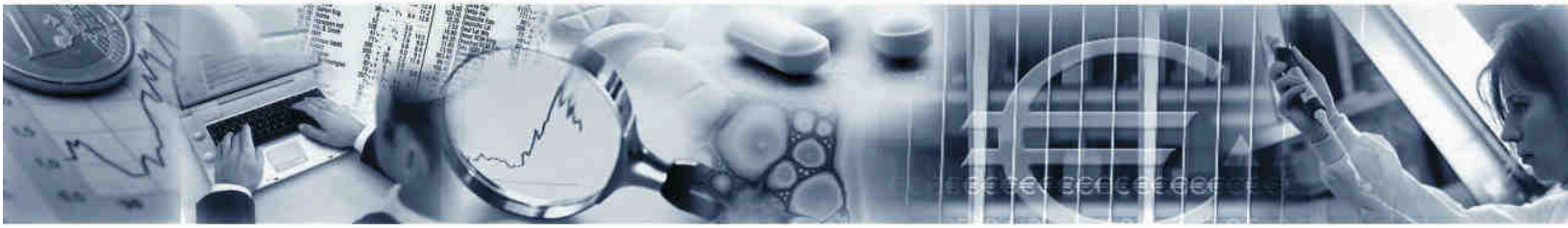

Update Report

Addex Therapeutics

Unlocking Value in PD-LID

Chief Research Analyst

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Date: 27 August 2019

Name:	**Addex Therapeutics**
Country:	**Switzerland**
Price:	**CHF 1.60**
ISIN Code:	**CH0029850754**
Reuters Code:	**ADXN.SW**
Market Cap (CHF m):	**42.2**
EV (CHF m):	**0.5**
Cash & cash eq. (CHF m):	**41.7**
Shares outstanding (m):	**32.8**
Volume:	**13,989**
Free float:	**63%**
52-week Range:	**1.43-2.88**

	2016A	2017A	2018A
Total Revenues	0.40	0.50	6.70
Net (Loss)/Profit	(3.13)	(3.24)	(1.65)
Net loss per share (cents)	(0.28)	(0.25)	(0.07)
R&D costs	2.46	2.46	4.90
Cash increase/(decrease)	(1.20)	1.22	39.08
Cash and marketable sec.	1.40	2.59	41.67

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 2020Q1. Addex has a proprietary small molecule allosteric modulator discovery platform. The allosteric space is getting more attention as an increasing number of big pharma players have developed or in-licensed allosteric drugs.

- The potential market for PD-LID drugs has increased substantially following the substantial prices of PD therapeutics. Drugs like Nuplazid and Gocovri were initially 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.

- The share price has suffered from the announcement that its partner Indivior decided to stop the development of ADX71441 in addiction and shift efforts to back up drug candidates. Besides, Indivior had its own issues after the State of Virginia claimed that Indivior's pain killer SUBOXONE was prescribed to too many people in too high doses. Indivior however has indicated that it wants to accelerate the development of other compounds against addiction that are part of the agreement with Addex so the agreement is still in place with a slight delay.

- The Company's current cash is very strong and amounts to CHF 43.5 million following a successful raise of CHF 40 million last year and the first payment from its partner Indivior. This provides a runway through 2021 and should be sufficient to carry out the further development of its pipeline and the important completion of the Phase IIb/III pivotal

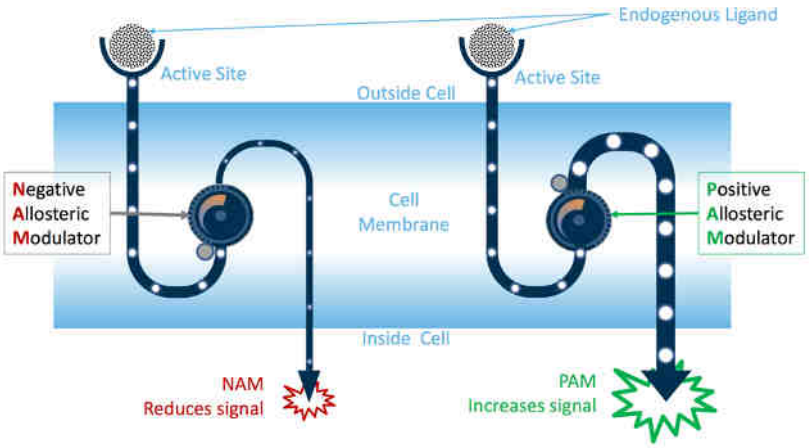
registration trial with dipraglurant in PD-LID in 2021H2.

