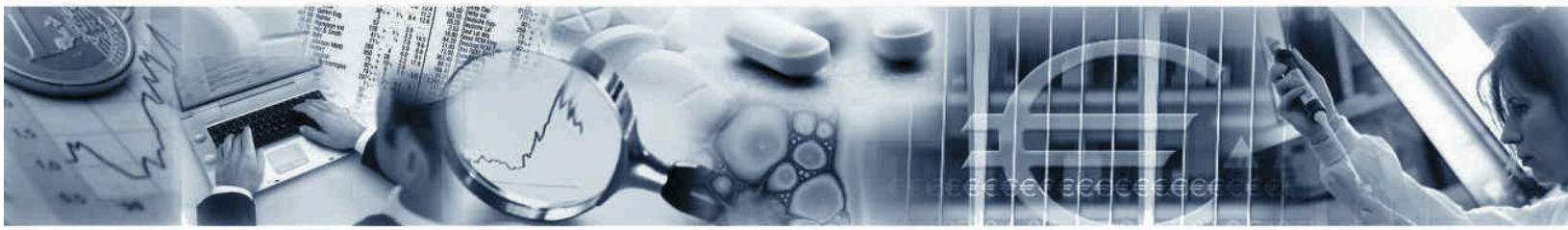

Update Report

Addex Therapeutics

Well Funded and Starting Pivotal Clinical Trial

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Name:	**Addex Therapeutics**
Country:	**Switzerland**
Price:	**CHF 2.35**
ISIN Code:	**CH0029850754**
Reuters Code:	**ADXN.SW**
Market Cap (CHF m):	**67.1**
EV (CHF m):	**22.8**
Cash & cash eq. (CHF m):	**43.6**
Shares outstanding:	**28,564,031**
Volume:	**25,374**
Free float:	**63%**
52-week Range:	**2.12-4.00**

	2016A	2017A	2018E
Total Revenues	0.40	0.50	6.00
Net (Loss)/Profit	(3.13)	(3.24)	0.30
Net loss per share (cents)	(0.28)	(0.25)	0.12
R&D costs	2.46	2.46	5.00
Cash increase/(decrease)	(1.20)	1.22	37.41
Cash and marketable sec.	1.40	2.59	40.00

Contents

Executive Summary

- Addex Therapeutics is a Swiss based biopharmaceutical company that is developing innovative oral therapies with a focus on neurological disorders. Addex' lead program is scheduled to start a Phase IIb/III pivotal registration study for levodopa-induced dyskinesia associated with Parkinson's disease (PD-LID) in 2019H2. Addex has a proprietary small molecule allosteric modulator discovery platform which has generated a pipeline of 4 drug programs in or close to the start of clinical development and another 6 in preclinical development.

- The potential market for PD-LID drugs has increased substantially following the significant price increases of PD therapeutics. Drugs like Nuplazid and Gocovri are currently priced at USD 30,000 and USD 28,500 per year respectively. That would value the US LID market at USD 4.2 billion. Dipraglurant is estimated to reach US peak sales of USD 1-1.5 billion.

- Next to its clinical stage pipeline, the company has an extensive preclinical stage pipeline that should set the stage for long term growth. We believe that Addex should be capable of entering licensing deals for one or more of these programs. The company has shown that it is highly successful at achieving licensing deals with big pharma companies at an early stage (eg: Janssen Pharmaceuticals, Merck & Co. and Indivior) that already brought in more than 50 million in payments.

- The Company's current cash position has dramatically improved recently and amounts to CHF 43.6 million following a successful raise of CHF 40 million in March 2018 from specialist US healthcare investors, NEA, New Leaf Venture Partners and CAM Capital. In addition, the company received USD 5.0 million from its partner Indivior. The current cash position should be sufficient to carry out the further development of its pipeline and importantly complete the Phase IIb/III pivotal registration trial with dipraglurant in PD-LID.

- **Based on our NPV based valuation, we believe that Addex is substantially undervalued at the current share price of CHF 2.36. Using our valuation model and taking into account the future revenues from its late stage clinical pipeline the company's current total value should be CHF 350-400 million, or CHF 12.25-14.00 per share. Furthermore, recent M&A activity in the Parkinson's disease field indicates that industry could justify a valuation above CHF500 million.**

Company Profile

Addex Therapeutics is a Swiss based biopharmaceutical company that is developing an emerging class of oral small molecule drugs known as allosteric modulators. Allosteric modulators target a specific receptor or protein and alter the effect of the body's own signaling molecules on that target through a novel pharmacological mechanism of action. The company enjoyed a first-mover advantage in the process of discovering and developing allosteric modulators, and has developed a proprietary allosteric modulator discovery technology platform. This platform comprises an allostery-biased library of more than 70,000 compounds and biological assays which enable detection, optimization and confirmation of the mechanism of action of allosteric compounds. Currently, Addex has a diverse pipeline of proprietary compounds that cater to a number of major diseases. The platform is broadly applicable and has generated a deep pipeline of programs focused on central nervous system (CNS) disorders with significant commercial potential.

Addex lead product, dipraglurant has successfully completed a Phase IIa POC trial in Parkinson's disease levodopa induced dyskinesia (PD-LID). The drug is scheduled to start a Phase IIb/III pivotal registration study for the treatment of PD-LID in 2019H2.

Pipeline: Focus on CNS related indications

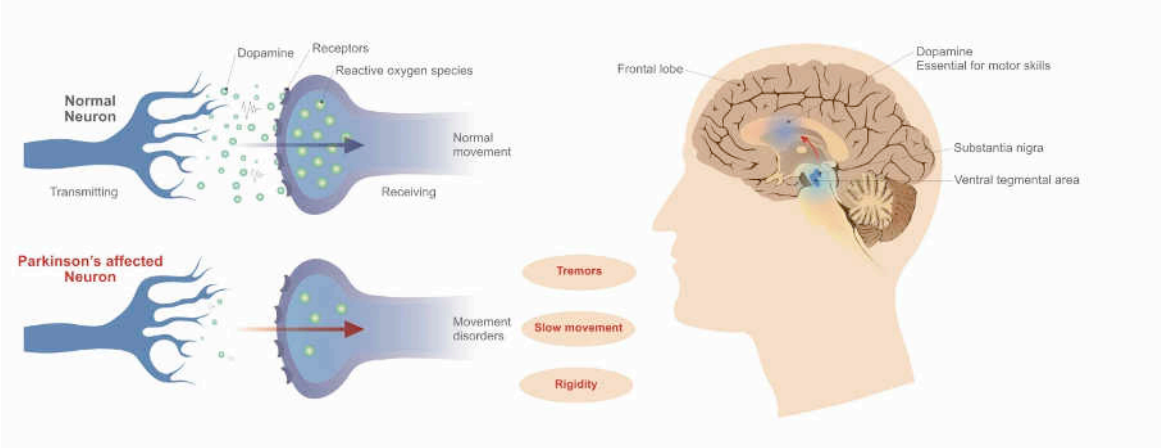
Using its allosteric modulator discovery capabilities, Addex has developed an extensive pipeline of proprietary clinical and preclinical stage drug candidates. Addex allosteric modulator discovery platform is broadly applicable and can be applied to the discovery of small molecule allosteric modulators for any protein target, however Addex has focused its efforts on metabotopic glutamate receptors and gamma aminobutyric acid subtype B receptor (GABAb) for CNS disorders which are a lower risk approach due to the extensive clinical validation of the receptor classes. Addex clinical and late preclinical portfolio is as follows:

Molecule / MoA	Preclinical	Phase 1	Phase 2	Phase 3 Pivotal
Dipraglurant-IR *(mGluR5 NAM)*	Parkinson's disease levodopa-induced dyskinesia			
Dipraglurant-ER *(mGluR5 NAM)*	Focal cervical dystonia			
ADX71149 *(mGluR2 PAM)*	Epilepsy			janssen
ADX71441 *(GABAB PAM)*	Addiction			INDIVIOR

Source: Addex Therapeutics

An Introduction to PD and PD-LID

Parkinson's disease (PD) is a neurodegenerative brain disorder that results from the death of dopamine-generating cells in the substantia nigra region of the midbrain. PD is also characterized by the accumulation of a protein called alpha-synuclein into inclusions called Lewy bodies in neurons. The cause of PD is generally idiopathic, although some atypical cases have a genetic origin. There are approximately 1,000,000 patients with Parkinson disease in the US, with 50,000 to 60,000 more diagnosed each year. Worldwide, there are approximately 4 million individuals afflicted (2.7 million in the US, Japan, and the 5 major European markets). Since the incidence of PD increases with age (the average age of onset is 60), the number of patients is likely to climb as the population of older patients grows.



