to the point of expected licensing, and in the case of JNJ-40411813, a probability-adjusted contribution from the known milestones. Since J&J is bearing all the costs of JNJ-40411813 this contributes the largest share of the valuation, currently 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.

Exhibit 5: Results of the Phase II study in PD-LID	
Study	76-pt pts (dipraglurant, n=52; pbo, n=24) with moderate or severe PD-LID 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. Dyskinesia provoked by taking levodopa (LID occurs 60-90 mins 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 a mAIMS score at baseline ≥7 with a score ≥3 in at least one body area.
Safety/ tolerability (primary endpoint)	50mg and 100mg doses both well tolerated with incidence of AEs similar in active and placebo groups (88.5% vs 75%). Typical mGluR5-type AEs (vertigo, visual disturbance, feeling drunk) seen in <10% of pts on dipraglurant but were not severe or dose limiting. 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. Achieved targeted magnitude of effect (defined as either a 30% reduction or a 20% separation from pbo) at Day 1, 14 and 28. **AUC mAIMS evaluation** (in three-hour post-levodopa dosing period). 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 30-45mins (eg 2-2.3hr vs 1.6hrs) and up to 70 mins. No increase in "off time" seen, in fact 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 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.

Exhibit 6: 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 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.
Current approach to management	Levodopa, usually given in combination with carbidopa, is considered the gold-standard treatment, but its use is limited by the development of dyskinesias. 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. Dopamine agonists have disinhibitory effects that can lead to impulse control disorders (eg pathological gambling) and/or hyper-sexual behaviour. Delaying levodopa has the drawback it is when the drug is finally introduced patients are less able to respond.
PD-LID	Dyskinesia (abnormal movements) 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.

Exhibit 7: Competing development programmes for PD-LID

Product	Company	Mechanism	Development stage/notes
Mavoglurant (AFQ056)	Novartis	mGluR5 NAM	92-pt Phase II study (150/200mg bid; results: Nov 2012); 63-pt 12-wk fixed dose Phase II study with titration at 2-wk intervals (results: June 2012). 108-pt Phase II, titration to target (or highest tolerated) dose (results: Nov 2015); 119-pt open-label extension (results: Dec 2014). 197-patient Phase IIb trial shows sig difference in terms of mAIMS and UPDRS-IV item 32 only for pts on highest dose.
Safinamide	Newron/Meiji/ Zambon	MAO-B inhibitor	36-pt Phase II trial in PD-LID (completed, no results yet). Primarily in development of PD.
Amantadine	Adamas	NMDA antago	80-pt Phase II/III study (results: Dec 2012).
AQW051	Novartis	α-7 nAChR inhib	80-pt Phase II/III study (results: Dec 2012).
NP002	Neuraltus	nicotine agonist	65-pt Phase II trial showed clinically relevant trends and/or 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.

Exhibit 8: 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	OA pain/other	Preclinical	2016	5%	2%	10.0

Source: Edison Investment Research

Dipraglurant's competitive position is an important factor in the valuation and, if this were to improve (eg if Novartis were to discontinue mavoglurant in PD-LID for commercial reasons) it would significantly enhance the valuation as a higher market share could be assumed. Inputs used in the valuation are tabulated in Exhibit 8.

Sensitivities

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

Financials

Pending new guidance, we have retained our current model, which shows R&D expenditure of CHF20m in 2012 and CHF15m in 2013. However, note that Addex has recently undergone a reorganisation that reduced its headcount by around 28 people (from 82 to 54). We understand the move was largely driven by the cost differential of performing certain research functions in low cost countries relative to Switzerland. We estimate the restructuring could save CHF2m in 2012 (net of one-off costs) and some CHF4-6m in 2013 with the same research functions achieved at lower cost. Hence this should extend its cash reach to the end of 2013. A CHF5m financing requirement for 2013 is currently shown in the model as long-term debt. Our financial model is shown in Exhibit 9.