- Based on our NPV based valuation, we believe that Addex remains substantially undervalued at the current share price of CHF 1.60. We believe the share price decrease of the last few months to be unjustified and it rather provides a strong buying opportunity. Using our valuation model and taking into account the future revenues from its late stage clinical pipeline as well as its current partnership with Indivior, we increase our valuation to CHF 360-395 million, or CHF 11.00-12.00 per share. This represents a substantial upside from the current share price.

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 mechanism of action. The company enjoyed first-mover advantage in the process of discovering and developing allosteric modulators. Addex has developed 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 several molecules for indications with significant commercial potential with a focus on central nervous system (CNS) disorders with orphan drug potential.

What are Allosteric modulators?



Allosteric modulators potential to unlock undruggable targets

There is an opportunity to use an allosteric modulator approach to find drug candidates for well-validated targets which have no approved drugs because traditional orthosteric approaches have

failed to deliver. Hitting previously undruggable targets is an increasingly exciting space with the vast majority of well understood drug targets currently being undruggable. Allosteric sites are largely unexplored for drug discovery although it is an increasingly hot area. There are a number of proprietary technologies that Addex has developed to identify new allosteric approaches in addition to many years of "know-how" held by the company. Allosteric approaches are also interesting as the IP landscape is less crowded so there may be greater freedom to operate.

Also a number of big pharma companies have taken an interest in the area with several drugs in clinical development and/or in-licensed (see table below).

Company	Allosteric Drug	Target	Dev Phase	Primary Indication
Roche	RG7816	GABAA alpha5	Phase I/II	Autism
Sanofi	RMC-4630	SHP2	Phase I/II	Solid Tumours
Astellas	ASP-4345	D1R	Phase II	Cognitive Impairment in SCZ
Eli Lilly	LY3154207	D1R	Phase II	Dementia in PD
AstraZeneca	Selumetinib	MEK1/2	Phase II	Liver Cancer

Source: Addex Therapeutics

Lead drug candidate, dipraglurant entering pivotal registration studies

Addex' lead product is dipraglurant that 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 in PD-LID in 2020Q1 with topline data expected in 2021H2. The study is already fully funded.

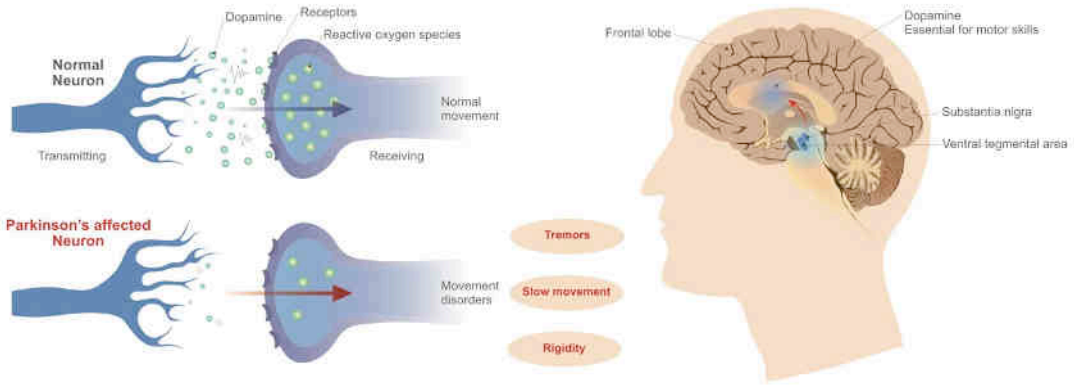
Strategic partnership with Indivior going forward

Addex' current business strategy includes the possibility of entering into collaborative arrangements with third parties to complete the development and commercialization of its proprietary drug candidates. It currently has two partnerships with big pharma. For ADX71149 in

the treatment of epilepsy and other undisclosed CNS disorders, it has a partnership with Janssen Pharmaceuticals. Since 2017, Addex has a strategic partnership with Indivior PLC for the global development and commercialization of the GABAB PAM programs in 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). Earlier this year, Addex announced that Indivior had elected to stop development of ADX71441 and to concentrate resources on alternative GABAB PAM compounds. For the total program, the adjustment in the partnership does not have an impact.

Parkinson's Disease and Levodopa Induced Dyskinesia

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.