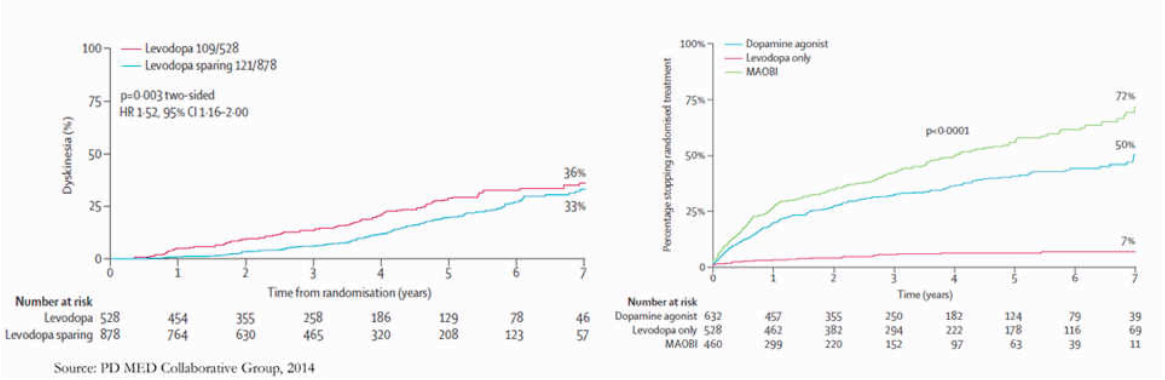
There is no cure for PD. Instead, physicians attempt to manage the symptoms of the disease through a multidisciplinary approach that may include pharmacological, social, and surgical options. The most common pharmaceutical treatment options are those which look to increase the level of dopamine in the brain. These include dopamine replacement therapies (DRT) combined with dopa decarboxylase inhibitors, dopamine agonists, and MAO-B inhibitors.

The most commonly used DRT therapy is Levodopa. It has been available for over 30 years. Levodopa (L-DOPA) is converted into dopamine in the dopaminergic neurons by dopa decarboxylase. The administration of levodopa temporarily diminishes the motor symptoms associated with the lack of dopamine in the substantia nigra. Unfortunately, only about 5-10% of L-DOPA crosses the blood-brain barrier. As a result, despite its effectiveness in reducing motor symptoms associated with Parkinson's disease, physicians often attempt to delay Levodopa therapy until the disease progresses to a more moderate-to-severe stage. Most early stage PD patients start out on MAO-B inhibitors and/or dopamine agonists, or low-dose Levodopa. However, PD is a progressive and degenerative disease, and patients typically progress to the point where starting Levodopa or increasing the Levodopa dose is necessary in five years after initial diagnosis. After a decade on therapy, almost all PD patients require high doses of Levodopa, as well as surgical options including deep brain stimulation (DBS). As the dose and use of Levodopa increases, the incidence of dyskinesia also increases. Levodopa also has a relatively

short half-life, requiring dosing averaging three to four times a day. Peak plasma concentrations of Levodopa occur 60 to 90 minutes after dosing. Unfortunately, this is also when peak side effects such as dyskinesia occur. The hefty dosing requirement of Levodopa creates compliance issues, especially at night when patients may sleep through their dose schedule – dosing every six hours. The peaks and troughs associated with Levodopa create significant "on" and "off" treatment times for PD patients. On times are when the drug is in their system and they may be experiencing dyskinesia, and off times are when the Levodopa has left their system and the patient may awake in a frozen or rigid state.

Despite the occurrence of Levodopa Induced Dyskinesia, Levodopa remains the mainstay in PD treatment. In a large clinical study that was done in 2000-2009 in the UK, 1620 patients were randomized to receive Levodopa, dopamine agonists and MAO-B inhibitors. The patients were followed for 7 years to get their responses to the drugs. It showed that patients who were treated with levodopa sparing approaches, had similar rates of dyskinesia over time. Besides, the trial showed that the rate of discontinuations were considerably lower in the patient group using Levodopa (7% discontinuations) compared to 72% for MAO-B inhibitors and 50% for dopamine agonists. This validated Levodopa as the gold standard in PD treatment (see graphs below)

Comparison of Dyskinesia Rates

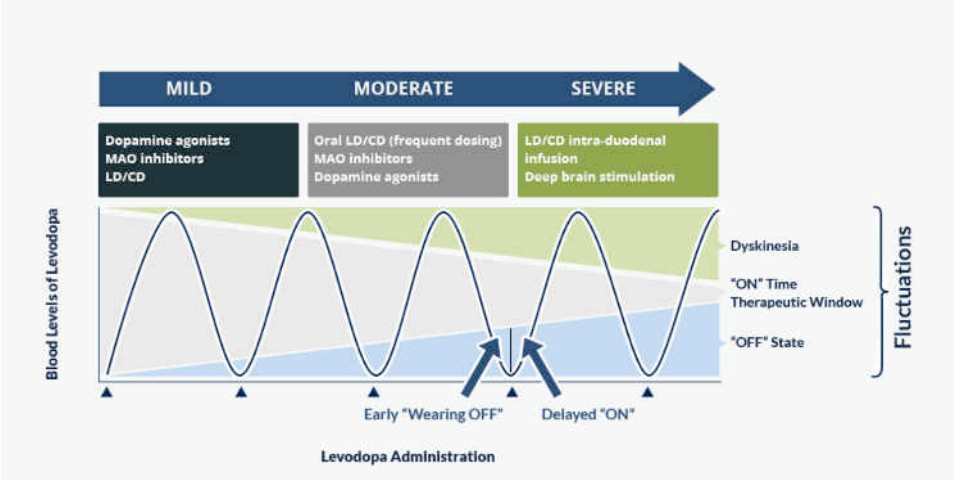


Source: PD MED Collaborative Group, 2014

Comparison of Discontinuations

Long-term Levodopa use is invariably associated with the development of dyskinesias that become as disabling as the PD symptoms themselves. Dyskinesias result from the neurodegenerative process that underlies PD. The dopamine replacement does not lead to dyskinesia per se, but is

thought to lower the triggering threshold for symptoms, as the neurodegeneration progresses. LID is characterized by hyperkinetic movements, including chorea (abnormal involuntary movement), dystonia (sustained muscle contraction, abnormal posture), and athetosis (involuntary convoluted movements). It is most common at times of peak Levodopa plasma concentrations (peak-dose dyskinesia), although it may also occur when plasma concentrations of Levodopa rise and fall (diphasic dyskinesia) or during off-time (off-period dystonia).



Approximately 50% of PD patients will experience LID after 3 years on L-DOPA therapy. The number rises to 90% after 9 to 15 years on Levodopa therapy. It is a significant problem for patients and physicians seeking treatment for PD. In fact, a survey of key opinion leaders (KOLs) in the Parkinson's treatment space showed that dyskinesia is the most important unmet medical need in the treatment of PD after a disease modifying agent (Datamonitor 2011). Although the first treatment for PD-LID was approved by the FDA last year (Gocovri from Adamas Pharma), the most common treatment for LID is to reduce the dose of Levodopa. However, reducing the dose of Levodopa causes increased parkinsonism and worsening motor performance. Therefore, once established, LID becomes difficult to treat.

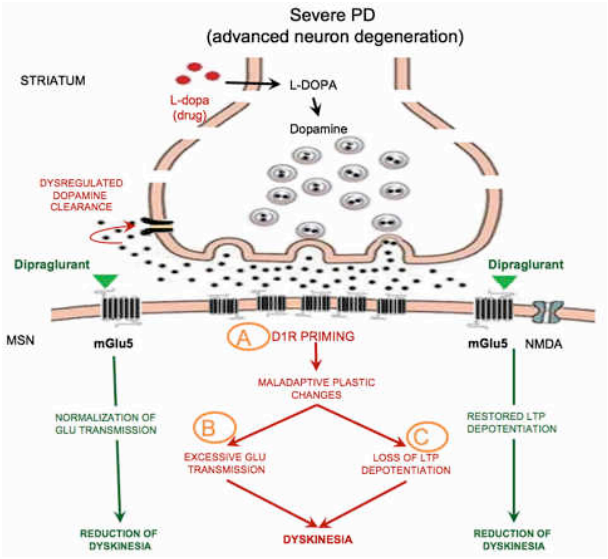
Dipraglurant IR in PD-LID

Addex lead program, dipraglurant for PD-LID has seen a dramatic increase in its market potential due to increased pricing, a clearer view on the number of patients, receipt of orphan drug designation from the FDA. The program is fully funded and has patent protection through 2034 without extensions. In addition, orphan drug status provides 7 years market exclusivity in the US from the date of launch. Dipraglurant is a highly selective oral small molecule, which inhibits the metabotropic glutamate receptor 5 (mGluR5) and has potential to be used in combination with levodopa or dopamine agonists for treatment of Parkinson's disease (PD).

The potential market for PD-LID drugs has increased substantially following the significant price increases of PD therapeutics. Drugs like Nuplazid and Gocovri are currently priced at USD 30,000 and USD 28,500 per year respectively. That would value the US LID market at USD 4.2 billion. Dipraglurant is estimated to reach US peak sales of USD 1-1.5 billion.