Exhibit 9: Financial summary

Year ending 31 December	CHF'000s	2009	2010	2011	2012e	2013e
PROFIT & LOSS						
Revenue		**4,503**	**4,000**	**3,743**	**600**	**600**
Cost of sales		0	0	0	0	0
Gross profit		4,503	4,000	3,743	600	600
EBITDA		**(39,044)**	**(29,353)**	**(27,163)**	**(21,674)**	**(17,163)**
Operating profit (before GW and except.)		(41,758)	(32,178)	(29,607)	(22,856)	(17,876)
Amortisation		(121)	(116)	(63)	(40)	(20)
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)	(30,974)	(24,200)	(19,200)
Net interest		362	(48)	(167)	200	0
Profit before tax (norm)		**(41,396)**	**(32,225)**	**(29,774)**	**(22,656)**	**(17,876)**
Profit before tax (FRS 3)		**(42,692)**	**(33,645)**	**(31,141)**	**(24,000)**	**(19,200)**
Tax		0	0	0	0	0
Profit after tax (norm)		(41,396)	(32,225)	(29,774)	(22,656)	(17,876)
Profit after tax (FRS3)		(42,692)	(33,645)	(31,141)	(24,000)	(19,200)
Average number of shares outstanding (m)		5.7	6.1	7.5	7.8	7.8
EPS - normalised (CHF)		**(7.2)**	**(5.3)**	**(4.0)**	**(2.9)**	**(2.3)**
EPS - FRS 3 (CHF)		**(7.4)**	**(5.6)**	**(4.2)**	**(3.1)**	**(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**	**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
Refund from assumption of dev costs		0	0	0	0	0
Other		405	1,037	1,551	1,551	1,551
Current assets		**78,399**	**66,495**	**38,068**	**16,389**	**4,021**
Stocks		0	0	0	0	0
Debtors		737	1,199	667	667	667
Cash		76,560	63,797	36,065	14,386	2,019
Other		1,102	1,499	1,336	1,336	1,336
Current liabilities		**(10,890)**	**(9,277)**	**(8,728)**	**(8,728)**	**(8,728)**
Trade payables		(4,524)	(3,147)	(1,686)	(1,686)	(1,686)
Short term borrowings		0	0	0	0	0
Provisions		0	0	(215)	(215)	(215)
Finance lease liabilities		0	0	0	0	0
Other current liabilities		(5,679)	(5,835)	(6,828)	(6,828)	(6,828)
Current portion deferred income		(687)	(295)	0	0	0
Long Term Liabilities		**(83)**	**(592)**	**(1,052)**	**(1,052)**	**(6,052)**
Long-term borrowings		0	0	0	0	(5,000)
Provisions		(83)	(592)	(1,052)	(1,052)	(1,052)
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**	**11,140**	**(6,757)**
CASH FLOW						
Operating cash flow		(39,376)	(31,341)	(26,551)	(21,674)	(12,163)
Net interest		315	(48)	(167)	200	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)	0	0
Dividends		0	0	0	0	0
Other		(73)	(452)	(15)	(15)	(15)
Net cash flow		(42,957)	(12,397)	(27,083)	(21,679)	(12,368)
Opening net debt/(cash)		**(119,471)**	**(76,560)**	**(63,797)**	**(36,065)**	**(14,386)**
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)**	**(14,386)**	**(2,019)**

Source: Edison Investment Research, company accounts

Registered in England, number 4794244. Edison Investment Research is authorised and regulated by the Financial Services Authority.
www.edisoninvestmentresearch.co.uk

London +44 (0)20 3077 5700
Lincoln House, 296-302 High Holborn
London, WC1V 7JH, UK

New York +1 212 551 1118
380 Lexington Avenue, Suite 1724
NY 10168, New York, US

Sydney +61 (0)2 9258 1162
Level 33, Australia Square, 264 George St,
Sydney, NSW 2000, Australia