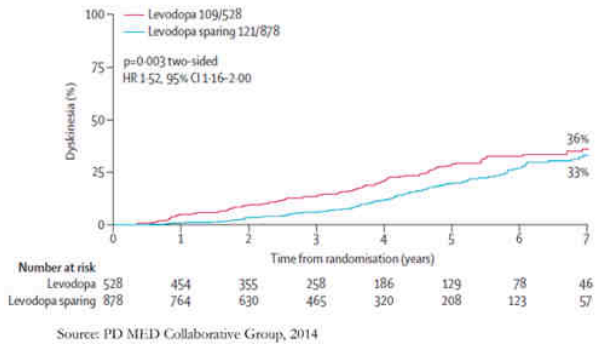
There is no cure for PD. Instead, physicians attempt to manage the symptoms of the disease through a multidisciplinary approach that may include pharmacological, social, and surgical options. The most common pharmaceutical treatment options are those which look to increase the level of dopamine in the 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 dopamine in the substantia nigra. Unfortunately, only about 5-10% of LDOPA crosses the blood-brain barrier. The remainder is often metabolized to dopamine elsewhere, causing a variety of side effects including nausea, dyskinesias and joint stiffness. 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.

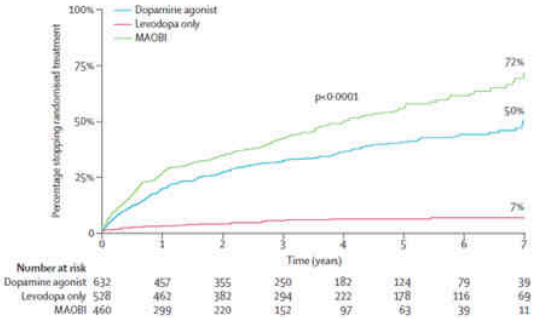
Despite the occurrence of Levodopa Induced Dyskinesia, Levodopa remains the mainstay in PD treatment. In a large clinical study that was done in 2000-2009 in the UK, 1620 patients were randomized to receive Levodopa, dopamine agonists and MAO-B inhibitors. The patients were followed for 7 years to get 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

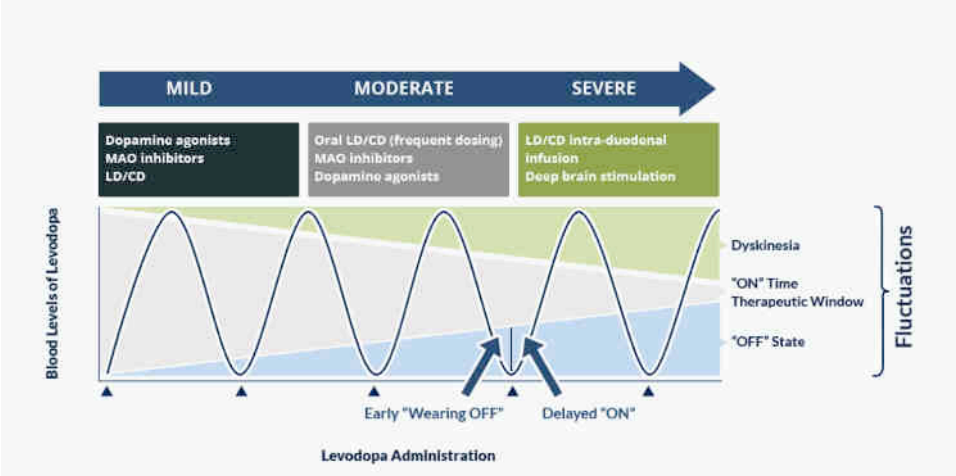


Source: PD MED Collaborative Group, 2014

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 in 2017 (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.

Gocovri (amantadine) first treatment for PD-LID

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. 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 and generated USD 34 million in sales for 2018FY, and USD 24.4 million in 2019H1 which was rather disappointing.

The mechanism by which Gocovri exerts efficacy in the treatment of dyskinesia in patients with PD is unknown. Amantadine is thought to reduce glutamate hyperactivity by blocking the glutamate NMDA receptor. But not all amantadine-based medicine are designed the same way. Govocri QHS is the only amandatine dosed at bedtime. With bedtime dosing of Govocri amantadine concentrations rise slowly during the night when the patient is asleep and are high upon awakening and during the day. Gocovri QHS is designed to give a high plasma concentration in the morning to reduce glutamate hyperactivity before the first dose of levodopa. Glutamate hyperactivity is thought to be dampened by gocovri QHS which may therefore reduce to associated effects or large fluctuations in dopamine levels due to levodopa treatment.

