LifeSci Capital

Addex Therapeutics (ADXN.SW)

Initiation Report

LifeSci Investment Abstract

Addex Therapeutics (SIX: ADXN.SW) is a clinical-stage biotechnology company focused on the development of allosteric modulators to treat a wide range of central nervous system (CNS) disorders. The Company's lead program is dipraglurant for the treatment of levodopa-induced dyskinesia in patients with Parkinson's disease (PD). PD affects approximately 1.5% of people over the age of 65. As the disease progresses, the majority of patients will develop some degree of dyskinesia during peak levodopa exposure. Addex has successfully completed a Phase II study of dipraglurant with support from the Michael J. Fox Foundation and expects to launch a pivotal Phase III study in the second half of 2017.

Key Points of Discussion

- **Addex is Developing Dipraglurant to Address Levodopa-Induced Dyskinesia**. Addex is developing an immediate-release formulation of dipraglurant to reduce the frequency and severity of levodopa-induced dyskinesia (LID) in PD patients. Although levodopa is the most commonly prescribed treatment for PD, its long-term use is associated with the emergence of disabling motor fluctuations and dyskinesias. Dipraglurant is a small molecule, negative allosteric modulator of the metabotropic glutamate receptor 5 (mGluR5) that dampens glutamatergic signaling in the basal ganglia thought to underlie dyskinesias. Addex has completed a Phase IIa study evaluating dipraglurant with the support of a grant from the Michael J. Fox Foundation and plans to launch a pivotal Phase III study in the second half of 2017.

- **Phase IIa Data Show Substantial Reductions in Dyskinesia**. Addex has studied dipraglurant in a Phase IIa study as well as 3 Phase I studies, demonstrating that the drug is safe, well-tolerated, and capable of reducing dyskinesia in PD patients. In the Phase IIa trial, dipraglurant therapy was associated with a 30% reduction in dyskinesia, as measured with the modified Abnormal Involuntary Movement Scale (mAIMS). Addex plans to launch a registration-directed Phase III study for dipraglurant in the second half of 2017, once the Company has secured funding for the trial. Addex recently conducted a receptor occupancy study and was able to identify higher doses of dipraglurant to be tested in the Phase III study.

Expected Upcoming Milestones

- Q3 2016 – Launch of investigator-sponsored study for dipraglurant ER in dystonia.
- Q4 2016 – Initiate a Phase II proof-of-concept study with dipraglurant ER for focal cervical dystonia.
- Q4 2016 – Results from pilot study in dystonia.
- H1 2017 – Initiate a Phase I study with ADX71441.
- H2 2017 – Results of a Phase II trial with dipraglurant ER for focal cervical dystonia.
- H2 2017 – Initiate a Phase III trial with dipraglurant IR for levodopa-induced dyskinesia (LID).
- H2 2017 – Results of a Phase I study with ADX71441.
- H1 2018 – Initiate a Phase II trial with ADX71441 for Charcot Marie Tooth Type 1A.

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Market Data

Price	$2.50
Market Cap (M)	$34
EV (M)	$30
Shares Outstanding (M)	13.4
Avg Daily Vol	20,515
52-week Range:	$2.17 - $3.73
Cash (M)	$3.6
Net Cash/Share	$0.27
Annualized Cash Burn (M)	$2.7
Years of Cash Left	1.4
Debt (M)	$0.0

Financials

FY Dec		2014A	2015A	2016A
EPS	H1	(0.11)A	(0.28)A	NA
	H2	NA	NA	NA
	FY	(0.20)A	(0.41)A	NA

For analyst certification and disclosures please see page 33

- **Dosing and Pharmacokinetics that Match Levodopa Serum Concentrations**. Dipraglurant has a similar pharmacokinetic profile to levodopa and Addex intends for the drugs to be taken concurrently. The obvious benefit of this dosing strategy is that the peak concentration and maximal effect of dipraglurant coincide with peak levodopa activity, which is when dyskinesias are most likely to occur. Competing programs from Adamas (NasdaqGS: ADMS) and Osmotica (Private) are focused on the development of extended-release formulations of amantadine that allow for once-daily dosing. The drug's peak concentration does not coincide with levodopa administration and its pharmacokinetic profile may be variable due to patient differences in gut motility and gut absorption. Dosing unpredictability has been an issue with the absorption of sustained-release formulations of levodopa.[1]

- **Large Market Opportunity Due to High LID Rates**. PD affects approximately 1.5% of people over the age of 65. As the disease progresses, the majority of patients will progress to having some degree of dyskinesia during peak levodopa exposure. Across all PD patients, the overall 5-year risk of developing LID is roughly 40%. However, by 15 years after diagnosis, greater than 90% of PD patients have developed LID. In the US, the emergence of LID results in a roughly 42% increase in the cost associated with treating PD. With the population over age 65 expected to double between now and 2030, is also likely to increase dramatically. We estimate a current LID patient population of roughly 160,000 patients in the US. These individuals would likely benefit from an effective therapy to treat LID symptoms, particularly as the disease state becomes more advanced. Acadia's (NasdaqGS: ACAD) pricing of *Nuplazid* (pimavanserin), their recently approved drug for psychosis associated with PD, at $23,000 per year may provide a suitable reference point for the pricing that may be possible for a new chemical entity (NCE) like dipraglurant.

- **Addex is Developing Extended-Release Dipraglurant for Focal Cervical Dystonia.** Addex is also developing an extended-release formulation of dipraglurant for the treatment of focal cervical dystonia. Dystonia is a neurological disorder that causes involuntary, sustained muscle contractions leading to abnormal movements and postures. The most common type of dystonia is focal cervical dystonia, which causes tremors, jerking, and twisting of the head, neck, and shoulders. This variant of dystonia affects approximately 16,000 people in the US alone, and Addex plans to file for Orphan Drug designation in this indication. First-line treatment is an injection of botulinum toxin (BoNT) required every 3 months, but 15-30% of patients don't respond to this treatment and 10-15% eventually become refractory to treatment. Addex plans to launch a Phase II proof-of-concept study in the fourth quarter of 2016 to evaluate the safety and efficacy of dipraglurant ER in treating patients with focal cervical dystonia.

- **Domain Expertise in Development of Novel Allosteric Modulators**. Addex has a proprietary drug discovery platform used to identify novel allosteric modulators with therapeutic potential. The Company presently has two allosteric modulators in the clinic in addition to a broad preclinical portfolio of drugs targeting orphan indications. In addition to dipraglurant, Addex has a collaboration with Janssen Pharmaceuticals (NYSE: JNJ) for the development of ADX71149, a positive allosteric modulator of the metabotropic glutamate receptor 2 (mGluR2), as a potential epilepsy treatment. ADX71149 has been evaluated in more than 8 clinical studies to date and plans are underway to launch a Phase IIa proof-of-concept study to assess the potential of this drug as a treatment for epilepsy. To date, Addex has received €10.2 million ($11.6 million) from Janssen and is eligible to receive an additional €109 million ($124.6 million) in milestones plus low double-digit royalties on net sales. Other allosteric modulators, still in preclinical development, are being developed for a broad range of CNS conditions and provide a foundation for Addex's long-term growth.

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[1] Nyholm, D, et al., 2003. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. *Clinical Neuropharmacology*, 26(3), pp156-163.

Financial Discussion

2015 Financial Results. On April 29th, Addex reported full-year financial results for 2015. The Company reported income of CHF 0.8 million ($0.8 million) for 2015, which included CHF 0.3 million ($0.3 million) in grants from the Michael J. Fox Foundation for Parkinson's Research. For 2014, Addex reported CHF 1.0 million ($1.0 million). In 2015, Addex had research and development expenses of CHF 1.8 million ($1.9 million), compared with CHF 0.9 million ($0.9 million) in the prior year. This change resulted from an increase in costs associated with the preparation of dipraglurant for Phase III development. General and administrative expenses were CHF 1.7 million ($1.8 million), which was in line with the CHF 1.9 million ($2.0 million) spent in 2014. Addex reported a comprehensive net loss of CHF 4.2 million ($4.4 million), or CHF 0.39 ($0.40) per share, for the year, compared to CHF 1.8 million ($1.9 million), or CHF 0.18 ($0.19) per share, in 2014. As of December 31, 2015, the Company had CHF 2.6 million ($2.7 million) in cash and cash equivalents.
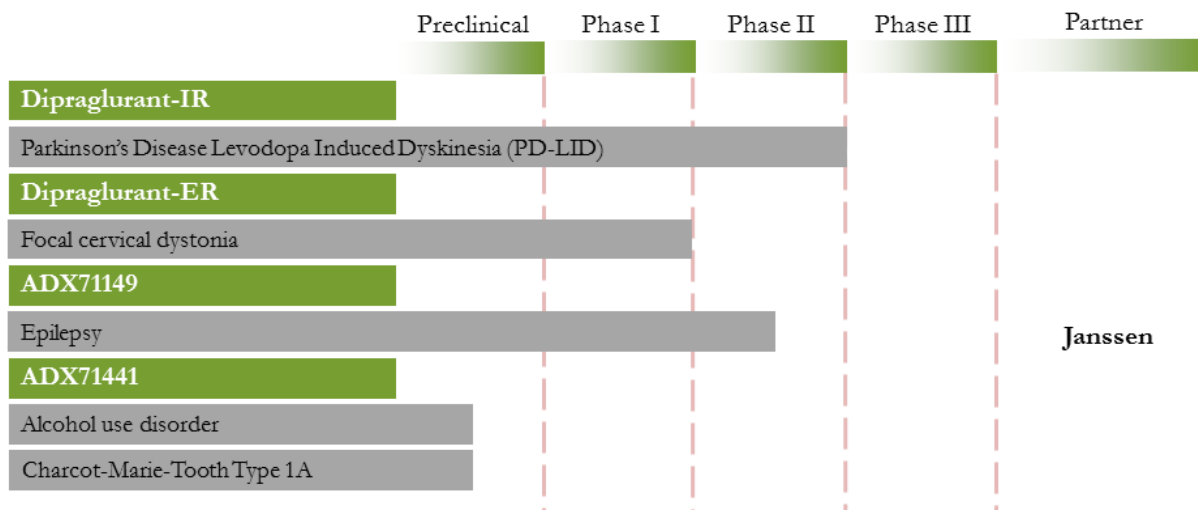
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Company Description

Addex Therapeutics is a clinical-stage biotechnology company focused on the development of allosteric modulators to treat a wide range of central nervous system (CNS) disorders. The Company's full pipeline is shown in **Figure 1**. Their lead program is dipraglurant, a negative allosteric modulator of the metabotropic glutamate receptor 5 (mGluR5), for the treatment of levodopa-induced dyskinesia in patients with Parkinson's disease (PD). Levodopa is an effective and widely prescribed PD treatment, although its long-term use is associated with disabling fluctuations in motor symptoms and dyskinesias as the disease progresses. As the disease progresses, the majority of patients will develop some degree of dyskinesia during peak levodopa exposure. By 15 years after diagnosis, greater than 90% of PD patients have developed LID.