Mechanism of Action of Dipraglurant

As mentioned earlier, the loss of substantia nigra neurons combined with the non-physiological pulsatile stimulation of dopamine receptors are at the basis of LID development.



In the striatum, LID is caused by:

- A: D1 receptor priming
- B: Abnormal glutamate transmission
- C: Loss of LTP depotentiation

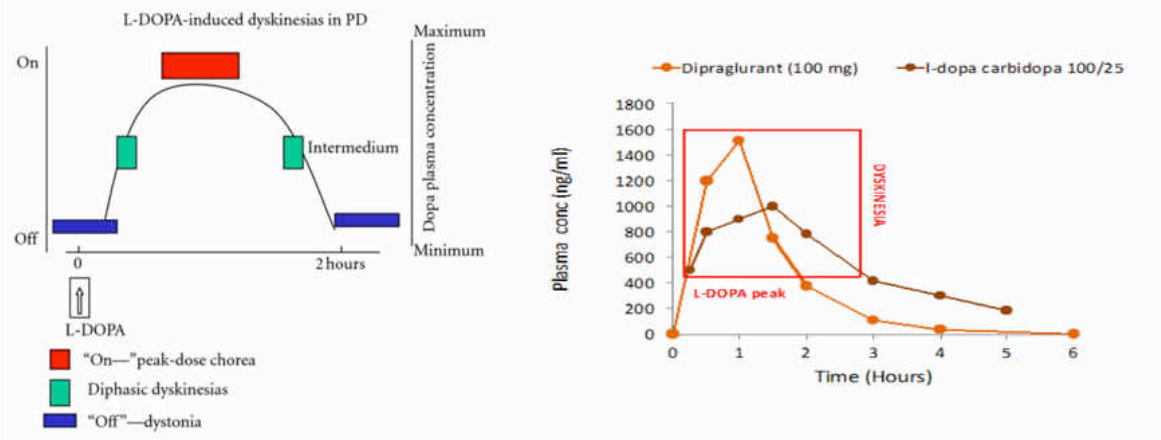
Metabotropic glutamate receptors, or mGluRs perform a variety of functions in the central and peripheral nervous systems: For example, they are involved in learning, memory, anxiety and the perception of pain. They are attractive drug targets due to their modulatory action to normalize glutamatergic activity and the restoration of LTP depotentiation. mGlu5 receptors are implicated in the control of glutamate transmission. Glutamate is a powerful excitatory neurotransmitter that is released by nerve cells in the brain. It is responsible for sending signals between nerve cells, and under normal conditions it plays an important role in learning and memory. Data, also from the Phase II study with Dipraglurant showed that a mGluR5 blockade controls dyskinesia.

Unique Pharmacokinetic profile of Dipraglurant

Addex has specifically developed an immediate release (IR) formulation of dipraglurant that mimics the uptake of levodopa in patients, since peak-dose dyskinesia is the most frequent levodopa-induced dyskinesia. Levodopa has to be given 3-4 times a day due to its relatively short half-life. Peak plasma concentrations are reached 60 to 90 minutes after dosing, when peak-dose dyskinesia occurs. Dipraglurant IR, which is taken together with levodopa, has a rapid onset of action similar to levodopa, and rapid clearance that reduces unnecessary drug exposure and unwanted side effects. This profile is ideal to offset unwanted peak-dose dyskinesia.

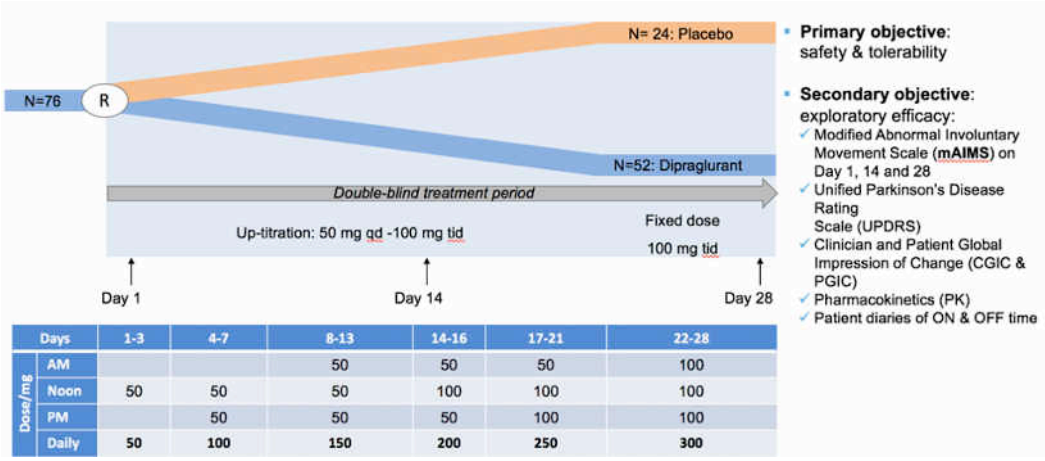
The immediate release (IR) formulation is ideally suited for acute treatment of PD-LID because:

- Its pharmacokinetic profile is similar to levodopa so drug is delivered precisely when needed.
- Its rapid onset of action is ideal for dyskinesia which can occur within 30 minutes of dosing.
- The rapid clearance reduces unnecessary drug exposure, between levodopa doses and should reduce side effects as a result.
- The PK characteristics of dipraglurant IR have potential to give flexibility of use, which is common practice and desirable in PD treatment



Dipraglurant Phase II data in PD-LID

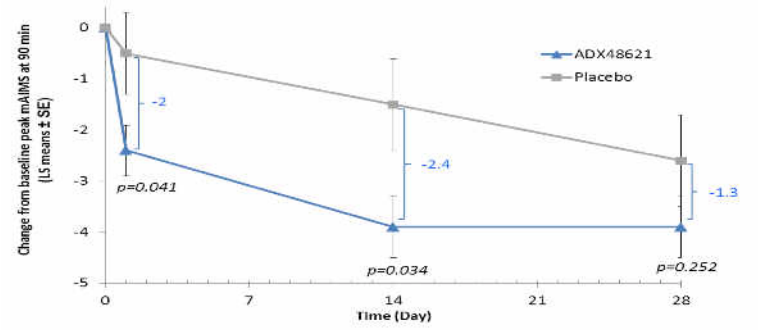
Addex is primarily testing dipraglurant for the treatment of PD levodopa-induced dyskinesia (PD-LID). In a double-blind, placebo-controlled, US and European Phase II study in PD-LID, data showed that dipraglurant met the primary objective of the study by exhibiting a good safety and tolerability profile. Dipraglurant also demonstrated a statistically significant reduction in LID severity with both 50 and 100 mg doses. Dipraglurant reduced dystonia severity in addition to chorea, the two major LID components. The trial was supported by a grant from The Michael J. Fox Foundation for Parkinson's Research.



Days		1-3	4-7	8-13	14-16	17-21	22-28
Dose/mg	AM			50	50	50	100
	Noon	50	50	50	100	100	100
	PM		50	50	50	100	100
	Daily	**50**	**100**	**150**	**200**	**250**	**300**

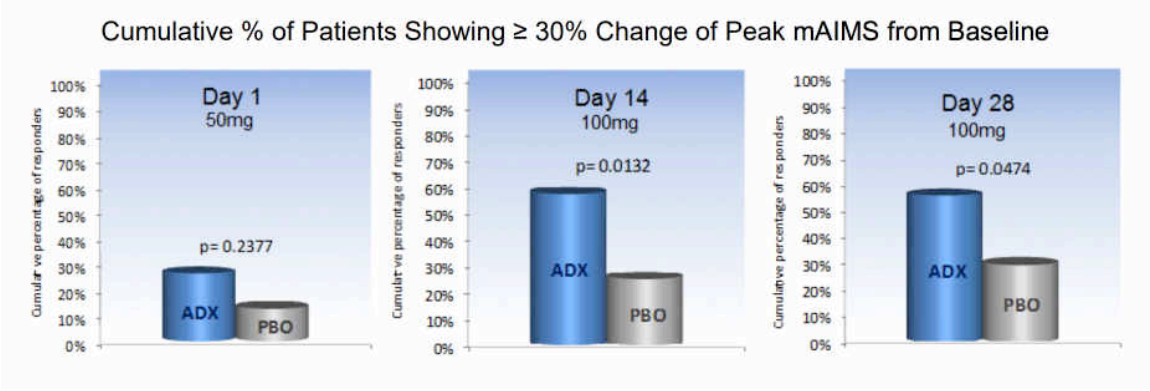
Source: Addex Therapeutics

This study found that dipraglurant therapy resulted in substantial improvements on multiple efficacy endpoints. Patients taking dipraglurant had significant reductions in modified Abnormal Involuntary Movement Scale (mAIMS) during peak levodopa concentrations and this response was maintained during the 3-hour post-dosing period. Participants receiving 50 mg dipraglurant on day 1 had a 19.9% reduction in mAIMS as compared to 4.1% for placebo (p = 0.042). After being titrated up to a 100 mg dose of dipraglurant, participants experienced a 32.3% reduction in mAIMS as compared to 12.6% for placebo (p = 0.034) on day 14. On day 28 the effect of the 100mg dose was maintained, however the study lost statistical significance due to an increased placebo response.