We believe the disappointing commercial launch of Gocovri is not surprising as it is amantadine and is therefore competing against the cheap generic. Despite the extended release formulation, the safety profile is not improved over generic amantadine. In addition, an alternative long acting once daily formulation of amantadine, Osmolex ER, was developed by Osmotica Pharmaceuticals and launched by Vertical Pharmaceuticals in February 2018. We do not believe the disappointing commercial launch of Gocovri has a negative read through to dipraglurant, in fact, we believe it demonstrates that a new mechanism of action with a safer and better tolerated profile is what PD-LID patients are looking for. Dipraglurant is a highly selective mGlu5NAM and based on the data generated, so far, has a much cleaner safety and tolerability profile than amantadine.

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
Dipraglurant-IR *(mGlu5 NAM)*	Parkinson's disease levodopa-induced dyskinesia			
Dipraglurant-ER *(mGlu5 NAM)*	Focal cervical dystonia			
ADX71149 *(mGlu2 PAM)*	Epilepsy		janssen	
$GABA_B$ PAM	Addiction	INDIVIOR		

NAM = Negative Allosteric Modulator
PAM = Positive Allosteric Modulator

Source: Addex Therapeutics

Dipraglurant IR in PD-LID

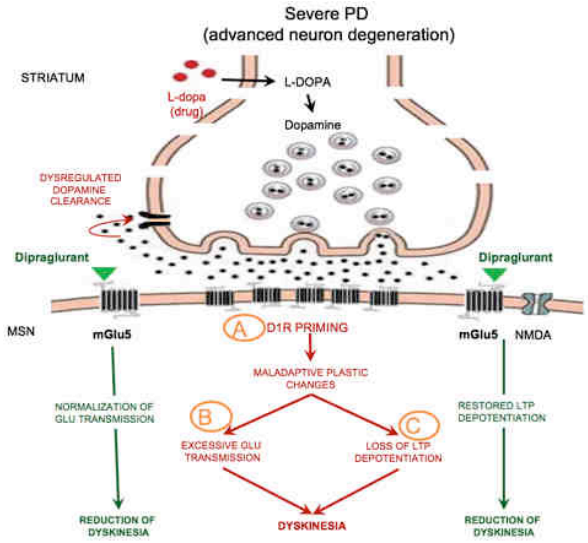
Addex lead program, dipraglurant for PD-LID has seen a dramatic increase in its market potential due to increased pricing, a clearer view on the number of patients, receipt of orphan drug designation from the FDA. The program is fully funded and has patent protection through 2034 without extensions. 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 were initially priced at USD 30,000 and USD 28,500 per year respectively. That would value the US LID market at USD 4.2 billion. However, due to the commercial disappointing roll out and the approval of Osmolex ER (Vertical Pharmaceuticals) for PD, prices have gone down. 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

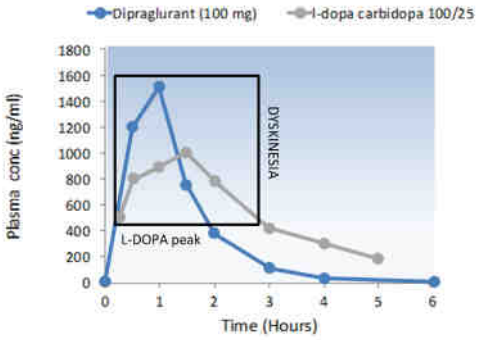
Metabotropic glutamate receptors, or mGluRs perform a variety of functions in the central and peripheral nervous systems: For example, they are involved in learning, memory, anxiety and the perception of pain. They are attractive drug targets due to their modulatory action to normalize glutamatergic 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