Dipraglurant dampens activation of mGluR5 receptors in key structures within the basal ganglia, which is thought to reduce aberrant corticostriatal signaling that may contribute to dyskinesias. The drug is intended to be dosed concurrently with levodopa and has similar pharmacokinetics to standard levodopa formulations, ensuring peak drug activity when there is the greatest risk of LID.[2] Addex has completed a Phase II study on dipraglurant with support from the Michael J. Fox Foundation and expects to launch a pivotal Phase III study in the second half of 2017. The Company is also developing an extended-release formulation of dipraglurant for the treatment of focal cervical dystonia and expects to launch a Phase II study for this indication in the fourth quarter of 2016.

Figure 1. Addex's Development Pipeline

Source: LifeSci Capital

Addex has a proprietary drug discovery platform for the identification of a broad range of allosteric modulators. In addition to dipraglurant, the Company has identified a GABA$_B$ receptor (GABA$_B$R) positive allosteric modulator, ADX71441, which is being investigated as a potential treatment for alcohol use disorder, addiction to nicotine or cocaine, and Charcot-Marie-Tooth disease. Addex has also discovered AX71149, a positive allosteric modulator of
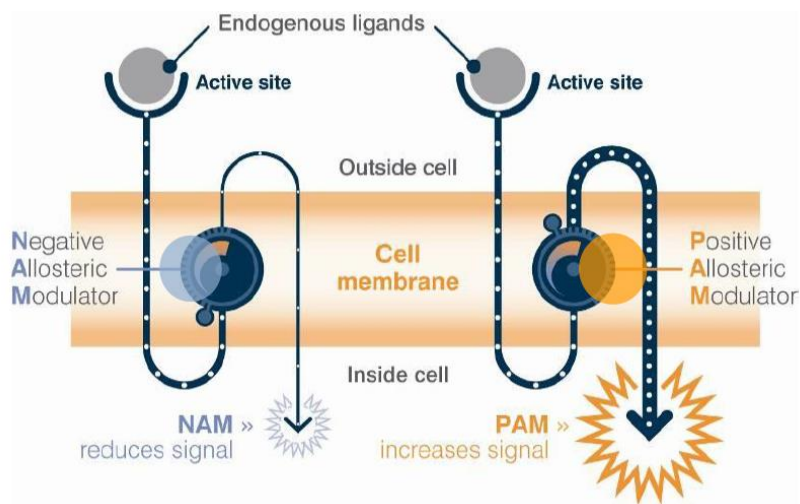
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[2] Khor, SP and Hsu, A, 2007. The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. *Current Clinical Pharmacology*, 2, pp234-243.

the metabotropic glutamate receptor 2 (mGluR2), and is developing the candidate in collaboration with Janssen Pharmaceuticals (NYSE: JNJ). AX71149 has been evaluated in more than 8 clinical studies to date and plans are underway to launch a Phase IIa proof-of-concept study to assess the potential of this drug as a treatment for epilepsy. To date, Addex has received €10.2 million ($11.6 million) from Janssen and is eligible to receive an additional €109 million ($124.6 million) in addition to low double-digit royalties on net sales.

Dipraglurant IR: An Immediate-Release Modulator to Treat Levodopa-Induced Dyskinesia

Dipraglurant is a negative allosteric modulator (NAM) of the metabotropic glutamate receptor 5 (mGluR5), which is an excitatory G-protein-coupled receptor. As an allosteric modulator, dipraglurant binds to a different site than glutamate, the endogenous ligand of this receptor. Allosteric modulators allow for greater receptor subtype specificity and may reduce the frequency of adverse events that can result from off-target activity.[3,4] **Figure 2** shows a schematic diagram highlighting the binding of a positive or negative allosteric modulator to a transmembrane receptor. As shown in the figure, a NAM reduces the activity of the receptor induced by the binding of the natural ligand, while a positive allosteric modulator (PAM) increases the receptor signal.

Figure 2. Schematic Diagram of Positive and Negative Allosteric Modulators

Source: Company Reports

Mechanism of Action. While levodopa is an effective dopamine replacement therapy, its administration tends to result in pulsatile stimulation of dopamine receptors in the basal ganglia as opposed to the low-level, tonic activation that occurs from endogenously-released dopamine in healthy individuals. As a consequence of this, peak levodopa activity can lead to overstimulation of excitatory D1 receptors on direct pathway neurons and inhibitory D2 receptors

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[3] Nickols, HH and Conn, PJ, 2014. Development of allosteric modulators of GPCRs for treatment of CNS disorders. *Neurobiology of Disease*, 61, pp55-71.
[4] van Westen, GJP, et al., 2014. Chemical, Target, and Bioactive Properties of Allosteric Modulation. *PLOS Computational Biology*, 10(4), e1003559.

on indirect pathway neurons. This results in hyperactivity in the direct pathway and hypoactivity in the indirect pathway, which can result in a wide range of dyskinesias.

The degeneration of nigrostriatal dopaminergic terminals is also thought to contribute to the pathogenesis of LID and may explain the delay from the initiation of levodopa therapy to the onset of LID symptoms. Levodopa, once taken up into the presynaptic terminals of dopamine neurons, is converted into dopamine and released from the synapses when these neurons are active. As dopamine neurons are lost, there are fewer and fewer sites in the brain to convert levodopa to dopamine, reducing the buffering capacity and shifting towards a more pulsatile activation of dopamine receptors.[5] With fewer dopamine neurons, a greater amount of levodopa may end up in non-dopaminergic terminals that have substantially different release profiles.[6,7,8] This contributes to large swings in the extracellular concentration of dopamine in the striatum, which become worse as the disease progresses. Investigators from the United Kingdom have demonstrated that increased dopamine release from serotoninergic terminals in the striatum may underlie the emergence of LID in some PD patients.[9]

Abnormal glutamate signaling in the basal ganglia is thought to play a key role in the manifestation of LID in PD patients.[10,11] The primary input into the basal ganglia circuit is glutamatergic projections from the cortex to the striatum, and dopamine plays an important role in modulating this glutamatergic input. The shift towards the direct pathway resulting from abnormal dopamine levels can exaggerate the brain's response to endogenous corticostriatal glutamate release. By dampening the response of striatal neurons to glutamate, dipraglurant may be able to reduce the risk of dyskinetic episodes resulting from the swings in dopamine concentration. There has been strong interest in developing LID treatments that target glutamate signaling in the basal ganglia, including Addex's dipraglurant and Adamas' *Nurelin* (amantadine ER).

Preclinical Studies

Investigators tested the effect of dipraglurant on a macaque model of PD induced by repeated daily administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[12] Once parkinsonism was present, the macaques were treated with levodopa for 4-5 months at individually-tailored dose that fully reversed PD symptoms. During the treatment period, these animals developed consistent dyskinesias. **Figure 3** highlights the changes in chorea scores (on the left) and dystonia scores (on the right) following treatment with dipraglurant or placebo. Treatment with 30 mg/kg of

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[5] Huot, TH, et al., 2013. The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. *Pharmacological Reviews*, 65(1), pp171-222.

[6] Ng, KY, et al., 1970. L-Dopa induced release of cerebral monoamines. *Science*, 170(3953), pp76-77.

[7] Ng, KY, et al., 1971. Effects of L-dopa on efflux of cerebral monoamines from synaptosomes. *Nature*, 230(5292), pp331-332.

[8] Tanaka, H, et al., 1999. Role of serotonergic neurons in L-DOPA-derived extracellular dopamine in the striatum of 6-OHDA-lesioned rats. *Neuroreport*, 10(3), pp631-634.

[9] Politis, M, et al., 2014. Serotonergic mechanisms responsible for levodopa-induced dyskinesias in Parkinson's disease patients. *The Journal of Clinical Investigation*, 124(3), pp1340-1349.

[10] Rascol, O, et al., 2014. Use of metabotropic glutamate 5-receptor antagonists for treatment of levodopa-induced dyskinesias. *Parkinsonism and Related Disorders*, 20, pp947-956.

[11] Chase, TN, et al., 2003. Striatal glutamatergic mechanisms and extrapyramidal movement disorders. *Neurotoxicity Research*, 5(1-2), pp139-146.

[12] Bezard, E, et al., 2014. The mGluR5 Negative Allosteric Modulator Dipraglurant Reduces Dyskinesia in the MPTP Macaque Model. *Movement Disorders*, 29(8), pp1074-1079.

dipraglurant resulted in statistically significant reductions in chorea and dystonia scores relative to the vehicle-treated group. Dosing with the 3 or 10 mg/kg did not have significant effects.
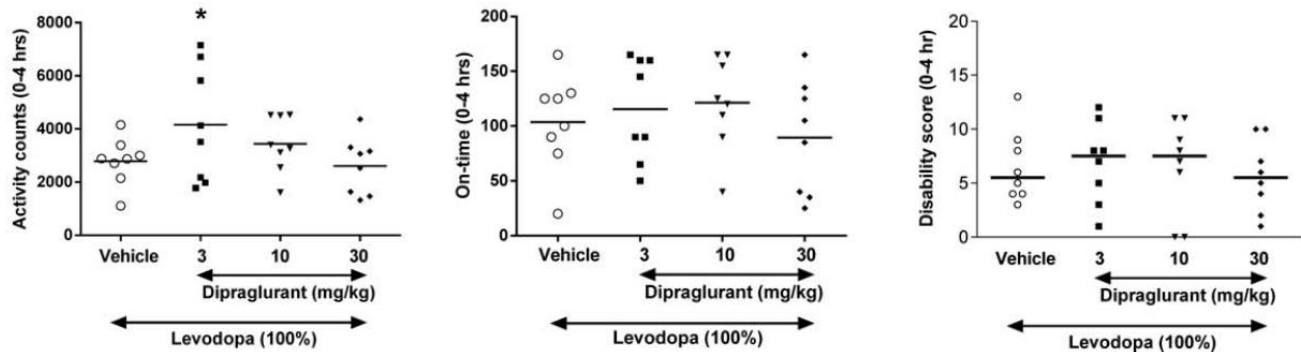
Figure 3. Chorea and Dystonia Scores Following Treatment with Dipraglurant or Placebo

Source: Bezard et al., 2014

Figure 4 displays the effect of dipraglurant or placebo on multiple measures of the severity of PD motor symptoms in the study. At all doses tested, dipraglurant treatment did not alter activity scores (left), ON time (middle), or disability scores (right), indicating that the drug did not affect the efficacy of levodopa. This is an important finding, since an LID treatment must not compromise the motor improvements achieved with levodopa.

Figure 4. Preservation of Levodopa Activity with Dipraglurant Treatment

Source: Bezard et al., 2014

Safety Profile. To date, the safety and tolerability of dipraglurant has been evaluated in three Phase I trials in healthy volunteers and a Phase IIa trial in PD patients experiencing moderate to severe LID. The results from all of the trials indicate that dipraglurant is generally safe and well-tolerated. The Phase I trials enrolled more than 36 adults, including

patients over 50 years old, and there were no safety or tolerability concerns arising from dipraglurant use under fasting or well-fed conditions. During the Phase IIa trial, treatment with dipraglurant did not affect safety parameters such as 12-lead electrocardiogram, heart rate, blood pressure, hematology, and biochemistry. The most common adverse events in patents receiving dipraglurant included dyskinesia, dizziness, nausea, and fatigue. Treatment was discontinued in two patients at the highest dose due to dyskinesia and sweating in one patient, and nausea, dizziness, and anxiety in the other patient. The safety and tolerability profile of dipraglurant observed to date has been considered favorable and supports Addex's plan to continue development for the LID indication.