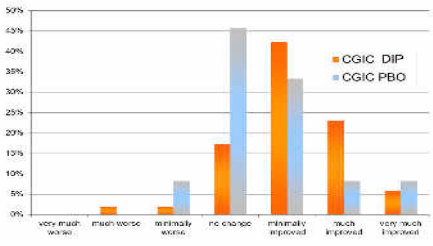
Source: Addex Therapeutics

Responder analysis measuring the cumulative percentage of patients showing a 30% change in peak mAIMS from baseline demonstrated dipraglurant 100mg dose had a significant benefit at both day 14 and day 28, which reinforces the robustness of dipraglurants anti-dyskinetic effect.



Source: Addex Therapeutics

When looking at Clinical Global Impression of Change (CGIC), there was even a greater improvement in dyskinesia with dipraglurant according to clinicians (p <0.05). CGIC is a relatively simple scale that reflects the everyday clinical practice. The assessment is done by the treating physician which makes it a more objective assessment than the more subjective mAIMS.



	Dipraglurant	Placebo
Improved (p<0.05)	71.2%	49.9%
No change	17.3%	45.8%

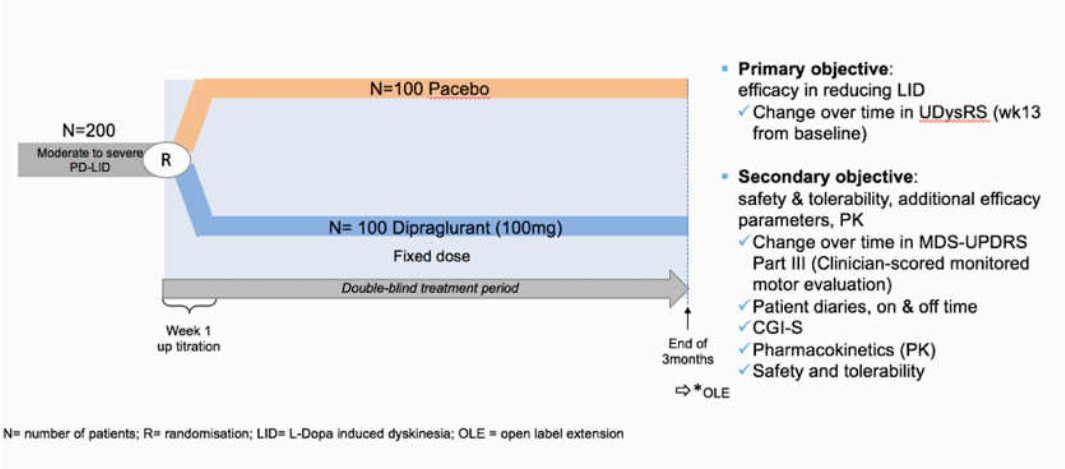
Source: Addex Therapeutics

Despite the escalating placebo response which confounded significance of the study at day 28, we believe that the study demostrated a robust effect of dipraglurant in PD-LID. In addition, the company has hired a team with experience in managing late stage studies in Parkinson's patients and in particular the implementation of technics to mitigate placebo response in this patient population. It was noted that technics such as the use of centralized independent raters who are blinded to the visit number were not deployed in the proof of concept study.

Upcoming Phase IIb/III study Dipraglurant

The company has launched a pivotal development program with the first clinical trial starting in 2019H2 to support regulatory filings for dipraglurant. This randomized, double blind, placebo-controlled Phase IIb/III pivotal registration study will assess the safety and efficacy of dipraglurant for the treatment of 200 patients with moderate to severe levodopa induced dyskinesia. Patients will be randomized 1:1 to receive dipraglurant or placebo three times daily, with levodopa treatment regimens remaining consistent. The optimal dose will be determined via titration over a two-week period, followed by 11 weeks of a maintenance dose. The primary endpoint is change in Unified Dyskinesia Rating Scale (UDysRS). The secondary endpoints include change in clinician-scored Unified Parkinson's disease rating scale (UPDRS) Part III, patient diaries for on and off time.

Dipraglurant 1st Pivotal LID Study (301)



N= number of patients; R= randomisation; LID= L-Dopa induced dyskinesia; OLE = open label extension

Dipraglurant ER in Focal Cervical Dystonia (CD)

In October 2016, Addex announced that it will conduct a Phase IIa POC Study of dipraglurant in focal cervical dystonia (CD). The study was developed with support from the Dystonia Medical Research Foundation and in collaboration with investigators from the Dystonia Coalition, an international network of experts devoted to advancing research in dystonia. Addex's Phase IIa Proof of Concept study will include 18 focal CD patients who are currently sub-optimally treated with botulinum toxin (BoNT). The single center study will be double-blinded and placebo-controlled. A single dose of dipraglurant will be administered in a crossover design. CD is the most prevalent form of dystonia; recent international prevalence estimates place the number of CD patient in the US between 50,000 and 100,000 - a range which is much higher than previously reported and considers the large portion of undiagnosed population. CD has been demonstrated to have a significant impact on quality of life. Current treatment options for focal CD include botulinum toxin BoNT injections, which generally reduce muscle spasms emporarily for a few months. However, the interval between BoNT injections is usually longer than the duration of action, leaving patients with sub-optimal symptom relief towards the end of the treatment for weeks. In addition, most patients rarely experience any symptom free days.

ADX71149: Epilepsy (partnership with Janssen Pharmaceuticals)

ADX71149 is a novel, first-in-class potent, oral, small molecule positive allosteric modulator (PAM) of metabotropic glutamate receptor 2 (mGluR2), a Family C class of G Protein Coupled Receptor (GPCR). The development of ADX71149 is part of a worldwide research collaboration and license agreement between Addex and Janssen Pharmaceuticals, to discover, develop and commercialize a novel mGluR2 PAM medication for the treatment of anxiety, schizophrenia and other undisclosed indications. Under the terms of the agreement, Addex is eligible for up to a total of EUR 112 million in milestone payments based on potential development and regulatory achievements. In addition, Addex is eligible for low double-digit royalties on sales of any mGluR2 PAM medication developed under the agreement.

Epilepsy is one of the most common serious neurological disorders, affecting about 65 million people globally (Thurman et al. 2011). It affects 1% of the population by age 20 and 3% of the population by age 75. Epilepsy describes a condition in which a person has recurrent seizures due to a chronic, underlying process. It also refers to a clinical phenomenon rather than a single disease entity, since there are many forms and causes of epilepsy. Epilepsy is a disease of the brain defined by any of the following conditions:

- at least two unprovoked (or reflex) seizures occurring more than 24 hours apart;
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
- diagnosis of an epilepsy syndrome.

The synaptic vesicle protein 2A (SV2A) has been identified as a broad spectrum anticonvulsant target in models of partial and generalized epilepsy, and studies in animal models and human tissue suggest that changes in the expression of SV2A are implicated in epilepsy (Mendoza-Torreblanca et al. 2013; Kaminski et al. 2012). SV2A ligands include levetiracetam (Lynch et al. 2004), which is an anti-epileptic drug commercialized under trademark Keppra®, approved in Europe and USA as a monotherapy or add-on therapy in patients diagnosed with epilepsy. In the 6Hz psychomotor seizure test, a preclinical model of epilepsy considered to be the most relevant model of pharmacoresistant limbic seizures, ADX71149 demonstrated efficacy both stand alone

and in combination with SV2a ligands including levetiracetam (Metcalf et al. 2017). In particular, the data show that while seizures are reduced when mGluR2-acting compounds are administered alone, their combination with levetiracetam result in a potent reduction of doses required to produce full efficacy, which is important because higher doses of levetiracetam are associated with dose-limiting side effects, such as aggression, nervousness/anxiety, somnolence and fatigue. In this study, a fixed dose of ADX71149 was seen to increase the potency of levetiracetam, leading to an approximate 35-fold increase in its potency. Conversely, using a fixed dose of levetiracetam with varying doses of ADX71149 resulted in an approximate 14-fold increase in ADX71149 potency. If this effect can be translated in the clinic, it will strongly support a rational polypharmacy concept in the treatment of epilepsy patients. ADX71149 is currently being prepared for a Phase II study in patients with epilepsy.

ADX71149 was included in a review of 13 of the latest advances related to the discovery and development of drugs aimed at improving the management of people with epilepsy. The review, titled *"Progress report on new antiepileptic drugs: A summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). I. Drugs in preclinical and early clinical development"*, was published in October issue of Epilepsia.