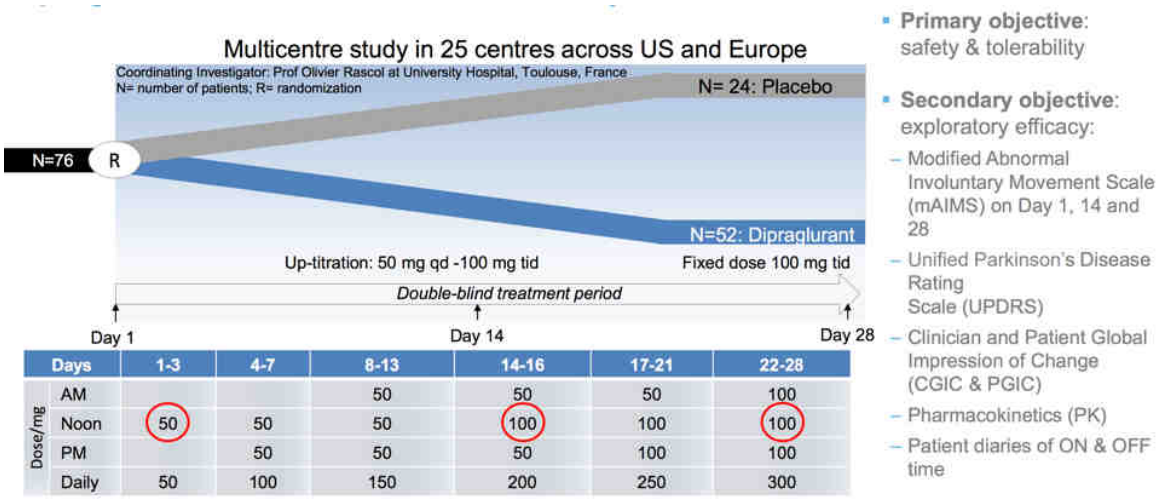
Addex has specifically developed an immediate release (IR) formulation of dipraglurant that mimics the uptake of levodopa in patients, since peak-dose dyskinesia is the most frequent levodopa-induced dyskinesia. Levodopa has to be given 3-4 times a day due to its relatively short half-life. Peak plasma 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 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



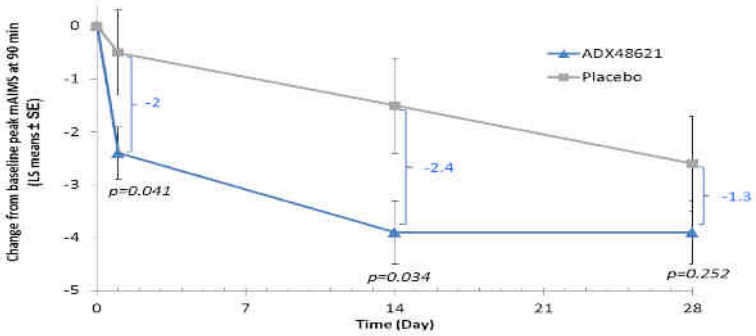
In a double-blind, placebo-controlled, US and European Phase II study in PD-LID, data showed that dipraglurant met the primary objective of the study by exhibiting a good safety and tolerability profile. Dipraglurant also demonstrated a statistically significant reduction in LID severity with both 50 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

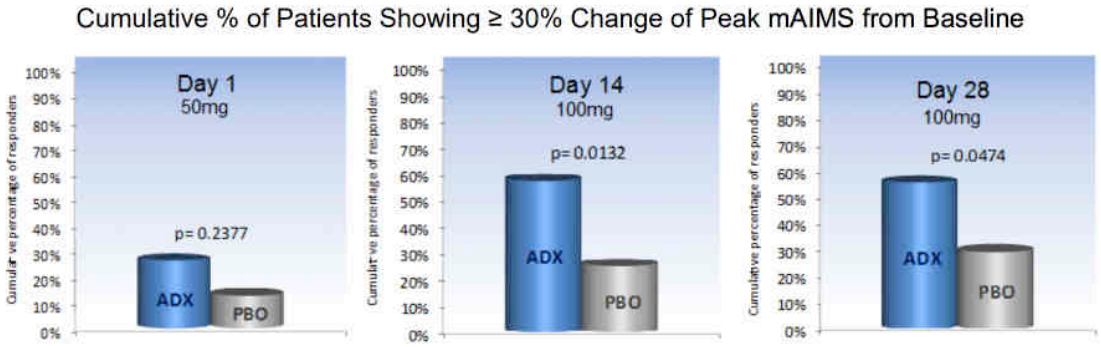
This study found that dipraglurant therapy resulted in substantial improvements on multiple efficacy endpoints. Patients taking dipraglurant had significant reductions in modified Abnormal Involuntary Movement Scale (mAIMS) during peak levodopa concentrations and this response was maintained during the 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 dipraglurant's 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%