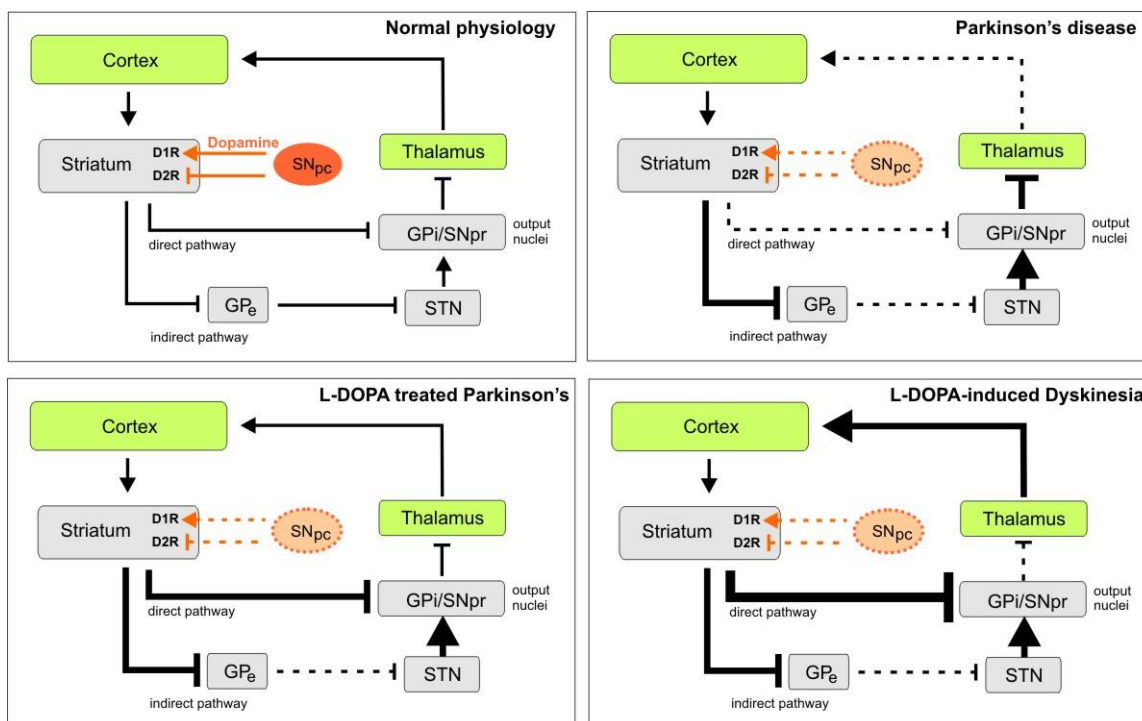## Levodopa Induced Dyskinesia (PD-LID) in Parkinson's Disease Patients

First described in 1817 by James Parkinson, Parkinson's disease (PD) is an adult-onset, progressive neurodegenerative disorder, second in prevalence only to Alzheimer's disease. PD is characterized by the gradual loss of neurons that release dopamine and other catecholamines, leading to primary symptoms which include shaking (tremors), rigidity, slowness of movement (bradykinesia), and difficulty with the initiation and coordination of movement. Degeneration of dopamine neurons leads over time to a range of difficulties performing normal motor activities. Disruptions to the dopamine system in PD first manifest themselves in movement problems but later begin to affect these other systems as well. Motor symptoms generally do not present until most of the neurons have died.

Parkinson's Disease Background. The primary symptoms of PD result from abnormalities in the output of the basal ganglia (BG), an assembly of interconnected subcortical nuclei involved in a wide range of motor, emotive, behavioral, and cognitive functions. The input nucleus of the BG is the striatum, which is mainly composed of GABAergic medium spiny neurons (MSNs) receiving extensive glutamatergic projections from the cortex. There is a topographic organization to the striatum with most if not all areas of the cortex having a corresponding compartment within the striatum. The striatum gives rise to the direct and indirect pathways, and the brain is able to coordinate complex movements through these pathways. The basal ganglia has two primary output nuclei, the internal globus pallidus (GPi) and the substantia nigra pars reticulata (SNr).

In general, activation of the direct pathway decreases activity in the GPi and SNr, while activation of the indirect pathway increases activity in these nuclei. MSNs that are a part of the direct pathway express excitatory D_1 dopamine receptors (D_1R), while MSNs for the indirect pathway express inhibitory D2 dopamine receptors (D_2R). Both pathways receive glutamatergic cortical input that is modulated by dopamine release from the synaptic terminals of neurons located in the substantia nigra pars compacta (SNc). Increasing levels of dopamine in the striatum shift the basal ganglia towards the direct pathway. In the context of motor control, the direct pathway promotes movement, while the indirect pathway inhibits it.

Figure 5 highlights the main connections of the basal ganglia under normal conditions, and shows the changes to the basal ganglia brought on by PD, levodopa treatment, and levodopa-induced dyskinesia. Within the figure, the main sources of glutamate in the basal ganglia are the cortex and the subthalamic nucleus. In this figure, line thickness indicates the level of activity with thicker lines indicating higher levels of activity and dashed lines signifying reduced activity. In PD patients, dwindling amounts of dopamine released in the striatum shift the basal ganglia towards the indirect pathway, which may account for many of the motor symptoms associated with the disease.
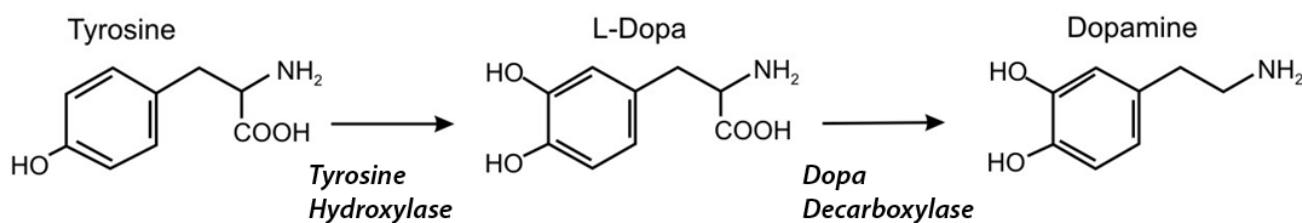
Figure 5. Normal and Parkinsonian Basal Ganglia Pathways

Source: LifeSci Capital

Levodopa and Dopamine Replacement Therapy. Dopamine replacement therapies (DRTs) provide patients with dopamine lost due to the death of dopamine-producing neurons. Levodopa treatment is the primary type of dopamine replacement therapy. DRT has been available since the 1960s and has been the standard of care for PD for the past 30 years. Nearly everyone who develops PD will receive DRT as part of his or her treatment. During DRT, patients receive levodopa alone or with one or two other active ingredients. Endogenous dopamine is synthesized from tyrosine, with levodopa as an intermediate, through the activity of two enzymes, as shown in **Figure 6**. DRT is used to provide levodopa because dopamine itself cannot cross the blood-brain barrier. For DRT, levodopa is administered and crosses the blood-brain barrier and subsequently relies on dopa decarboxylase for conversion to dopamine in the brain.

Figure 6. Dopamine synthesis

Source: LifeSci Capital

Levodopa administration is able to boost dopamine levels in the striatum in order to shift the basal ganglia towards a more physiological balance between the direct and indirect pathways. However, in certain instances, excessive activation of striatal dopamine receptors can lead to dyskinesias, dystonias, and other aberrant movements. One such instance where this occurs is during peak levodopa exposure.

Although DRT has been the standard of care for PD for several decades, it has limitations and significant side effects. Most PD patients experience some form of freezing episodes, commonly occurring at the start (latency to on) or end of a dose of levodopa (wearing off), but also spontaneously in some patients.[13,14] These fluctuations can become extreme, resulting in rapid and unpredictable succession of ON and OFF states. There is both a minimum level of levodopa needed to reach therapeutic efficacy and a maximum level above which adverse dyskinesias and other motor disturbances develop. This range is known as the therapeutic window. Ideal treatment of PD motor symptoms would maintain stable levodopa and consequently CNS dopamine levels within this range. However, the reality is a bit more complicated.
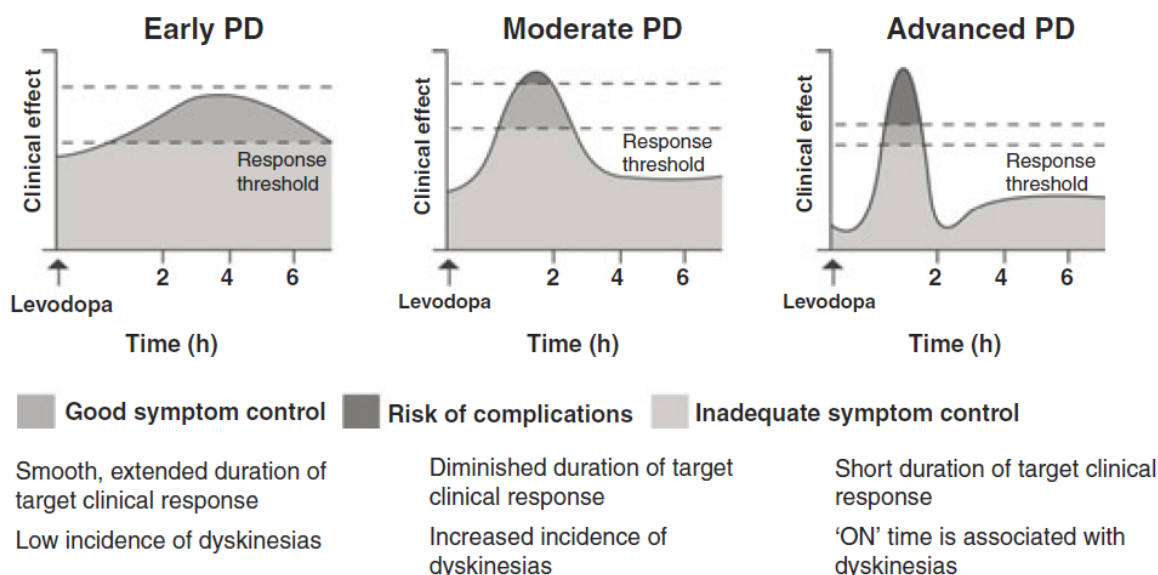
Levodopa is most commonly administered orally. Levodopa uptake in the gut is a slow process, and after it is absorbed levodopa must be converted to dopamine. This means that there is a delay, which can be significant, between when a patient takes a levodopa pill and the effects are felt. The patient must also be careful not to take the doses too close together as this can also lead to dyskinesias and other motor fluctuations. Furthermore, whereas there is a slow ramp up to effective concentrations of levodopa, at the end of the dose levels can drop unpredictably and lead to an OFF episode. A patient's response to levodopa also changes as PD progresses.

Levodopa Therapeutic Window. The graph in **Figure 7** illustrates the changing response that patients experience to levodopa over time. Early in the disease progression the levodopa response is predictable and provides patients with therapeutic amounts of the drug. While this works fairly well early on, patient response becomes less predictable as more dopamine neurons die and the disease becomes more advanced. The progression of dopaminergic cell death results in fewer and fewer sites in the brain that can metabolize levodopa into dopamine, altering the kinetics and minimizing the effectiveness of levodopa treatment. As illustrated, the therapeutic window narrows and patients have greater propensity to experience concentrations of levodopa above the therapeutic window and associated dyskinesias.