GABAB PAM: Addiction

ADX71441 (GABAB PAM) is the third program drug in Addex' proprietary allosteric modulation technology platform and is targeted for the treatment of addiction (alcohol use disorder, cocaine and nicotine addiction) and has been licensed to Indivior PLC. Researchers have shown that GABAB receptor agonists such as baclofen are effective in reducing drug self-administration, cravings, and anxiety, and thus promote abstinence. Baclofen, also known as chlorophenibut, is a conventional (orthosteric) stimulator (agonist) of the GABAB receptor and is primarily used to treat spasticity and is in early development for treating alcoholism. Addex' partner Indivior is developing ADX71441 for the treatment of addiction. Under the terms of the agreement, Addex received USD 5 million upfront and is eligible for USD 330 million of development, regulatory and commercialization milestones, tiered royalties up to double digit and a minimum of USD 4 million in research funding

over 2 years. In addition, Addex retains the right to select compounds from the research collaboration for exclusive development in certain indications, including Charcot-Marie-Tooth type 1a neuropathy (CMT1A). Indivior is focused on commercializing Suboxone® for opioid addiction (2017 revenue: USD 1.1 billion) and advancing its therapeutic pipeline to address the growing health epidemic of addiction and related mental health disorders. Given Indiviors world leading position in addiction therapeutics, we believe Addex has found a very strong partner for ADX71441. We expect Addex' partner, Indivior to start a Phase I clinical trial in H1 2019.

In October last year, the company announced that ADX71441 has received a grant from the US National Institute for Drug Abuse ("NIDA") of USD 5.3 million to fund Phase I and a Phase Ib cocaine interaction study. The grant was issued as part of the Grand Opportunity in Medications Development for Substance-Use Disorders (U01), a cooperative agreement providing for both financial assistance and significant scientific support from the NIH to selected clinical programs. Addex expects Indivior to initiate a Phase I clinical trial of ADX71441 in 2019H1. Addiction is an indication with significant commercial opportunity. Existing therapies often do not provide effective control of symptoms or have side effects that discourage adherence.

Pre-clinical Pipeline: Long Term Growth

Next to its clinical stage pipeline, the company has an extensive preclinical stage pipeline that should set the stage for long term growth. We feel that Addex should be capable to close licensing deals for one or more of these programs. The company has shown that it is highly successful in reaching licensing deals with big pharma companies at an early stage (eg Janssen Pharmaceuticals and Indivior) that already brought in millions in upfront payments.

Molecule / MoA	Hit to Lead	Lead Optimization	Clinical Candidate
mGluR4 PAM	Parkinson's Disease		
mGluR2 NAM	Mild Cognitive Impairment		
GABAB PAM	Charcot-Marie-Tooth 1A Neuropathy		
mGluR7 NAM	Psychosomatic Disorders (PTSD) & Hearing Loss		
mGluR3 PAM	Neurodegenerative Disorders		
TrkB PAM	Neurodegenerative Disorders		

mGluR4 PAM: Parkinson's Disease

The metabotropic glutamate receptor 4 (mGluR4) belongs to the Group III mGluRs (Class C G Protein-Coupled Receptors) and is negatively coupled to adenylate cyclase via activation of the G**α**i/o protein. mGluR4 PAM is a novel non-dopaminergic approach to treat Parkinson's disease that has the potential to treat both motor and non-motor symptoms. It has disease modifying neuroprotective potential. Besides, it has the potential to treat a broad range of debilitating autoimmune diseases that are linked to aberrant TH17 responses like rheumatoid arthritis, inflammatory bowel disease and uveitis. Recently interest in this field was raised following the acquisition of Prexton Therapeutics by Lundbeck. The deal value was EUR 905 million and includes the acquisition of the rights to foliglurax, a small molecule that works by stimulating mGluR4 that

activates a compensatory neuronal system in the brain. Foliglurax is currently in a Phase II trial, data are expected by 2019H2.

mGluR2 NAM: Mild Cognitive Impairment

The metabotropic receptor mGluR2 belongs to the class C G Protein-Coupled Receptor family (group II mGluRs). This receptor shows a broad distribution throughout the cortex as well as high expression in the hippocampus and perforant path. Importantly, activation of mGluR2 leads to inhibition of glutamate release in the synapse. In this respect, Addex believes that inhibition of mGluR2 with a selective negative allosteric modulator (NAM) may be of therapeutic use to treat medical conditions which may be linked to low glutamate levels in the brain, like Alzheimer's and Major Depressive Disorder.

GABAB PAM: Charcot-Marie-Tooth 1A Neuropathy

GABAB PAM is a third preclinical program targeted for the treatment of Charcot-Marie-Tooth (CMT) disease. CMT type 1A encompasses a heterogeneous group of inherited, progressive, chronic peripheral neuropathies. The most common type of CMT, is an orphan disease affecting at least 125,000 people in Europe and the U.S. The genetic mutation responsible for CMT1A is a duplication of the PMP22 gene coding for a peripheral myelin protein. Overexpression of this gene causes degradation of the neuronal sheath (myelin) responsible for nerve dysfunction, followed by loss of nerve conduction. As a result of peripheral nerve degradation, patients suffer from progressive muscle atrophy of legs and arms causing walking, running, balance problems and abnormal hand functioning. CMT1A patients end up in wheelchairs in at least 5% of cases. In October, Pharnext announced positive topline results from its pivotal phase III trial (PLEO-CMT) of PXT3003 for treatment of CMT1A. PXT3003 is fixed-dose combination of baclofen, naltrexone and sorbitol which has also shown positive results in both preclinical and Phase 2 studies for the treatment of CMT1A. Baclofen is an orthosteric agonist of GABAB and consequently these data provide a certain degree of clinical validation of the Addex GABAB PAM approach in CMT1A. Furthermore, in preclinical studies, both ADX71441 and PXT3003 have been shown to inhibit the

overexpression of the PMP22 gene, improve myelination of peripheral nerves and motor / sensory impairments.

mGluR7 PAM: PTSD & hearing loss

The mGlu7 receptor is the most highly conserved of all metabotropic glutamate receptor subtypes across mammalian species exhibiting the widest distribution in the brain among mGluRs. It is localized in the presynaptic active zone and abundantly expressed in brain regions such as neocortex, hippocampus, amygdala, locus coeruleus, thalamus and hypothalamus, structures involved in the control of fear and emotion. mGlu7 is expressed both at glutamatergic and GABAergic synapses and has been postulated to be one of the most important mGluR subtypes in regulating CNS function. Behavioural studies have shown that mGluR7 knockout animals exhibit reduced anxiety- and depression-like responses in a variety of stress-related paradigms and deficits in amygdala-dependent behaviours. mGlu7 receptor inhibition appears as a novel and well differentiated approach for the treatment of anxiety and stress-related disorders. In addition, the expression of mGlu7 receptor in the inner ear suggests its modulation could represent a potential treatment of hearing disorders such as age-related hearing impairment and tinnitus.

mGluR3 PAM: Neurodegenerative Diseases

mGlu3 receptor is part of group II mGluRs (class C G Protein-Coupled Receptors) and inhibits adenylate cyclase, leading to a decrease in the second messenger cAMP in cells upon activation. The receptor is expressed both in neuronal and glial cells where it helps modulating glutamate action. mGlu3 receptor activation or potentiation represents an exciting new avenue for treating neurodegenerative disorders such as Alzheimer's, Parkinson's or Huntington's diseases. In particular, it has been shown that such an approach induces a neuroprotective effect, most probably mediated through stimulation of growth factor expression.

TrkB PAM: Neurodegenerative Diseases

Tropomyosin receptor kinase B (TrkB), is a receptor for brain-derived neurotrophic factor (BDNF), as well as neurotrophin-3 and -4. As such, TrkB mediates the effects of these neurotrophic factors which include neuronal differentiation and survival. Addex' TrkB PAM approach is novel exciting

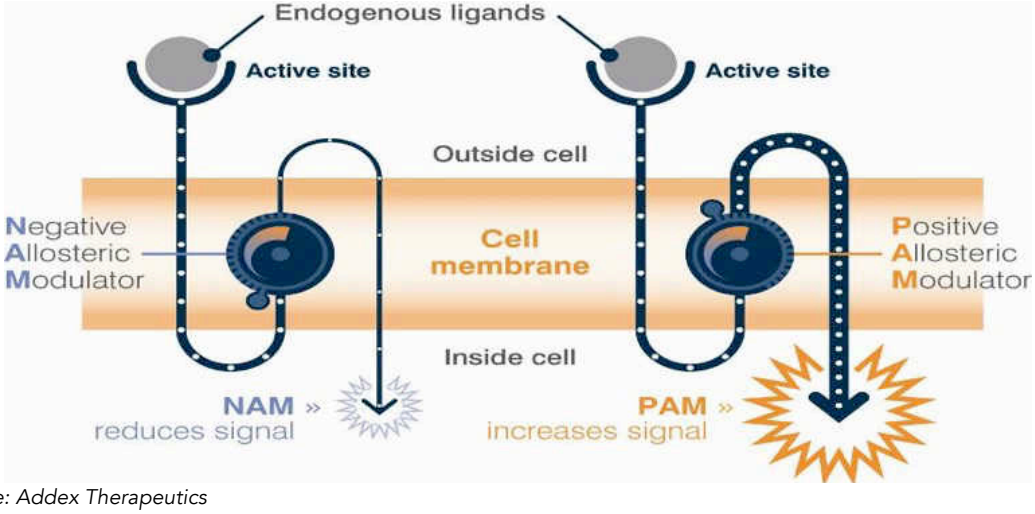
approach for the treatment of neurodegenerative diseases such as Alzheimer's, Parkinson's, or Huntington's disease with potential both as disease-modifying and symptomatic treatment. The chemical series of TrkB PAMs are in Lead generation stage. The Addex TrkB project has received a USD 835K grant from The Michael J Fox Foundation to support the chemical exploration of our series, as well as a CHF 440K grant from the InnoSuisse supporting our collaboration with UniGE to test TrkB PAM molecules in complex models of neurodegenerative diseases.