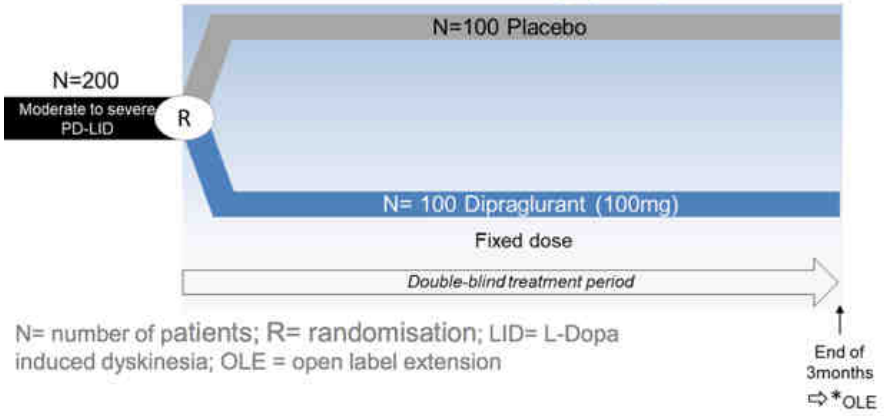
Source: Addex Therapeutics

Upcoming Phase IIb/III study Dipraglurant

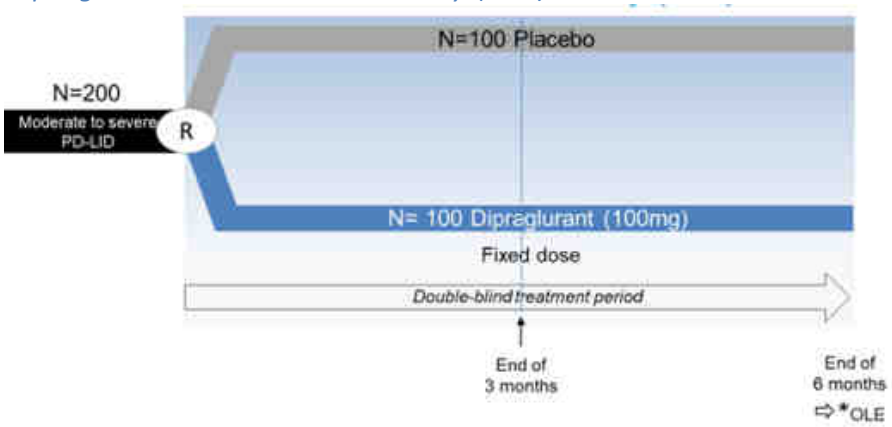
The company has launched a pivotal development program with the first clinical trial starting in 2020Q1 to support regulatory filings for dipraglurant. This randomized, double blind, placebo-controlled Phase IIb/III pivotal registration study will assess the safety and efficacy of dipraglurant for the 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) Part IV. This is important as UDysRS has been shown to be less prone to placebo effect compared to mAIMS. Besides UDysRS is also the recommended scale by the Movement Disorder Society and with the approval of Gocovri by the FDA, there is precedence for the use of UDysRS. Furthermore, it contains anchored objective clinician evaluated measures of dyskinesia. UDysRS was developed in 2009 specifically for dyskinesia in PD patients, whereas mAIMS was developed in 1970 to assess tardive dyskinesia in psychiatric patients.

Secondary endpoints include changes 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)



Dipraglurant 2nd Pivotal LID Study (302)



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. 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 temporarily 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. We understand that the delay in starting this study is due to the focus on starting the dipraglurant PD-LID study and ongoing preclinical work to better understand the potential of dipraglurant in PD-LID. We expect the company to start the dystonia study by early 2021.

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

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 the GABAB program 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. Earlier this year, Indivior decided to stop further evaluation of ADX71441, the lead drug candidate, under investigation in the GABAB PAM program, and refocus future research on alternative PAM compounds targeting GABAB currently under development within the agreement.

GABAB PAM targeted for the treatment of Charcot-Marie-Tooth type 1A neuropathy (CMT1A) disease is a fourth program. CMT1A is one of the most common inherited neurological disorders, affects motor and sensory nerves throughout the body. It is usually not life-threatening, and rarely affects the brain. CMT1A is also called hereditary motor and sensory neuropathy (HMSN), or peroneal muscular atrophy. CMT1A is caused by a chromosome mutation that is inherited from one or both parents. This mutation results in defects in the fibers or protective sheath of the peripheral nerves (the nerves that send signals between the spinal cord and the other parts of the body). Because of these defects, the peripheral nerves do not function properly and are highly susceptible to damage. CMT1A is a progressive disease that commonly begins to affect people in adolescence or early adulthood. In many cases, symptoms begin in the lower legs and feet. The person may experience pain, numbness, weakness muscle degeneration and problems with balance and coordination. The person may develop deformities of the feet such as high arches and

hammertoes, and may experience foot drop (a difficulty in holding up the foot when the leg is lifted). The most common type of CMT1A, 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.