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[13] Chen, J. J. & Obering, C., 2005. A review of intermittent subcutaneous apomorphine injections for the rescue management of motor fluctuations associated with advanced Parkinson's disease. *Clinical therapeutics*, 27, pp1710-1724.
[14] Stacy, M. & Silver, D., 2008. Apomorphine for the acute treatment of "off" episodes in Parkinson's disease. *Parkinsonism & related disorders*, 14, pp85-92.

Figure 7. Changes in PD Patient Levodopa Response over Time

Source: Schapira et al., 2009

Assessment for LID. The fluctuating nature of PD motor symptoms can complicate the diagnosis of LID. Dyskinetic episodes can vary in frequency, severity, and duration, even within the same day. Several scales have been developed and are commonly used to objectively measure dyskinesia, disability, and impact on quality of life. Importantly, an ideal instrument for dyskinesia measurement should take into account patient perceptions, anatomical distribution, time factors of dyskinesia, and disability.[15] A task force from the Movement Disorder Society has reviewed several scales for assessing dyskinesia and given guidance on the scales that meet their recommended criteria. These scales include:

- Modified Abnormal Involuntary Movement Scale (mAIMS).
- Rush Dyskinesia Rating Scale (RDRS).
- 26-item Parkinson Disease Dyskinesia Scale (PDYS-26).
- Unified Dyskinesia Rating Scale (UDysRS).

Treatment for LID

PD patients who experience LID have few approved treatment options. The first option is to manage the levodopa dose used in order to balance positive motor effects and the emergence of LID symptoms. Lowering the dose of levodopa is not typically an option, since this will reduce the efficacy of the drug in treating PD motor symptoms and predispose the patient to more OFF time. As an alternative, the standard approach for treating LID is to fractionate

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[15] Colosimo, C, et al., 2010. Task force report on scales to assess dyskinesia in Parkinson's disease critique and recommendations. Movement Disorders, 25(9), pp1131- 1142.

the dose into smaller, more frequent doses.[16] Unfortunately, this is not a long-term solution and creates problems with treatment compliance.

Changes in Levodopa Formulation. Sustained-release formulations of levodopa are designed to prevent sharp spikes in levodopa exposure but can also lead to prolonged dyskinetic episodes. These sustained-release formulations have also been shown to have unpredictable rates of absorption in the gut, which may exacerbate motor complications.[17] In addition, a long-term study found no difference in LID frequency between individuals using immediate-release or sustained-release formulations of levodopa.[18] Continuous enteral infusion is an alternative means of levodopa delivery that has reduced rates of dyskinesia and OFF episodes.[19,20] However, this strategy is costly, invasive, and impractical for many of the elderly patients affected by PD.

Dopamine Agonists. In clinical practice, dopamine receptor agonists like ropinirole or apomorphine may be added to levodopa therapy to reduce the dose of levodopa needed to achieve improvements in motor symptoms.[21] Dopamine agonists may even be used as first-line therapy in place of levodopa in younger PD patients, who have a particularly high incidence rate of LID.[22] Clozapine, a weak dopamine agonist and high-affinity serotoninergic agonist, has also been prescribed off-label for LID, but its clinical use has limited by severe side effects, including agranulocytosis, depression, seizures, dementia, and myocarditis.[23,24,25]

Drugs Acting on Glutamatergic Signaling. Amantadine, an antagonist of the NMDA receptor, has been used off-label as a treatment for dyskinesia. Investigators evaluated amantadine in a randomized, double-blind, placebo controlled study and determined that the drug reduced LID time by 60%.[26,27] However, there are several problems associated with the use of amantadine. It is exclusively cleared by the kidneys, and as a result, high levels of the drug

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[16] Brooks, DJ, 2008. Optimizing levodopa therapy for Parkinson's disease with levodopa/carbidopa/entacapone: implications from a clinical and patient perspective. *Journal of Neuropsychiatric Disease and Treatment*, 4(1), pp39-47.

[17] Nyholm, D, et al., 2003. Optimizing levodopa pharmacokinetics: intestinal infusion versus oral sustained-release tablets. *Clinical Neuropharmacology*, 26(3), pp156-163.

[18] Thanvi, B, et al., 2007. Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment. *Postgraduate Medical Journal*, 83(980), pp384-388.

[19] Olanow, CW, et al., 2006. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurology*, 5(8), pp677-687.

[20] Nutt, JG, et al., 2000. Continuous dopamine-receptor stimulation in advanced Parkinson's disease. *Trends Neuroscience*, 23(10supp), pp109-115.

[21] Deleu, D, et al., 2004. Subcutaneous apomorphine: an evidence-based review of its use in Parkinson's disease. *Drugs & Aging*, 21(11), pp687-709.

[22] Manson, A, et al., 2012. Levodopa-Induced-Dyskinesias Clinical Features, Incidence, Risk Factors, Management and Impact on Quality of Life. *Journal of Parkinson's Disease*, 2(3), pp189-198.

[23] Daneault, JF, et al., 2013. Drug-induced dyskinesia in Parkinson's disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia? *BMC Medicine*, 11, pp76.

[24] Alvir, JM, et al., 1993. Clozapine-induced agranulocytosis: Incidence and risk factors in the United States. *New England Journal of Medicine*, 329, pp162-167.

[25] Haas, SJ, et al., 2007. Clozapine-associated myocarditis: a review of 116 cases of suspected myocarditis associated with the use of clozapine in Australia during 1993-2003. *Drug Safety*, 30, pp47-57.

[26] Verhagen, ML, et al., 1998. Amantadine as treatment for dyskinesias and motor fluctuations in Parkinson's disease. *Neurology*, 50(5), pp1323-1326.

[27] da Silva-Júnior, FP, et al., 2005. Amantadine reduces the duration of levodopa-induced dyskinesia: a randomized, double-blind, placebo-controlled study. *Parkinsonism & Related Disorders*, 11(7), pp449-452.

can accumulate in patients with renal failure.[28] This can cause a wide range of neuropsychiatric toxic effects on the patient. Considering the typical age of PD patients, renal problems may impact dosing and complicate the use of amantadine. Amantadine is also associated with sleep disturbances including insomnia, vivid dreams, and abnormal muscle contractions. Dosing of the extended-release formulation before bed is intended to reduce the rate of sleep disturbances. However, changes in gut motility and absorption as the disease progresses may impact the intended pharmacokinetics of these sustained-released formulations. There are also indications that some patients do not respond to amantadine, particularly in cases with an early onset of disease.[22]

Neurosurgery. Surgery can be considered for advanced PD cases that involve medically intractable motor fluctuations, dyskinesias, or tremors.[29] Deep brain stimulation (DBS), targeting the internal globus pallidus (GPi) or the subthalamic nucleus (STN), has become the preferred surgical option, since it is reversible and the device settings can be adjusted to meet clinical needs. DBS of the STN and GPi are associated with 60% and 80% reductions in disabling dyskinesias, respectively.[30,31] STN stimulation is also associated with greater reductions in dopamine medications, which may decrease the risk of LID and contribute to an improved quality of life.[32] As an invasive procedure, neurosurgery to implant the stimulating leads carries obvious risks and may not be an optimal solution for elderly patients with advanced PD. It is also very costly relative to pharmacotherapy. Complications from DBS can include cognitive side effects, such as postoperative depression, impulsivity, apathy, and decreased verbal fluency.[33]

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[28] Ing, TS, et al., 1979. Toxic effects of amantadine in patients with renal failure. *Canadian Medical Association Journal*, 120(6), pp695-698.

[29] Bronstein, JM, et al., 2011. Deep brain stimulation for Parkinson disease: An expert consensus and review of key issues. *Archives in Neurology*, 68(2), pp165.

[30] Krach, P, et al., 2003. Five year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine*, 349, pp1923-1934.

[31] Volkmann, J, et al., 2004. Long-term results of bilateral pallidal stimulation in Parkinson's disease. *Annals of Neurology*, 55(6), pp871-875.

[32] Rascol, O, et al., 2011. Milestones in Parkinson's disease therapeutics. *Movement Disorders*, 26(6), pp1072-1082.

[33] Contarino, MF, et al., 2007. Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 78(3), pp248-252.

Market Information

Epidemiology. PD affects approximately 1.5% of people over the age of 65. The average age of onset is 60, though 5-10% of cases occur before 50. Men are more likely to suffer from the disease than women.[34] Worldwide prevalence of PD is estimated at 4 to 10 million people,[35] with 1.5 to 2.5 million people affected in US and Europe. In **Figure 8**, we estimate the population of PD patients in the US to be nearly 1.0 million. This estimate is based on the following assumptions:

- **Population** – We used data from the US Census Bureau estimating the US population by age.
- **Prevalence** – We obtained data broken down by age on the prevalence of PD in the North America from Pringsheim *et al*.[36] Early-onset PD makes up 5-10% of cases, so we conservatively assume an additional 48,600 early-onset cases.

Figure 8. PD Prevalence in the US

Age	US Population	PD Prevalence (per 100,000)	PD Patients
Early Onset (<40)	212.8 M	23	48,600
40-49	40.9 M	41[#]	16,800
50-59	43.9 M	113	49,600
60-69	35.5 M	540	191,700
70-79	19.4 M	1,612	310,500
80+	12.6 M	2,953	371,100
		Total:	988,300

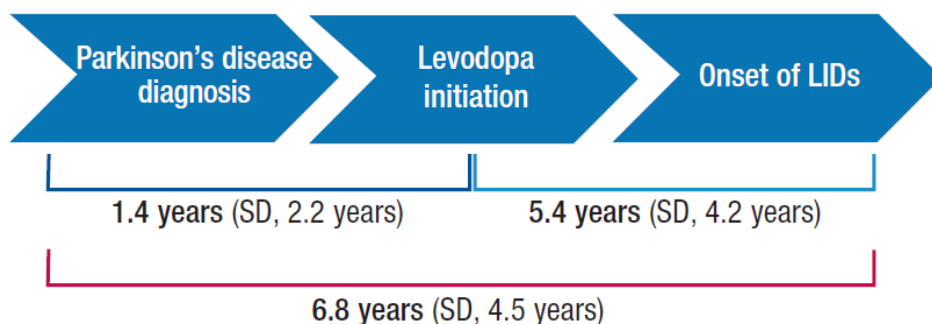# Based on worldwide prevalence

Source: LifeSci Capital

As shown in **Figure 9**, the progression to dyskinesia for a PD patient takes on average 5 years from the initiation of levodopa therapy and nearly 7 years from the time of the original PD diagnosis. As the disease progresses, the majority of patients will progress to having some degree of dyskinesia during peak levodopa exposure. By 15 years after diagnosis, greater than 90% of PD patients have developed LID.