Allosteric Modulator Discovery Platform

Allosteric modulation is a mechanism to control the function of proteins. This is done by binding an effector molecule, called an allosteric modulator, at the protein's allosteric site i.e., at the site other than the protein's active site. Natural ligands, which are produced by the body, bind to a receptor's active site. Most of the available drugs compete with these natural ligands to bind to the active site. However, since allosteric modulators bind to the protein at a site other than the active site, they do not compete with the body's natural ligands. They can bind with the receptor even in the presence of natural ligand-receptor binding. As a result, allosteric modulators act as a dimmer switch controlling the level of activation or inhibition, rather than switching the receptor on or off, allowing the body to retain its natural control over receptor activation. The allosteric modulator affects the conformation of the receptor and hence changes its shape, and by doing so it affects the signals sent by the receptor intracellularly, resulting in the alteration of the protein's activities.

There are two types of effectors:

- Allosteric activators: Effectors that increase the protein's activity.
- Allosteric inhibitors: Effectors that decrease the protein's activity.



Source: Addex Therapeutics

Advantages of allosteric modulation

Allosteric modulators with lower potency can be effective in situations where a similar potency orthosteric modulator fails. This is because allosteric modulators do not compete with the natural ligands, in contrast to orthosteric drugs, as they bind with the receptor on the allosteric site. Allosteric modulators are highly selective. Receptors comprise multiple functional domains and transmit several message signals to the cell. While an orthosteric drug competes with the natural ligand for it's highly conserved binding site, allosteric modulators use a different binding site, the allosteric site, which has not been subjected to conservatory evolutionary pressure. Therefore, allosteric modulators are found to be highly selective for one receptor of interest, and thus have the potential to have an increased safety profile compared to other drugs.

Since allosteric modulators bind to the receptor at a site other than the active site, the natural biological rhythm is preserved, which is lost/altered in the case of orthosteric modulators.

Addex has developed proprietary screening systems to identify allosteric modulators that modify the molecular response of the therapeutic target. These systems screen G-Protein Coupled Receptors (GPCRs) and non-GPCR drug targets, and provide the pharmacological data that allow lead optimization through medicinal chemistry. The company has patented several aspects of these technologies while keeping certain others as trade secrets to maintain its competitive advantage.

GPCRs are the largest protein family known, members of which are involved in all types of stimulus-response pathways, from intercellular communication to physiological senses. The diversity of functions is matched by the wide range of ligands recognized by members of the family, from photons (rhodopsin, the archetypal GPCR) to small molecules (in the case of the histamine receptors) to proteins (for example, chemokine receptors). Drugs targeting members of this integral membrane protein superfamily, which transmit chemical signals into a wide array of different cell types, represent the core of modern medicine. They account for the majority of bestselling drugs and about 40% of all prescription pharmaceuticals on the market.

Glutamate, like dopamine and serotonin, is a key signaling molecule (neurotransmitter) in the human brain involved in the control of multiple brain functions including mood, memory,

perception and motor function. Too much glutamate can lead to seizures and the death of brain cells. Too little glutamate can cause psychosis, coma and death. Glutamate exerts these effects by interacting with many receptors in the brain, especially NMDA, AMPA and kainate receptors. In addition to these primary receptors, glutamate triggers other receptors, termed metabotropic because they adjust the amount of glutamate that cells release rather than simply turning glutamate transmission on or off. Eight types of metabotropic glutamate receptors (mGluR), each with different functions, have been identified. These mGluRs are attractive targets for drug treatment because of their ability to fine-tune glutamate signaling. Research shows that mGluR drugs have potential for the treatment of schizophrenia, anxiety, Parkinson's disease, fragile X syndrome, Alzheimer's disease, depression and post-traumatic stress disorder. Addex has discovered selective orally available small molecule allosteric modulators for each of the eight subtypes of mGluR, as well as for the metabotropic GABAb receptor. GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter in the central nervous system (CNS). GABA-ergic inhibition is seen at all levels of the CNS, including the hypothalamus, hippocampus, cerebral cortex and cerebellar cortex. GABA pathways are abundant in the brain, with 50% of the inhibitory synapses in the brain being GABA mediated.

Financials

For the first six months of 2018, Addex reported an income of CHF 5.4 million compared to CHF 0.2 million in 2017H1. The company received an upfront payment of USD 5 million fort he saled of the GABAB PAM license to Indivior. It also received grants totalling CHF 0.5 million from the Michael J. Fox Foundation for Parkinson's Research to fund research activities in the dipraglurant Parkinson's program and the TrkB PAM program. In all this amounted to a net income of CHF 2.4 million in 2017 compared to a net loss of CHF 1.8 million in 2017H1. R&D expenses increased by CHF 0.9 million to CHF 2.1 million in 2018H1, compared to CHF1.2 million in 2017H1, mainly due to an increase in resources deployed on the dipraglurant program and outsourced research costs on the TrkB PAM program. G&A expenses remained stable at CHF 0.8 million in 2018H1 compared to 2016.

Cash and cash equivalents amounted to CHF 43.6 million at 30 June 2018, an increase of CHF 40 million compared to CHF 3.6 million at 30 June 2017. This strong increase was due to the proceeds from the capital increase completed on 28 March 2018.

Profit & Loss Statement

CHF million	2015A	2016A	2017A	2018H1A	2018E
Revenues	0.8	0.411	0.500	5.367	6.000
R&D Costs	(1.8)	(2.461)	(2.629)	(2.084)	(4.000)
SG&A	(1.7)	(1.080)	(1.106)	(0.825)	(1.500)
Tax escrow account write-off	(1.2)	(-)	(-)	(-)	(-)
Operating Profit/(Loss)	(3.9)	(3.130)	(3.235)	2.458	0.500
Finance result	(0.3)	0.019	(0.045)	(0.104)	(0.150)
Net Profit/(Loss)	(4.2)	(3.149)	(3.280)	2.354	0.350

Consolidated statement of cash flows

CHF million	2016A	2017A	2018H1A
Cashflow from operating activities	(2.694)	(2.135)	3.582
Cash flow from investing activities	(0.01)	(0.02)	(0.002)
Cash flow from financing activities	1.492	3.355	37.457
Cash and cash equivalents at beginning of the period	2.633	1.416	2.590
Net change in cash and cash equivalents	(1.204)	1.219	41.037
Cash and cash equivalents at the end of the year	1.416	2.590	43.573

Valuation

We value Addex Therapeutics at CHF 350-400 million or CHF 12.25-14.00 per share. Earlier valuation models did not address value to the preclinical programs in Addex' pipeline, including its ADX71441 programs. Following the deal with Indivior, this program already has a potential value of at least USD 330 million, taking into account the future milestones and up to double digit royalties. When taking into account a LOA for this program of 15% and peak sales of USD 600-700 million, the risk adjusted NPV of the program would be value at CHF 50-85 million or CHF 1.75-3.00 per share.

Another measurement for the potential value of Addex Therapeutics, is making a comparison with companies that have programs in development in PD-LID (dipraglurant), Parkinson's and in addiction (ADX71441) since we believe these programs to be the most promising. We should note that in the past few years there has been considerable M&A activity in this Parkinson's field. In 2014 Acorda Therapeutics acquired Civitas for USD 525 million in cash in order to get the rights to its PD drug CVT301, later named Inbrija. The drug is currently under review for approval by the FDA. Sunovion acquired Cynapsus in 2016 for USD 624 million to get the rights to Cynapsus' Phase III PD candidate APL-130277. Sunivion filed for approval in March 2018. Last year Israeli company Neuroderm was bought by Mitsubishi Tanabe Pharma for USD 1.1 billion. Neuroderm has three clinical stage product candidates in development for PD. And last but not least, Lundbeck acquired Prexton Therapeutics in a deal worth EUR 905 million and obtained rights to Foliglurax. Foliglurax is currently in Phase II for the treatment of PD.