Financials

Income was CHF 6.7 million in 2018 compared to CHF 0.5 million in 2017. In 2018, the Group recognized CHF 6 million under the licensing and research agreement with Indivior and CHF 0.6 million from The Michael J. Fox Foundation for Parkinson's Research related to dipraglurant development in PD-LID and TrKB PAM discovery activities. In all this amounted to a net loss of CHF 1.6 million in 2018 compared to a net loss of CHF 3.3 million in 2017. R&D expenses increased by CHF2.3 million to CHF4.9 million in 2018, compared to CHF2.6 million in 2017, mainly due to an increase in the number of staff and consultants deployed in the preparation of dipraglurant for registration studies in PD-LID and outsourced research costs related to our GABAB PAM and our TrkB PAM programs. R&D expenses consist primarily of costs associated with research, preclinical and clinical testing and related staff costs. G&A expenses increased by CHF2.1 million to CHF3.2 million in 2018, compared to CHF1.1 million in 2017, mainly due to the grant of equity incentive units, whose cost reached CHF1.4 million compared to CHF0.3 million in 2017.

Cash and cash equivalents increased to CHF41.7 million at December 31, 2018, compared to CHF2.6 million at December 31, 2017. This increase of CHF39.1 million is mainly due to the proceeds from the capital increase completed on March 28, 2018 and a positive cash flows from operating activities that reached CHF1.9 million. In July 2019, Addex announced that an Addex-led consortium aimed at the development of small-molecule negative allosteric modulators (NAMs) targeting the metabotropic glutamate receptor 7 (mGlu7) as a potential treatment to reduce fear memory in post-traumatic stress disorder (PTSD), was awarded a EUR 4.85 million Eurostars grant to cover research activities performed by all participants, including Naason Science (South Korea), Endotherm Germany), Nucro Technics (Canada) and Radboud University (Netherlands), in addition to Addex.

Profit & Loss Statement

CHF million	2015A	2016A	2017A	2018A
Revenues	0.8	0.411	0.500	6.701
R&D Costs	(1.8)	(2.461)	(2.629)	(4.920)
SG&A	(1.7)	(1.080)	(1.106)	(3.209)
Tax escrow account write-off	(1.2)	(-)	(-)	(-)
Operating Profit/(Loss)	(3.9)	(3.130)	(3.235)	(1.425)
Finance result	(0.3)	0.019	(0.045)	(0.220)
Net Profit/(Loss)	(4.2)	(3.149)	(3.280)	(1.645)

Consolidated statement of cash flows

CHF million	2016A	2017A	2018A
Cashflow from operating activities	(2.694)	(2.135)	1.752
Cash flow from investing activities	(0.01)	(0.02)	(0.062)
Cash flow from financing activities	1.492	3.355	37.390
Cash and cash equivalents at beginning of the period	2.633	1.416	2.579
Net change in cash and cash equivalents	(1.204)	1.214	39.080
Cash and cash equivalents at the end of the year	1.416	2.579	41.670

Valuation

We value Addex Therapeutics at CHF 360-395 million or CHF 11-12 per share. Earlier valuation models did not address value to the preclinical programs in Addex' pipeline, including its GABAB PAM programs in addiction. Based on the partnership with Indivior, this program still 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 1.50-2.50 per share. At this moment, we not take a value for the Dystonia Program into account as Addex has the program currently under review.

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 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 the 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 Inbrija. The drug received approval by the FDA in January. Sunovion acquired Cynapsus in 2016 for USD 624 million to get the rights to Cynapsus' Phase III PD candidate APL-130277. Sunovion 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.