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[34] Parkinson's disease foundation

[35] Dorsey, E.R. et al., 2007. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, 68(5), pp384-386; National Parkinson's Foundation; Parkinson's Disease Foundation

[36] Pringsheim, T, et al., 2014. The Prevalence of Parkinson's Disease: A Systematic Review and Meta-analysis. *Movement Disorders*, 29(13), pp1583-1590.
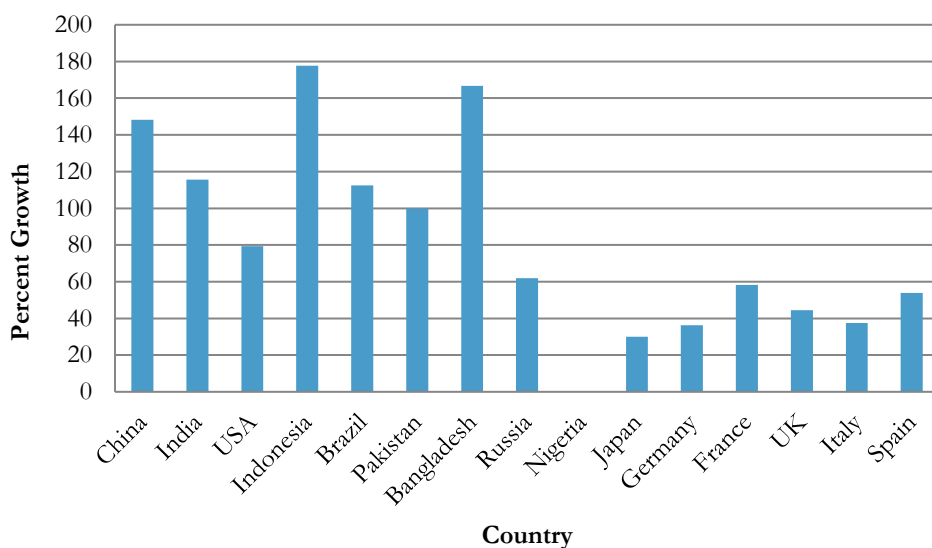
Figure 9. Progression to Levodopa-Induced Dyskinesia

Source: Lennert et al., 2012

The graph in **Figure 10** indicates the expected growth in incidence of PD in various countries by 2030. With the population over age 65 expected to double between now and 2030, the number of people with PD could also double in that period.[37] During this time period, the US patient population is expected to grow by approximately 80%.

Figure 10. Projected Global Growth by 2030 in Incidence of Parkinson's Disease

Source: Dorsey et al., 2007

Market Estimates. In the US, the annual economic burden of treating PD patients is approximately $23 billion and is expected to reach $50 billion by 2040.[38] The treatment costs associated with PD prior to the onset of LID is on average $18,645 per year. In the US, the emergence of LID symptoms increases treatment costs by roughly $7,795 per

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[37] Population Reference Bureau.

[38] Daneault, JF, et al., 2013. Drug-induced dyskinesia in Parkinson's disease. Should success in clinical management be a function of improvement of motor repertoire rather than amplitude of dyskinesia? *BMC Medicine*, 11, pp76.

patient, reflecting a 42% increase.[39] Treatments that can reduce the frequency and/or duration of dyskinesia and other motor fluctuations could have a substantial impact on the overall healthcare costs associated with treating PD patients.

Figure 11 highlights the incidence rate of developing LID within 5 years of starting levodopa therapy broken down by age of onset. Across all PD patients, the overall 5-year risk of developing LID is roughly 40%, although this rate can exceed 90% in patients with early-onset PD.[40] These disparate incidence rates suggest that the age of onset may be an important risk factor for the development of dyskinesias.[41]

Figure 11. Five-Year Incidence Rate of LID by Age of Disease Onset

Age of Onset	LID Incidence Rate
< 40	94%
40-49	Data not available
50-59	53%
60-69	26%
70+	16%

Source: Kumar et al., 2005; Manson et al., 2012

For our estimate of the market opportunity for dipraglurant, shown in **Figure 12**, we make the following assumptions:

- **Anti-Parkinson Drug Use** – We assume that roughly 45% of PD patients are prescribed one or more anti-parkinson drugs.[42]
- **Levodopa Use** – Roughly 80% of these patients are prescribed levodopa.[42]
- **LID Prevalence** – We assume an average LID prevalence of 45%.

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[39] Suh, DC, et al., 2012. Treatment patterns and associated costs with Parkinson's disease levodopa induced dyskinesia. *Journal of the Neurological Sciences*, 319(1-2), pp24-31.

[40] Kumar, N, et al., 2005. Levodopa-Dyskinesia Incidence by Age of Parkinson's Disease Onset. *Movement Disorders*, 20(3), pp342-366.

[41] Manson, A, et al., 2012. Levodopa-Induced-Dyskinesias Clinical Features, Incidence, Risk Factors, Management and Impact on Quality of Life. *Journal of Parkinson's Disease*, 2(3), pp189-198.

[42] Crispo, JAG, et al., 2015. Trends in inpatient antiparkinson drug use in the USA, 2001–2012. *European Journal of Clinical Pharmacology*, 71, pp1011-1019.

Figure 12. Estimated US Patient Population

Age Group	Patients	Drug Use	Levodopa Use	LID Patients
Early Onset (<40)	48,600	21,900	17,500	7,900
40-49	16,800	7,600	6,000	2,700
50-59	49,600	22,300	17,900	8,000
60-69	191,700	86,300	69,000	31,100
70-79	310,500	140,000	111,800	50,300
80+	371,100	167,000	133,600	60,100
Totals	**971,500**	**444,700**	**356,000**	**160,100**

Source: LifeSci Capital

In total, there are roughly 160,000 PD patients that currently experience levodopa-induced dyskinesia in the US. In **Figure 13**, we conduct a scenario analysis for likely market penetrations of dipraglurant in the US. Capturing 30% of this market could translate into sales for Addex between $480 million and $960 million depending on pricing. We assume low and high price points of $10,000 and $20,000, respectively. Acadia (NasdaqGS: ACAD) has priced *Nuplazid* (pimavanserin), their recently approved drug for psychosis associated with PD, at $23,000 per year. *Nuplazid* is a new chemical entity like dipraglurant and targets a segment of the PD market similar in size to the subset of patients experiencing dyskinesias. Based on these factors, Addex may be able to achieve comparable pricing to *Nuplazid*. Adamas (NasdaqGM: ADMS) is expected to price *Nurelin*, if approved, in the ballpark of $10,000 per year, which we have taken as the low-end of the price range since *Nurelin* is not a new chemical entity and must compete with generic forms of immediate-release amantadine.

Figure 13. Scenario Analysis for US Sales of Dipraglurant by Market Penetration

Penetration	10%	20%	30%	40%	50%
Treated Patients	17,000	34,000	51,000	68,000	85,000
Price – Low	$10,000	$10,000	$10,000	$10,000	$10,000
Sales – Low	**$160 M**	**$320 M**	**$480 M**	**$640 M**	**$800 M**
Price – High	$20,000	$20,000	$20,000	$20,000	$20,000
Sales – High	**$320 M**	**$640 M**	**$960 M**	**$1,280 M**	**$1,600 M**

Source: LifeSci Capital

Clinical Data Discussion

Addex has studied dipraglurant in a Phase IIa study as well as 3 Phase I studies, demonstrating that the drug is safe, well-tolerated, and capable of reducing dyskinesia in PD patients. The Company recently completed a receptor occupancy study using positron emission tomography (PET) to quantify the dose curve for dipraglurant and identify the optimal dose for use in subsequent studies. Results from this receptor occupancy study indicated that the Company may achieve greater efficacy with the use of higher doses of dipraglurant. Addex plans to launch a registration-directed Phase III study for dipraglurant in the second half of 2017, once the Company has secured funding for the trial.

Phase I Trials

Addex has completed three Phase I studies evaluating the safety and tolerability of dipraglurant in healthy adult volunteers. The trials performed include:

- **Study 101** – a single-ascending dose and food effect study.
- **Study 102** – single and multiple ascending dose study. Part one of this study was a randomized, two-way crossover comparison to determine the, safety, tolerability, and pharmacokinetics of dipraglurant. Part two of this study was a double-blind, placebo-controlled, multiple-ascending repeat dose study.
- **Study 103** – gender and food effect study – Study 103 was a two-period crossover study performed to determine the safety, tolerability, and pharmacokinetics of single doses of dipraglurant after fasting and after a high fat meal.

Overall, these trials enrolled more than 36 individuals and demonstrated that dipraglurant is safe and well-tolerated in either a well-fed or fasting state. The Company announced the results of studies 102 and 103 in January 2009, which supported the initiation of Phase IIa studies with dipraglurant for LID.

Phase IIa Trial

Addex conducted a Phase IIa to evaluate the safety and efficacy of dipraglurant as a treatment for LID. The trial demonstrated that dipraglurant was safe, well-tolerated, and effective at reducing dyskinesia in PD patients. The favorable safety and tolerability profile for the 100 mg dose of dipraglurant suggest that Addex will be able to test higher doses in subsequent studies.
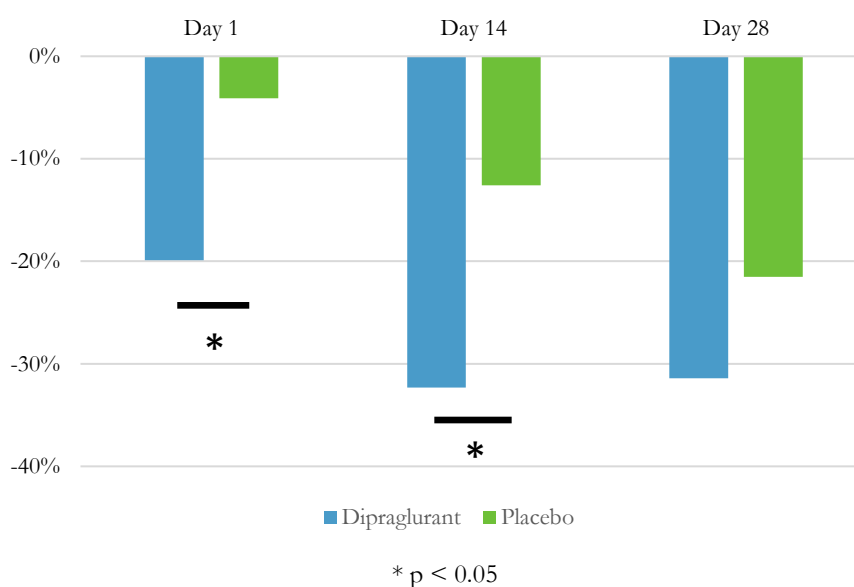
Trial Design. This randomized, double-blind, placebo controlled Phase IIa dose-titration study tested the safety and efficacy of dipraglurant in the treatment of 76 PD patients with moderate or severe LID.[43] Enrolled patients were randomized to receive either dipraglurant or placebo at a starting dose of 50 mg once daily and were titrated up to 100 mg three times per day at week 4. The primary endpoint was safety and tolerability, as assessed with adverse events, neurological examination, heart rate, blood pressure, echocardiogram (ECG), hematology, and blood biomarkers. Secondary endpoints included the dyskinesia severity score measured with the modified Abnormal Involuntary Movement Scale (mAIMS), change in disease severity evaluated by patient diary and clinician-scored Unified Parkinson's disease rating scale (UPDRS) Part III, as well as patient-rated and clinician-rated global impressions. Inclusion criteria contained: diagnosis of idiopathic PD via UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria (UKPDSBBCDC).