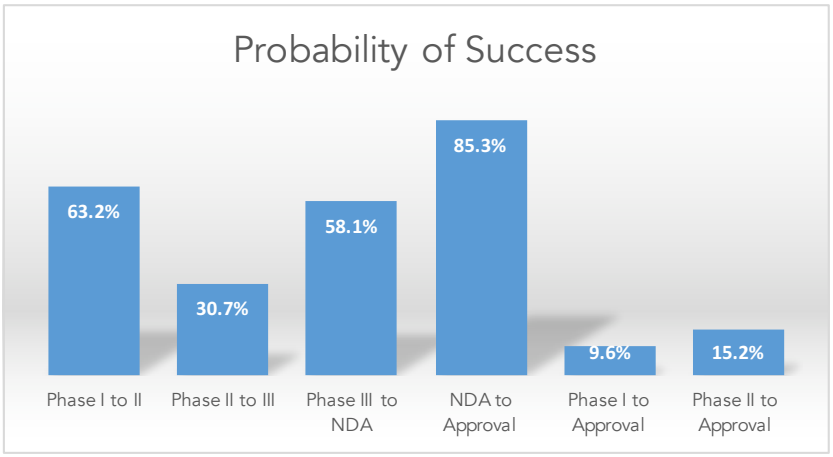
Company	Acquired by	Deal size	Comments
Civitas	Acorda Therap.	USD 525m	Acquired Civitas and got the rights to PD drug Inbrija. The drug is still under investigation by the FDA and is expected to get a final review in January 2019
Cynapsus	Sunovion	USD 624m	Acquired Cynapsus and got the rights to PD drug APL130277, currently in Phase III
Neuroderm	Mitsubishi Tanabe Pharma	USD 1.1bn	Lead product is ND0612 for the treatment of PD. Intend to submit regulatory applications for ND0612 in Europe by the end of 2018.
Prexton Therap.	Lundbeck	EUR 905m	Rights to PD drug Foliglurax, currently in Phase II, no clinical efficacy data yet.

Phase Success and Likelihood of Approval (LOA)

In estimating a value for the clinical programs with dipraglurant, we made use of several studies that were done on the clinical development success rates for investigational drugs to measure success rates for investigational drugs. We analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development. These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications. Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis.

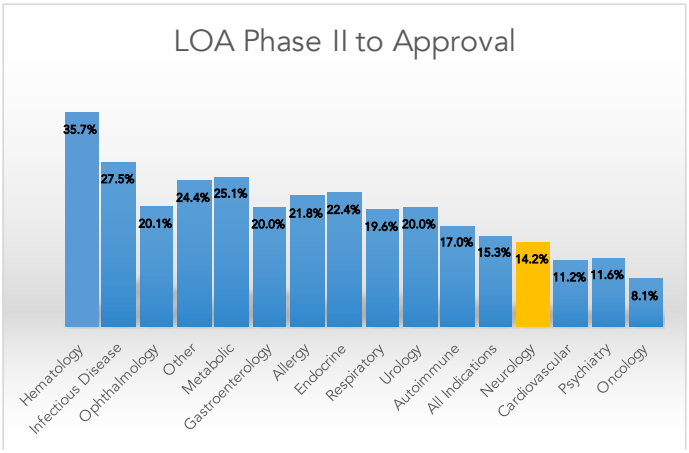
The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage where proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct. The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to

obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (see graph below)



Source: BIO Industry Analysis

Major disease areas were segmented according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. As can be seen in the graphs below, there is a wide range of Likelihood of Approval (LOA) from Phase I, II and III.



In estimating a value for dipraglurant in PD-LID, we took into account potential markets in the US and Europe with a total number of potential patients with PD-LID of 180,000 in the US and 225,000 in Europe, with a market launch in the US in 2022 and 2023 in Europe. We calculate a Risk adjusted Discount Rate of 14%. Annual pricing is conservatively set at USD 22,000 for the US and USD 12,000 for Europe which is actually lower than pricing of competitive drugs (Gocovri for PD-LID is priced at USD 28,500, Pimavanserin for PDP is priced at USD 24,000 and whereas Igrezza is even priced at USD 60,000-90,000) Although we believe that Addex will potentially partner its program in PD-LID with a large pharmaceutical, in our model we have calculated its value by marketing the drug independently. We estimate that a peak market share of 25-30% is possible. Compared with the report of BioMedTracker (see neurological disorders), we used a somewhat higher LOA of 20% as we believe that the vast amount of data justifies that. This leads to a total valuation of CHF 228 million or CHF 8.00 per share.

Valuation in PD-LID US Market

Year	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	
No of patients US (yoy growth 2.5% as of 2015)	229619	235360	241244	247275	253457	259793	266288	272945	279769	286763	
Penetration	0.5%	1.5%	3.0%	6.0%	10.0%	14.0%	18.0%	20.0%	21.0%	22.0%	
Total Revenues (USD m)	**25.3**	**77.7**	**159.2**	**326.4**	**557.6**	**800.2**	**1054.5**	**1201.0**	**1292.5**	**1387.9**	
Margin 50%	12.6	38.8	79.6	163.2	278.8	400.1	527.3	600.5	646.3	694.0	
WACC 14%	0.59	0.52	0.46	0.40	0.35	0.31	0.27	0.24	0.21	0.18	
NPV (million)	7.5	20.2	36.3	65.2	97.7	123.0	142.2	142.1	134.1	126.4	
Total NPV (million)											**768.3**
LOA 20%											**153.7**

Valuation in PD-LID European Market

Year	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	
No of patients Europe (yoy growth 2.5% as of 2015)	282432	289493	296730	304148	311752	319546	327534	335723	344116	352719	
Penetration	0.5%	1.5%	3.0%	6.0%	10.0%	14.0%	18.0%	20.0%	21.0%	22.0%	
Total Revenues (USD m)	**16.9**	**52.1**	**106.8**	**219.0**	**374.1**	**536.8**	**707.5**	**805.7**	**867.2**	**931.2**	
Margin 50%	8.5	26.1	53.4	109.5	187.1	268.4	353.7	402.9	433.6	465.6	
WACC 14%	0.52	0.46	0.40	0.35	0.31	0.27	0.24	0.21	0.18	0.16	
NPV (million)	4.4	11.9	21.3	38.4	57.5	72.4	83.7	83.6	78.9	74.4	
Total NPV (million)											**373.2**
LOA 20%											**74.6**

Partnership Leads to Substantial Higher Valuation

In previous valuation models, we did not address value to the preclinical programs in Addex' pipeline, including its ADX71441 programs. Following the deal with Indivior, this program already has a potential value of at least USD 330 million, taking into account the future milestones and up to double digit royalties. When taking into account a LOA for this program of 15% and peak sales of USD 600-700 million, the risk adjusted NPV of the program would be value at CHF 50-85 million or CHF 1.75-3.00 per share.

Valuation dipraglurant ER in Focal Dystonia

In estimating a value for dipraglurant in focal dystonia, here we also took into account potential markets in the US and Europe with a total number of potential patients with focal dystonia of 75,000 in the US and 90,000 in Europe, with a market launch in the US and Europe in 2023. We calculate a Risk adjusted Discount Rate of 14%. Annual pricing is set at USD 40,000 for the US and USD 20,000 for Europe which is comparable with pricing of competitive drugs. Although we believe that Addex will potentially partner its program in dystonia with a large pharmaceutical, in our model we have calculated its value by marketing the drug independently. We estimate that a peak market share of 20-25% is possible. Compared with the report of BioMedTracker (see neurological disorders), we used a LOA of 10%. This leads to a total valuation of CHF 53 million or CHF 1.85 per share.