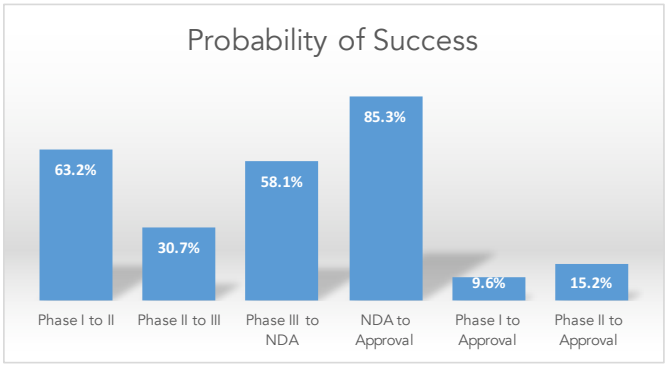
Company	Acquired by	Deal size	Comments
Civitas	Acorda Therap.	USD 525m	FDA granted approval for Inbrija in January 2019
Cynapsus	Sunovion	USD 624m	Acquired Cynapsus and got the rights to PD drug APL130277, currently in Phase III
Neuroderm	Mitsubishi Tanabe Pharma	USD 1.1bn	Lead product is ND0612 for 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.

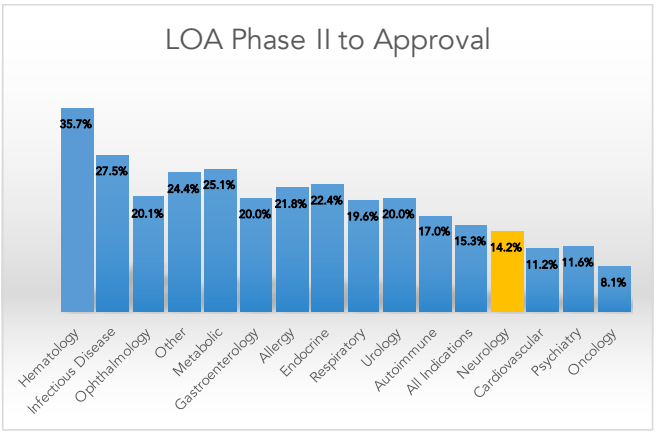
The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in 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.



Valuation dipraglurant HR in PD-LID

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 2024 and 2025 in Europe. We calculate a Risk adjusted Discount Rate of 15%. Annual pricing is conservatively set at USD 24,000 for the US and USD 15,000 for Europe which is actually lower than initial pricing of competitive drugs (Gocovri for PD-LID was first priced at USD 28,500, Pimavanserin for PDP was priced initially at USD 24,000 and whereas Igrezza is even priced at USD 60,000-90,000). We notice that pricing of Gocovri is decreasing following the disappointing commercial roll out of the drug. 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 22% as we believe that the vast amount of data justifies that. **This leads to a total valuation for dipraglurant of CHF 303 million or CHF 9.25 per share.**

Valuation in PD-LID US Market

Year	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	
No of patients US (yoy growth 2.5% as of 2015)	241244	247275	253457	259793	266288	272945	279769	286763	293932	301280	
Penetration	0.5%	1.5%	4.0%	7.0%	11.0%	15.0%	18.0%	21.0%	22.0%	23.0%	
Total Revenues (USD m)	**28.9**	**89.0**	**243.3**	**436.5**	**703.0**	**982.6**	**1208.6**	**1445.3**	**1552.0**	**1663.1**	
Margin 50%	14.5	44.5	121.7	218.2	351.5	491.3	604.3	722.6	776.0	831.5	
WACC 15%	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16	0.14	
NPV (million)	7.2	19.2	45.7	71.3	99.9	121.4	129.9	135.1	126.1	117.5	
Total NPV (million)											**873.5**
LOA 22%											**192.2**

Valuation in PD-LID European Market

Year	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	
No of patients Europe (yoy growth 2.5% as of 2015)	296730	304148	311752	319546	327534	335723	344116	352719	361536	370575	
Penetration	0.5%	1.5%	4.0%	7.0%	11.0%	15.0%	18.0%	21.0%	22.0%	23.0%	
Total Revenues (USD m)	**22.3**	**68.4**	**187.1**	**335.5**	**540.4**	**755.4**	**929.1**	**1111.1**	**1193.1**	**1278.5**	
Margin 50%	11.1	34.2	93.5	167.8	270.2	377.7	464.6	555.5	596.5	639.2	
WACC 14%	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16	0.14	0.12	
NPV (million)	4.8	12.9	30.6	47.7	66.8	81.2	86.8	90.3	84.3	78.6	
Total NPV (million)											**505.3**
LOA 22%											**111.2**

Partnership Leads to Substantial Higher Valuation

In previous valuation models, we did not address value to the preclinical programs in Addex' pipeline, including its GABAB 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 1.50-2.50 per share.

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:

- Dipraglurant first pivotal study in LID registration program – start dosing: **2020Q1**
- Dipraglurant first pivotal study in LID registration program – results: **2021H2**

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.