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[43] https://clinicaltrials.gov/ct2/show/NCT01336088

Trial Results. This study demonstrated that dipraglurant is safe and well-tolerated, and also provided early signs of efficacy for dipraglurant in the treatment of LID.[44] Treatment did not affect any safety parameters, including 12-lead electrocardiogram (ECG), heart rate (HR), blood pressure (BP), or hematology. Adverse events occurred at similar rates in the treatment and placebo groups, with the most common events being dyskinesia, dizziness, nausea, and fatigue. Adverse events occurred in 53% of patients when taking 50 mg of dipraglurant during weeks 1 and 2, as compared with an adverse event rate of 58% for the placebo group. During weeks 3 and 4, when patents were taking 100 mg doses of dipraglurant, adverse events occurred in 73% of patients as compared to 63% for placebo.

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. The complete data on this endpoint is shown in **Figure 14**. 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.

Figure 14. LID Reduction with Dipraglurant or Placebo Treatment

* p < 0.05

Source: LifeSci Capital

After 28 days, the response was maintained with a 31.4% reduction in mAIMS in the dipraglurant group, although this effect did not reach statistical significance due to a rising placebo response at day 28. The Company has attributed this effect to protocol differences between the US and Europe and the chosen statistical test originally specified in the study protocol. Using a linear mixed model during a *post hoc* analysis of the data determined a statistically significant difference between the treatment and placebo groups (p<0.001). Addex has made protocol adjustments to the planned Phase III trial which should correct for the elevated placebo response in this trial.

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[44] Tison, F, et al., 2016. A Phase 2A Trial of the Novel mGluR5-Negative Allosteric Modulator Dipraglurant for Levodopa-Induced Dyskinesia in Parkinson's Disease. *Movement Disorders*, ePub ahead of print.

The mAIMS data in this study were consistent with patient-reported data, which indicated that participants experienced a 50-minute reduction in OFF time and an increase of 2.3 hours of ON time without dyskinesia. The results of this Phase IIa study highlight the potential efficacy of dipraglurant in treating moderate-to-severe LID cases.

PET Receptor Occupancy Study

Addex conducted this study to quantify the dose curve and identify the optimal dose of dipraglurant to use in subsequent late-stage trials.

Trial Design. This open-label positron emission tomography (PET) study evaluated receptor occupancy following dosing with dipraglurant.[45] Part one determined a receptor occupancy dose curve, whereas part two determined the receptor occupancy profile over time. The study protocol for each part was performed as follows:

- **Part One –** Patients received 100, 200, or 300 mg of dipraglurant with concurrent use of [18F]-FPEB for radio imaging. Imaging scans were performed at baseline and at T_{max} of dipraglurant.
- **Part Two –** Patients received two doses of 300 mg dipraglurant (ADX48621) over the course of two days, with concurrent use of [18F]-FPEB. Imaging scans were performed at baseline, one hour post-dose on day 1, and 4-6 hours post-dose on day 2.

The primary endpoint is the maximum receptor occupancy and effective concentration to elicit 50% of the maximal response (EC50). Criteria for enrollment include: 18 to 60 years of age, body mass index (BMI) of 18-32 kg/m², and ability to understand and sign an Informed Consent Form (ICF). Exclusion criteria include: clinical history of various diseases, allergy or intolerance to various drug or food compounds, surgery that may alter drug absorption, and use of any drug for a study within 30 days.

Trial Results. Part one of this study enrolled a total of 12 participants, who were randomized to groups of 4 to receive 100, 200, or 300 mg of dipraglurant. Part two of the study enrolled the group of patients receiving 300 mg dipraglurant, who received a subsequent PET scan 3 hours after dosing. The receptor occupancy data from this study is presented in **Figure 15.** Participants in the 200 mg group had significantly higher receptor occupancy as compared to the 100 mg group (p < 0.001). Overall, receptor occupancy correlated with dosing and the appropriate plasma concentration to achieve 50-70% receptor occupancy was determined. The data from this study will help optimize dosing in the upcoming pivotal Phase III trial.

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[45] https://clinicaltrials.gov/ct2/show/NCT02447640

Figure 15. Interim Data on mGlu5 Receptor Occupancy in Healthy Adults

Number of Subjects	Dose (mg)	% Receptor Occupancy Mean ± SD
4*	100	27 ± 9%
4	200	44 ± 23%
4	300	54 ± 30%

* Denotes analysis of 3 subjects due to lack of arterial sampling in one patient

Source: LifeSci Capital

Phase III Trial

Addex plans to launch a pivotal Phase III trial in the second half of 2017 to support regulatory filings for dipraglurant. The Company plans to incorporate data from the receptor occupancy study into dose selection for this trial. Addex has received $1.0 million in grants from the Michael J. Fox Foundation (MJFF) to support ongoing preparations for this Phase III trial.

Trial Design. This randomized, double blind, placebo-controlled Phase III study will assess the safety and efficacy of dipraglurant for the treatment of 156 patients with moderate to severe levodopa-induced dyskinesia. Patients will be randomized 2:1 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 and 2 weeks of placebo. The primary endpoint is change in modified Abnormal Involuntary Movement Scale (mAIMS) over time. The secondary endpoints include change in Unified Dyskinesia Rating Scale (UDysRS) Part IV, clinician-scored Unified Parkinson's disease rating scale (UPDRS) Part III, patient diaries for on and off time, and Clinical Global Impression of Change (CGIC).

Other PD-LID Drugs in Development

There are several other drugs in development for LID in PD patients, including Phase III programs from Adamas Pharmaceuticals (NasdaqGM: ADMS) and Osmotica Pharmaceutical (Private) that are evaluating extended-release formulations of amantadine. Both of these companies are developing extended-release formulations of amantadine and anticipate filing NDAs for the LID indication by the end of 2016. Addex's program may be the most advanced new chemical entity in development for LID in PD patients. Otsuka's (TYO: 4578; Other OTC: OTSKY) AVP-923 and Neurim Pharmaceuticals' (Private) Neu-120 are also in development for LID, although both of these assets are in earlier stages relative to Addex. **Figure 16** highlights the other LID drugs in development.
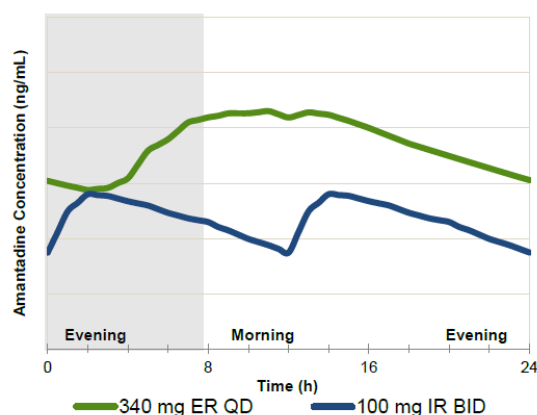
Figure 16. Other LID Drugs in Development

Drugs	Company	Mechanism	Stage
Nurelin	Adamas	Sigma 1 receptor, noncompetitive NMDA receptor antagonist, and α7 nicotinic acetylcholine receptor antagonist	III
Osmolex ER	Osmotica	Sigma 1 receptor, noncompetitive NMDA receptor antagonist, and α7 nicotinic acetylcholine receptor antagonist	III
Dipraglurant IR	Addex	Metabotropic glutamate receptor 5 (mGluR5) NAM	Phase III ready
AVP-923	Otsuka	Sigma 1 receptor agonist and noncompetitive NMDA receptor antagonist	II
Neu-120	Neurim	Noncompetitive NMDA receptor antagonist	I/II

Source: LifeSci Capital

Nurelin (amantadine ER) – Adamas Pharmaceuticals (NasdaqGM: ADMS).

Nurelin is an extended-release formulation of amantadine that is being developed by Adamas for LID in PD patients. An immediate-release form of amantadine has been marketed since the 1960s as a PD treatment, although a recent meta-analysis has called into question the long-term efficacy of this drug.[46] **Figure 17** shows a comparison of the pharmacokinetics of immediate-release and extended-release formulations of amantadine. Adamas' formulation is designed for once-daily dosing before bed to ensure peak amantadine concentrations in the morning when the patient may be at greatest risk for dyskinesia. This dosing strategy may also reduce the frequency of sleep problems, including insomnia, sleep disturbances, and vivid dreams, which are common side effects of amantadine use.

Figure 17. Pharmacokinetics of Immediate-Release and Extended-Released Amantadine

Source: Adamas Corporate Presentation

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[46] Crosby, NJ, et al., 2003. Amantadine in Parkinson's disease. *Cochrane Databases of Systematic Reviews*, 1, ppCD003468.

Adamas has demonstrated positive topline results in three ongoing Phase III studies and expects to present additional data from the trials at upcoming medical meetings. These Phase III studies, described in **Figure 18**, include two ongoing Phase III efficacy studies, EASE LID and EASE LID 3, as well as the open-label EASE LID 2 Phase III safety study. Adamas recently presented final data from the EASE LID Phase III study and interim data from the EASE LID 2 Phase IIII study at the 20th Annual International Congress of Parkinson's and Movement Disorders in Berlin, Germany in June. The company expects to file a New Drug Application (NDA) before the end of 2016.
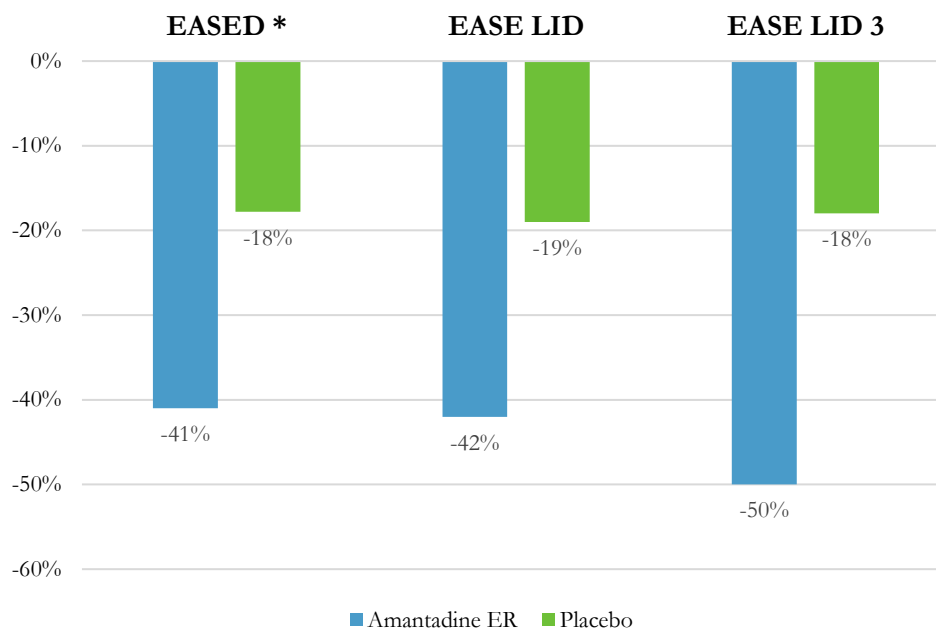
Figure 18. Clinical Development for Adamas' *Nurelin*

Trial	Phase	N	Status
EASED	II/III	83	–
EASE LID	III	130	-
EASE LID 2	III	200	Completion of enrollment TBD
EASE LID 3	III	77	Topline data announced April 2016

Source: LifeSci Capital

Efficacy. To date, Adamas has reported data from three clinical trials supporting the efficacy of *Nurelin* in treating dyskinesia. **Figure 19** highlights the change in dyskinesia scores obtained with the 340 mg dose of *Nurelin* or placebo in the EASED, EASE LID, and EASE LID 3 studies, as measured by the Unified Dyskinesia Rating Scale (UDysRS) total score. In April 2016, Adamas reported topline results from the EASE LID 3 Phase III study, which showed a 50% reduction in UDysRS score compared with a 18% reduction in the placebo group. These results are consistent with efficacy data from prior trials. These results were obtained without any worsening of PD symptoms, as measured with the MDS-UPDRS total score, indicating that extended-release amantadine was not disrupting the normal activity of levodopa.