Valuation in Focal Dystonia EU Market

Year	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	
No of patients in Europe)	94144	96498	98910	101383	103917	106515	109178	111908	114705	117573	
Penetration	1.0%	3.0%	6.0%	9.0%	12.0%	15.0%	17.0%	18.0%	19.0%	20.0%	
Total Revenues (USD m)	18,8	57,9	118,7	182,5	249,4	319,5	371,2	402,9	435,9	470,3	
Margin 50%	9,4	28,9	59,3	91,2	124,7	159,8	185,6	201,4	217,9	235,1	
WACC 14%	0.52	0.46	0.40	0.35	0.31	0.27	0.24	0.21	0.18	0.16	
NPV (million)	4.9	13.2	23.7	32.0	38.3	43.1	43.9	41.8	39.7	37.6	
Total NPV (million)											**241.0**
LOA 10%											**24.1**

Valuation in Focal Dystonia US Market

Year	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	
No of patients US (yoy growth 2.5% as of 2015)	78453	80415	82425	84486	86598	88763	90982	93256	95588	97977	
Penetration	1.0%	3.0%	6.0%	10.0%	14.0%	17.0%	19.0%	20.0%	21.0%	22.0%	
Total Revenues (USD m)	31,4	96,5	197,8	337,9	484,9	603,6	691,5	746,1	802,9	862,2	
Margin 50%	15,7	48,2	98,9	169,0	242,5	301,8	345,7	373,0	401,5	431,1	
WACC 14%	0.52	0.46	0.40	0.35	0.31	0.27	0.24	0.21	0.18	0.16	
NPV (million)	7.8	20.9	37.2	55.2	68.9	74.6	74.3	69.7	65.2	60.9	
Total NPV (million)											**408.6**
LOA 10%											**40.9**

Near Term Milestones

In the past 12 months, Addex has already reached a number of important milestones that brought the company back on track towards commercialization of its lead candidate. In the coming 12 months, we expect a number of important milestones that can drive the stock price upwards. These are:

- ADX71441 Phase I – start dosing: **2019H1**
- Dipraglurant first pivotal study in LID registration program – start dosing: **2019H2**

Competitive Landscape

Company	Drug	Comments
Adamas Pharma	Gocovri	Delayed released long acting reformulation of amentadine (once daily tablet). Approved in US for PD-LID and launched In 2018.
Amaranus	Eltoprazine	Small molecule 5HT1A/1B partial agonist in clinical development for the treatment of PD-LID
Lundbeck	foliglurax	Acquired Prexton Therapeutics and got the rights to PD drug Foliglurax, currently in Phase IIa
Newron	safinamide	Approved PD drug characterized by selective MAO-B inhibition, one daily dose. Scheduled to start a Phase 2a POC in PD-LID.
Osmotica	Osmolex ER	Reformulation of amentadine (once daily tablet). Recently approved in US for PD-LID and expected to be launched in 2018

Adamas Pharmaceuticals (ADMS)

Adamas is a pharmaceutical company that is developing medicines for neurologic disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis and epilepsy. Its lead program, GOCOVRI (formerly known as ADS-5102) was approved in 2017 by the FDA for the treatment of dyskinesia in PD patients. GOCOVRI is a high dose 274 mg amantadine (equivalent to 340 mg amantadine HCl) taken once-daily at bedtime that delivers consistently high levels of amantadine from the morning and throughout the day when dyskinesia occurs. Dyskinesia is a consequence of levodopa-based Parkinson's disease treatment and is characterized by involuntary and non-rhythmic movements that are purposeless and unpredictable, which impact the activities of daily living. GOCOVRI's positive benefit/safety profile was established in two Phase III controlled clinical trials in Parkinson's disease patients with dyskinesia. In Study 1, patients treated with GOCOVRI demonstrated statistically significant and clinically relevant reductions in dyskinesia, with a 37 percent reduction in Unified Dyskinesia Rating Scale (UDysRS) total score vs. 12 percent for placebo at Week 12. These results were confirmed in Study 2 in which GOCOVRI achieved a 46 percent reduction in UDysRS vs. 16 percent for placebo. Additionally, key secondary data from Parkinson's disease patient reported diaries in Study 1 and Study 2 respectively, showed that GOCOVRI-treated patients experienced a 3.6 and 4.0 hour increase in functional time daily (defined as ON time without troublesome dyskinesia) vs. a 0.8 and 2.1 hour increase for placebo-

treated patients at Week 12. The increases in functional time were achieved by decreases in both ON time with troublesome dyskinesia and OFF time. The placebo-adjusted reduction in OFF time in both studies was approximately 1 hour per day. The most commonly observed adverse reactions (> 10 percent and greater than placebo) with GOCOVRI were hallucinations, dizziness, dry mouth, peripheral edema, constipation, fall and orthostatic hypotension. Adamas started sales of GOCOVRI in January 2018. In the first nine months the company generated revenues of USD 20.7 million with GOCOVRI.

Amaranthus Bioscience (AMBS)

Amaranthus is a JLABS alumnus biotechnology company developing treatments and diagnostics for diseases in the areas of neurology, regenerative medicine and orphan diseases through its subsidiaries. AMBS' wholly-owned subsidiary Elto Pharma, Inc. has development rights to eltoprazine, a Phase 2b-ready small molecule indicated for Parkinson's disease levodopa-induced dyskinesia, Alzheimer's aggression and adult attention deficit hyperactivity disorder, commonly known as ADHD. Eltoprazine is a small molecule 5HT1A/1B partial agonist in clinical development for the treatment of Parkinson's disease levodopa-induced dyskinesia (PD-LID) and adult attention deficit hyperactivity disorder (ADHD). Eltoprazine has been evaluated in over 680 human subjects to date, and has a well-established safety profile. Eltoprazine was originally developed by Solvay Pharmaceuticals for the treatment of aggression. Upon Solvay's merger with Abbott Pharmaceuticals, the eltoprazine program was out-licensed to PsychoGenics. PsychoGenics licensed eltoprazine to Amarantus following successful proof-of-concept trials in PD-LID and adult ADHD.

Lundbeck (LUN.CO)

H. Lundbeck A/S is a global pharmaceutical company specialized in psychiatric and neurological disorders. Key areas of focus are Alzheimer's disease, depression, Parkinson's disease and schizophrenia. In March 2018 the company acquired Prexton Therapeutics in a deal worth EUR 905 million. By acquiring Prexton, Lundbeck obtained global rights of foliglurax, which currently is in clinical phase II testing for symptomatic treatment of OFF-time reduction in Parkinson’s disease

and dyskinesia (uncontrolled movements) including Levodopa Induced Dyskinesia (LID). Foliglurax is a small molecule, which works by stimulating a specific glutamatergic target (mGluR4) that activates a compensatory neuronal system in the brain. Pre-clinical studies have demonstrated positive effects in models of Parkinson's disease. The aim is to treat the motor symptoms of Parkinson's disease, such as resting tremor and dyskinesia. First data from the ongoing clinical phase II program is expected to be available in mid-2019.

Neurocrine Biosciences (NBIX)

Neurocrine Biosciences is a US based biotechnology company focused on neurologic and endocrine related disorders. One of the company's late-stage clinical programs is opicapone, a novel, once-daily, peripherally-acting, highly-selective catechol-o-methyltransferase inhibitor under investigation as adjunct therapy to levodopa in Parkinson's patients. Opicapone works through decreasing the conversion rate of levodopa into 3-O-methyldopa, thereby reducing the off-time and extending the on-time period associated with Parkinson's treatment. The two pivotal Phase III studies utilized for European approval, BIPARK-I and BIPARK-II, demonstrated that opicapone once-daily achieved a statistically significant decrease in off-time periods for Parkinson's patients compared to placebo. The BIPARK-I study was a placebo-controlled study of approximately 600 patients that also included entacapone as an active comparator. The results of this study also showed that once-daily opicapone was non-inferior to entacapone which is dosed multiple times per day. The BIPARK-II study was a placebo-controlled study of approximately 400 patients that also showed a significant decrease in off-time periods for Parkinson's patients. In both studies, opicapone was associated with significant improvements in both patient and clinician global assessments of change. The data from these two Phase III trials also demonstrated that opicapone improved motor fluctuations in levodopa-treated patients regardless of concomitant dopamine agonist or monoamine oxidase type B inhibitors used. Opicapone was generally well tolerated and was not associated with relevant electrocardiographic or hepatic adverse events. Both of the BIPARK Phase III trials included a one-year open-label extension where opicapone

sustained the decrease in off-time and increase in on-time periods that was demonstrated during the double-blind placebo-controlled portion of the studies.

Osmotica (OSMT)

Osmotica Pharmaceutical is a US based specialty pharmaceutical company engaged in developing pharmaceutical products. It is focused on drug delivery technologies with a special focus in neurology-based therapies. Osmotica Pharmaceutical uses its proprietary osmotic technology platform to develop branded and generic pharmaceutical products. Its Osmodex® is a family of proprietary technologies that combines laser drilled tablet technology with variety of single active and multiple active drug delivery devices. Osmolex ER, a once-daily extended-release tablet that uses the proprietary Osmodex drug delivery system, is indicated for the treatment of Parkinson's disease and drug-induced extrapyramidal reactions in adult patients. The company received FDA approval in February 2018, and it expects to launch this product in the second half of 2018. On February 16, 2018, upon receipt of approval for Osmolex ER from the FDA, Osmotica filed suit against Adamas in the U.S. District Court for the District of Delaware seeking a declaratory judgment that Osmolex ER does not infringe, directly or indirectly, any valid and enforceable claim of any of the 11 patents enumerated in its complaint. On September 20, 2018, Adamas filed an amended answer with counterclaims alleging infringement of certain patents included in Osmotica's complaint and requesting that the court grant Adamas damages, injunctive relief and attorneys' fees. Adamas commercializes a different amantadine product, an extended-release capsule marketed and sold as Gocovri™ (see above).

Analyst: Marcel Wijma MSc

Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.