Figure 19. Change in Dyskinesia Following Treatment with Amantadine ER or Placebo
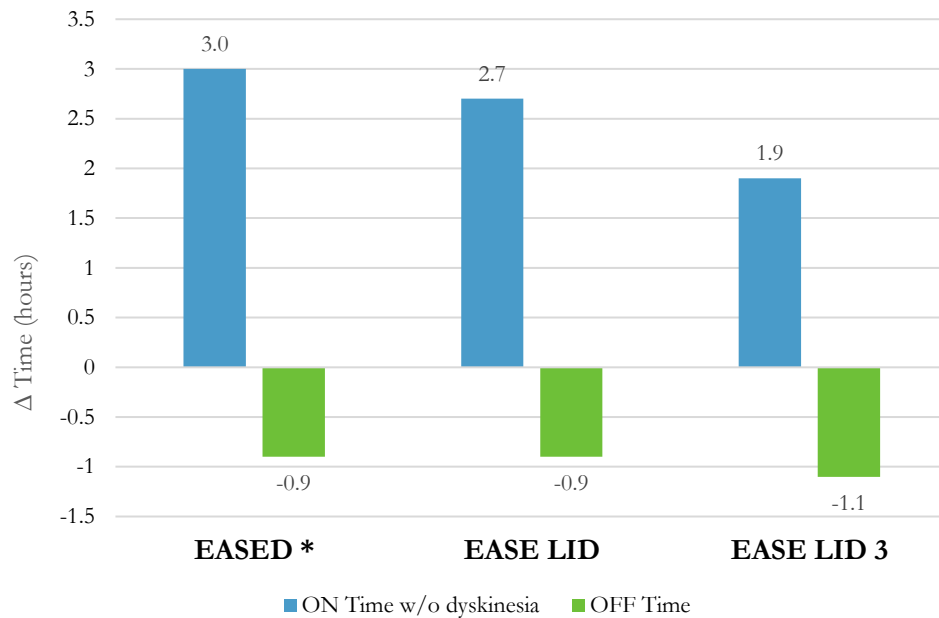

* Primary endpoint measured at 8 weeks instead of 12 weeks

Source: LifeSci Capital

In all three studies, treatment with *Nurelin* led to a statistically significant increase in the patient's self-reported ON time without troublesome dyskinesias. In the EASE LID and EASE LID 3 studies, patients experienced an increase of 2.7 and 1.9 hours of ON time without dyskinesia, respectively. For these two trials, there was also a concomitant reduction in OFF time that reached statistical significance. These results are shown in **Figure 20**.

Figure 20. Changes in ON and OFF Time Following Treatment with Amantadine ER Relative to Placebo

* Endpoints measured at 8 weeks instead of 12 weeks

Source: LifeSci Capital

Safety. Immediate-release formulations of amantadine have been approved for use in PD patients since the 1960s, resulting in a large safety database for the drug. Amantadine is considered to be safe and generally well-tolerated. The drug can cause side effects typical of CNS drugs such as drowsiness, dizziness, lightheadedness, and blurred vision. Amantadine is exclusively cleared by the kidneys, and as a result, high levels of the drug can accumulate in patients with renal failure.[47] This can cause a wide range of neuropsychiatric toxic effects on the patient. Considering the typical age of PD patients, renal problems may impact dosing and complicate the use of amantadine. Amantadine is also associated with sleep disturbances including insomnia, vivid dreams, and abnormal muscle contractions. Dosing of the extended-release formulation before bed is intended to reduce the rate of sleep disturbances.

Osmolex ER (amantadine ER) – Osmotica Pharmaceutical (Private).

Osmotica is also developing an extended-release formulation of amantadine, *Osmolex ER*, that is administered once-daily in the morning concurrent with the first dose of levodopa. *Osmolex ER* is designed with the company's *Osmodex*™ delivery technology. The company is currently testing two doses of *Osmolex ER* in two pivotal Phase III studies and expects to file an NDA via the 505(b)(2) pathway by the end of 2016.

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[47] Ing, TS, et al., 1979. Toxic effects of amantadine in patients with renal failure. *Canadian Medical Association Journal*, 120(6), pp695-698.

Phase III Program. Osmotica launched two randomized, double-blind, placebo controlled Phase III studies, ALLAY-LID I and ALLAY-LID II, in August 2014.[48,49] Each trial has a target enrollment of 162 patients and they are expected to read out in the second half of 2016. The studies are testing the safety and efficacy of 240 mg and 320 mg doses of *Osmolex ER* using the change in Unified Dyskinesia Rating Scale (UDysRS) as the primary endpoint. The ALLAY-LID I trial is a 16 week study, while the ALLAY-LID II study consists of a 26 week treatment period.

AVP-923 (dextromethorphan/quinidine) – Otsuka (TYO: 4578; Other OTC: OTSKY)

Otsuka is developing AVP-923 as a treatment for LID in PD patients. AVP-923 combines dextromethorphan, which is a sigma 1 receptor agonist and noncompetitive NMDA receptor antagonist, with quinidine, a CYP450 2D6 inhibitor that decreases the metabolism of dextromethorphan in the liver.[50] This drug combination has already been approved by the FDA for the treatment of pseudobulbar affect (PBA) at a different dose strength and is currently marketed under the brand name *Nuedexta*.[51] The company is also developing this drug for agitation and aggression symptoms in patients with Alzheimer's disease (AD).[52] Otsuka acquired this program with its purchase of Avanir Pharmaceuticals in early 2015 for $3.5 billion. Prior to the acquisition, Avanir successfully completed a Phase IIa study in 2015 that evaluated the safety and efficacy of AVP-923 in 14 PD patients experiencing LID. At present, Otsuka has not announced further plans for this program.

Phase IIa Trial. Avanir tested a dose of AVP-923 that contained 45 mg of dextromethorphan and 10 mg of quinidine.[53] Patients were randomized to receive either this dose of AVP-923 or placebo twice daily for 2 weeks. The primary endpoint was the change in part 3 of the Unified Dyskinesia Rating Scale (UDysRS) after 2 weeks. Secondary endpoints were also measured at 2 weeks and included part 4 of the UDysRS, Unified Parkinson's Disease Rating Scale (UPDRS) scores, bradykinesia, and a patient diary of motor symptoms. No data from this trial have been released to date.

Dipraglurant ER: An Extended-Release Formulation for Focal Cervical Dystonia

Addex Therapeutics is also developing an extended-release formulation of dipraglurant, for the treatment of focal cervical dystonia. Dystonias are a heterogeneous collection of movement disorders characterized by involuntary, sustained muscle contractions leading to irregular postures and movement.[54] Addex has demonstrated proof-of-concept in a preclinical dystonia model and plans to launch a Phase IIa proof-of-concept study in the fourth quarter of 2016 to test dipraglurant ER as a potential treatment for focal cervical dystonia.[55] The Company also intends to

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[48] https://clinicaltrials.gov/show/NCT02153645

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[53] https://clinicaltrials.gov/show/NCT01767129

[54] Jinnah, H.A. et al., 2014. The Focal Dystonias: Current Views and Challenges for Future Research. *Movement Disorders, 28*(7), pp926-943.

[55] Bezard, E. et al., 2014. The mGluR5 Negative Allosteric Modulator Dipraglurant Reduces Dyskinesia in the MPTP Macaque Model. *Movement Disorders, 29*(8), pp1074-1079.

apply for Orphan Drug designation, which could provide for 7 years of market exclusivity for dipraglurant in this indication.

Focal Cervical Dystonia

Dystonic movements are most commonly described as tremors, although other repetitive patterns or twisting movements also occur. These disorders occur in the primary setting without a known underlying cause or neurological explanation, and in the secondary setting due to neurological disease or injury. Dystonia beginning in childhood is considered early-onset, which has a strong genetic basis involving various dystonia (DYT) loci and genes. Conversely, adult-onset dystonia is believed to be caused by a combination of genes and environment and is much more common than childhood-onset dystonia. The number and location of dystonic muscles are used to classify the disorder into five different types: focal, generalized, segmental, multifocal, and hemi. The different types of dystonia are described in **Figure 21**.

Figure 21. Types of Dystonia

Type of Dystonia	Affected Muscle
Focal	Single body part affected
Segmental	At least 2 adjacent body parts affected
Multifocal	At least 2 non-adjacent body parts affected
Hemidystonia	One side of the body affected
Generalized	Most or all body parts affected

Source: LifeSci Capital

The pathogenesis of dystonia is similar among the different variants of the disorder, and includes loss of motor neuron inhibition, inability to differentiate spatial versus temporal neuronal signals, increased excitability of the cortex due to decreased inhibition, and repetition of motor function or excessive sensory stimulation.[56] Dysfunction of the basal ganglia is thought to be partially responsible due to its role in controlling cortical inhibition. Some muscle groups are more susceptible to dystonia than others. The muscles most commonly affected include neck, upper face, mouth and jaw, larynx, or limb.[57] Cervical dystonia (CD) affects the head, neck, and shoulders, and is the most common type of dystonia.[58] The overall prevalence of CD is 50 per 1,000,000 individuals, which translates to approximately 16,000 affected people in the US alone.[59]

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[57] Defazio, G. et al., 2007. Do primary adult-onset focal dystonias share aetiological factors? *Brain, 130*(5), pp1183-93.

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[59] Defazio, G. et al., 2013. Descriptive Epidemiology of Cervical Dystonia. *Tremor and Other Hyperkinetic Movements, 3*, pp1-8.

Cervical dystonia (CD) is a focal dystonia defined by uncontrollable cervical muscle contractions affecting the head, neck, and shoulders.[60] CD results in abnormal movements including turning or tilting of the head to either side, forward or backward, in addition to tremors or jerking. The muscle contractions may occur continuously, sporadically, or as a combination of both. Diagnosis is based on physical and neurological examination, as there is not a particular test that can be used to confirm dystonia. Due to the wide heterogeneity of CD and other manifestations that mimic the aforementioned symptoms, CD is often either misdiagnosed or undiagnosed.

The first-line treatment option for CD is botulinum toxin (BoNT) type A, and in the case of resistance BoNT type B treatment will be attempted.[61] BoNT treatment inhibits acetylcholine release presynaptically to block neuronal signal transmission to motor neurons and maintains an effect for approximately 3 months. Clinical changes related to BoNT therapy include greater functional capacity, reduced pain, and better patient-reported quality of life.[62] However, this treatment approach also has several drawbacks, including difficulty of administration and dosing, lack of efficacy, and adverse events. Approximately 15-30% of patients never respond to BoNT treatment, and 10-15% of patients initially respond but ultimately fail.[63] Second-line treatment options include the off-label use of anticholinergic, dopaminergic, or GABAergic agents, or deep-brain stimulation (DBS). Due to the vast number of patients that are non-responsive or resistant to first-line treatment options, there is currently a significant unmet need for CD patients.

Preclinical Data Supporting Use of Dipraglurant

Dipraglurant ER has demonstrated proof of concept in a preclinical study that utilized two mouse models for dystonia *ex vivo*. The dystonia models both lead to overexpression of the TOR1A mutation, causing abnormal neuronal signaling characterized by an excitatory D2 dopamine receptor (D2R) response.[64] Corticostriatal coronal slices were maintained *ex vivo* and treated with dipraglurant, and mGlu5 antagonists SIB1757 and MPEP. The samples showed a dose-dependent regulation of neuronal spikes when treated with quinpirole and dipraglurant, as compared to quinpirole alone. Quinpirole is a dopamine 2 and 3 receptor agonist that increases neuronal firing rate. SIB1757 and MPEP treatment had a similar result to dipraglurant on reducing neuronal spikes. This study shows the ability of dipraglurant to modulate neuronal firing, and supports mGlu5 receptor modulation in the treatment of dystonia.

Clinical Development of Dipraglurant ER for Focal Cervical Dystonia

Addex Therapeutics plans to launch an open-label, Phase IIa study to assess the safety and efficacy of dipraglurant ER in patients with focal cervical dystonia. This trial will enroll 18 patients with cervical dystonia nearing the end of a botulinum toxin treatment cycle. The trial design is shown on **Figure 22**. Following a 4 week screening period, patients will be randomized to receive a crossover sequence of a single dose of dipraglurant ER and placebo on day 1 and day 8. The primary endpoint will be the change in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) as compared to baseline. TWSTRS is a CD-specific, physician-rated questionnaire that scores several components of severity, disability, and pain to generate a cumulative score between 0-87 with 0 being best and 87 being most severe.

[60] Defazio, G. et al., 2013. Descriptive Epidemiology of Cervical Dystonia. *Tremor and Other Hyperkinetic Movements, 3*, pp1-8.

[61] Evidente, V.G.H. et al., 2014. Botulinum toxin Therapy for Cervical Dystonia: The Science of Dosing. *Tremor and Other Hyperkinetic Movements, 4*(273), pp1-10.
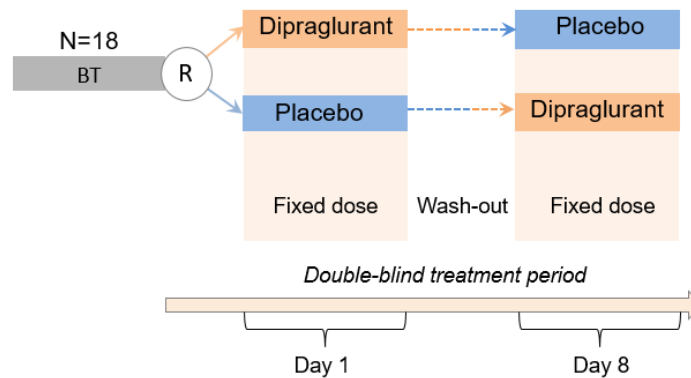
[62] Simpson, D.M. et al., 2008. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review). *American Academy of Neurology, 70*(19), pp1699-1706.

[63] Comella, C.L. et al., 2006. Treatment of cervical dystonia with botulinum toxins. *European Journal of Neurology, 13*(1), pp16-20.

[64] Sciamanna, C. et al., 2014. Negative allosteric modulation of mGlu5 receptor rescues striatal D2 dopamine receptor dysfunction in rodent models of DYT1 dystonia. *Neuropharmacology, 85*, pp440-450.

Secondary endpoints will include the Cervical Dystonia Impact Profile (CDIP-58), pharmacokinetics, and safety and tolerability. CDIP-58 is a 58-point evaluation covering symptoms of the head and neck, pain, and discomfort, upper limb activity, walking, sleep, annoyance, mood, and psychological functioning. Items are rated from 1 to 5 and converted into a cumulative score from 0-100, with higher scores indicating more severe symptoms. Addex plans to begin this trial in the fourth quarter of 2016 and anticipates reporting topline results in the second half of 2017.

Figure 22. Planned Phase IIa Trial Design

Source: Company Presentation

ADX71441: A GABA$_B$ Receptor Modulator for Cocaine Addiction and Alcohol Use Disorder

Addex is developing ADX71441, a positive allosteric modulator (PAM) of the GABA$_B$ receptor, as a potential treatment for cocaine addiction and alcohol use disorder. Researchers have shown that GABA$_B$ receptor agonists such as baclofen are effective in reducing drug self-administration, cravings, and anxiety, and thus promote abstinence. However, baclofen is associated with a number of side effects, including tolerance, sedation, and motor impairments, so targeting this receptor with a PAM may be a better therapeutic strategy. In preclinical studies, Addex has demonstrated the efficacy of ADX71441 in animal models of alcohol use disorder and nicotine withdrawal. In particular, the Company has conducted three preclinical alcohol use studies in collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The Company also recently announced positive results from a study evaluating ADX71441 in a primate model of cocaine addiction, which was conducted in collaboration with the National Institute of Drug Abuse (NIDA). In rhesus monkeys, pre-treatment with ADX71441 dose-dependently reduced cocaine self-administration to roughly 10% of control values. This effect was observed without any concomitant effect on food intake, suggesting that ADX71441 is not broadly affecting the reward circuitry in the brain. Addex plans to launch a Phase I study comparing the safety and efficacy of ADX71441 to baclofen. Baclofen is approved for the treatment of spasticity in the US, but not alcohol use disorder.[65] Addex is also exploring the use of ADX71441 as a potential treatment for Charcot-Marie-Tooth Type 1A (CMT1A) in collaboration with the Charcot-Marie-Tooth Association (CMTA), which represents an additional orphan opportunity for the Company.

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[65] Brennan, JL, et al., 2013. Clinical effectiveness of baclofen for the treatment of alcohol dependence: a review. Clinical Pharmacology, 5, pp99-107.

ADX71149: An mGluR2 Modulator to Treat Epilepsy

Addex discovered ADX71149, a positive allosteric modulator (PAM) of the metabotropic glutamate receptor 2 (mGluR2), in collaboration with Janssen Pharmaceuticals (NYSE: JNJ). Janssen has evaluated ADX71149 in more than 8 Phase I studies as well as 2 Phase II studies, including one study in schizophrenia and another in major depressive disorder. The companies plan to study ADX71149 as a potential adjunctive treatment for epilepsy based on positive results observed in a preclinical epilepsy model. In a 6 Hz psychomotor seizure test, designed to test the ability of drug candidates to block seizure activity, ADX71149 was shown to act synergistically with the antiepileptic levetiracetam, suggesting the potential for combination therapy. Investigators have shown that the activation of metabotropic glutamate receptors may contribute to the development of seizure activity, making mGluR2s an attractive therapeutic target.[66] To date, Addex has received €10.2 million in upfront, research funding, and milestone payments and is eligible to receive up to €109 million ($123 million) in pre-launch milestone payments, as well as low double-digit royalties on net sales.

Intellectual Property & Licensing

Addex Therapeutics has filed patents belonging to 16 different families and has been granted patents in 13 of the families. The Company has been granted a US patent for dipraglurant that covers composition of matter and method of use, offering protection until 2025. In addition to the active patent, an additional patent covering a related polymorph has also been filed, which has potential to extend protection until 2034. Addex has received Orphan Drug designation with *Dipraglurant* for PD-LID in the US, and has plans to apply for Orphan Drug designation for dystonia as well. If approved, this designation will provide Addex with 7 years of market exclusivity against generic competition for the granted indication.

A US patent (USP 8,344,138) covering composition of matter and method of use and for ADX71441 has been granted. This patent expires in 2027 and covers the use of ADX71441 or other GABA-BR PAM's for the treatment of central nervous disorders such as anxiety, depression, schizophrenia, migraine, and epilepsy, among others. The Company plans to apply for Orphan Drug designation with ADX71441 in Charcot-Marie-Tooth Type 1A Neuropathy. If approved, this designation will provide Addex with 7 years of market exclusivity against generic competition for the granted indication.

Management Team

Tim Dyer
Chief Executive Officer / Chief Financial Officer

Since co-founding Addex in 2002, Mr. Dyer has played a pivotal role in building the Addex Group, raising CHF 263 million of capital, including Addex IPO, and negotiating licensing agreements with pharmaceutical industry partners. Prior to joining Addex he spent 10 years with Price Waterhouse (PW) & PricewaterhouseCoopers (PwC) in the UK and Switzerland as part of the audit and business advisory group. At PwC in Switzerland, Mr Dyer's responsibilities included managing the service delivery to a diverse portfolio of clients including high growth start-up

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[66] Ure, J. et al., 2006. Metabotropic glutamate receptors and epilepsy. *Journal of the Neurological Sciences, 247*(1), pp1-9.

companies, international financial institutions and venture capital and investment companies. At PW in the UK, Mr Dyer gained extensive experience in audit and transaction support; spending 2 years performing inward investment due diligence on local financial institutions in the Ex-Soviet Union. Mr Dyer has extensive experience in finance, corporate development, business operations and the building of start-up companies and serves as a member of the Swiss government innovation promotion agency coaching team. He serves on the boards of Abionic SA, a private medical device start-up company focused on allergy diagnostics and Qwane Biosciences SA, a private drug development tool company focused on commercializing microelectrode array technologies. He is a UK Chartered Accountant and holds a BSc (Hons) in Biochemistry and Pharmacology from the University of Southampton.

Sonia Poli, Ph.D.
Chief Scientific Officer & Head of Development

Dr. Poli, who joined Addex in 2004, has broad expertise in drug development from lead generation through to entry in man. At Addex she has overseen the transition of multiple products from discovery projects to clinical development programs. She worked from 1997 to 2004 in the drug metabolism and pharmacokinetics (DMPK) area at Roche, where she was a key inventor and global head of a multidimensional optimization approach for drug discovery and development. As a result, she played an important role in selecting clinical candidates in central nervous system (CNS) indications, including Alzheimer's disease, Parkinson's disease, bi-polar disorders and anxiety. Dr. Poli obtained her degree and doctorate in Industrial Chemistry at the University of Milan in 1993 and completed a post doctoral fellowship at the CNRS, in Paris, in the group of Prof. D. Mansuy in 1997. Dr. Poli is co-author of more than 25 research publications and patents.

Risk to an Investment

We consider an investment in Addex to be a high-risk investment. While Addex has generated positive data, these positive results do not necessarily translate into late-stage success. There are clinical and commercialization risks associated with the dipraglurant program. The Company is planning to conduct a Phase III trial, but must secure a partner prior to launch. As with any company, Addex may be unable to obtain sufficient capital to fund planned development and commercialization activities. There are regulatory risks associated with the development of any drug, and Addex may not receive FDA or EMA approval for its candidates despite significant time and financial investment. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.

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