Addex Therapeutics (ADXN.SW)

Addex Details Plans for Future Clinical Development of Dipraglurant

Addex Therapeutics (SWX: ADXN.SW) has provided updated guidance on their clinical development for dipraglurant, a small molecule being developed to reduce the frequency and severity of levodopa-induced dyskinesia (LID) in patients with Parkinson's disease (PD). The Company plans to initiate two registration-directed studies—a Phase IIb study in H1 2018 followed by a Phase III trial in H1 2020—in order to support an NDA filing for dipraglurant. Recent activity, including a receptor occupancy study and further analysis of their Phase IIa data, has provided greater confidence in the potential of dipraglurant to address this unmet need among PD patients.

- **Addex Provides Update on Plan for Registration-Directed Studies**. Addex has announced plans to conduct two registration-directed trials for dipraglurant in LID. The Company anticipates conducting one Phase IIb study, testing 100 mg and 200 mg dose strengths, and one Phase III trial. The inclusion of the 200 mg dose is based on findings from Addex's receptor occupancy study, which suggested doses of dipraglurant higher than those used in the Phase IIa study may achieve greater efficacy. The trial will use the Unified Dyskinesia Rating Scale (UDysRS) as the primary endpoint, which is a very similar measure to the mAIMS scale used in the Phase IIa study. Addex is also considering a number of trial design modifications to minimize the placebo effect in the trial in order to improve the chances achieving a statistically significant response.

- **Appointment of Dr. Roger Mills as Chief Medical Officer Brings Validation to Dipraglurant Program**. The addition of an industry veteran like Dr. Mills, who has more than 25 years of experience in the biotechnology industry, is an important step in advancing dipraglurant to registration-directed trials. Dr. Mills was previously the Chief Medical Officer and Executive Vice President of Development for Acadia Pharmaceuticals (NasdaqGS: ACAD), and was directly responsible for overseeing the development of Acadia's *Nuplazid* (pimavanserin). Earlier this year, this drug was approved for PD patients with psychosis, which is a similarly sized subset of PD patients to Addex's target patient population.

Expected Upcoming Milestones

- Q3 2017 – Initiate a Phase II proof-of-concept study with dipraglurant ER for focal cervical dystonia.
- Q3 2017 – Initiate a Phase I study with ADX71441.
- Q1 2018 – Results of a Phase I study with ADX71441.
- H1 2018 – Initiate a Phase IIb trial with dipraglurant IR for LID patients.
- Q2 2018 – Results of a Phase II trial with dipraglurant ER for focal cervical dystonia.
- Q3 2018 – Initiate a Phase II trial with ADX71441 for Charcot Marie Tooth Type 1A.
- H1 2020 – Launch Phase III trial for dipraglurant IR in LID patients.

Analysts

David Sherman, Ph.D. (AC)
(212) 915-2570
dsherman@lifescicapital.com

Market Data

Price	$2.33
Market Cap (M)	$31
EV (M)	$27
Shares Outstanding (M)	13.5
Fully Diluted Shares (M)	14.6
Avg Daily Vol	18,507
52-week Range:	$1.70 - $3.10
Cash (M)	$3.9
Net Cash/Share	$0.29
Annualized Cash Burn (M)	$2.7
Years of Cash Left	~1.4
Debt (M)	$0.0

Financials

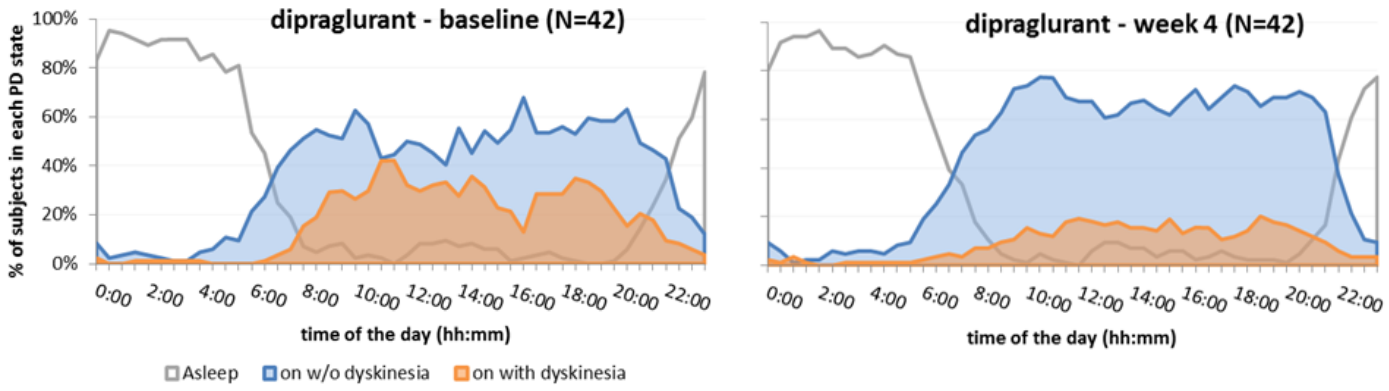
FY Dec		2014A	2015A	2016A
EPS	H1	(0.11)A	(0.28)A	(0.11)A
	H2	NA	NA	NA
	FY	(0.20)A	(0.41)A	(0.28)A

For analyst certification and disclosures please see page 6

- **Phase IIa Data Show Substantial Reductions in Dyskinesia**. Addex has studied dipraglurant in 3 Phase I studies as well as a Phase IIa study conducted with the support of a grant from the Michael J. Fox Foundation. These trials have shown 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), which is considered to be clinically meaningful. The mAIMS reduction was statistically significant at day 1 (p=0.042) and day 14 (p=0.034), although the results did not reach statistical significance at day 28 due to escalating placebo response, potentially an artifact of the trial design. A *post hoc* statistical analysis with the linear mixed model, which is the preferred statistical method by the FDA, found that the treatment effect was statistically significant (p<0.001). In addition, Addex has conducted a receptor occupancy study and found that 200 mg and 300 mg doses of dipraglurant led to higher rates of receptor occupancy than the 100 mg dose.

- **Additional Analysis Supportive of Dipraglurant's Safety and Efficacy**. Addex's most recent corporate deck provides additional *post hoc* analyses conducted by the Company to assess the performance of dipraglurant in the prior Phase IIa study. **Figure 1** highlights the on time without dyskinesia, represented in blue, at baseline (left) as compared to week 4 (right). The on time with dyskinesia (orange) was substantially reduced by week 4 and was maintained throughout the course of the day. This improvement is dyskinesia was achieved without an increase in off time, which would suggest that dipraglurant is not negatively impacting the overall efficacy of levodopa.

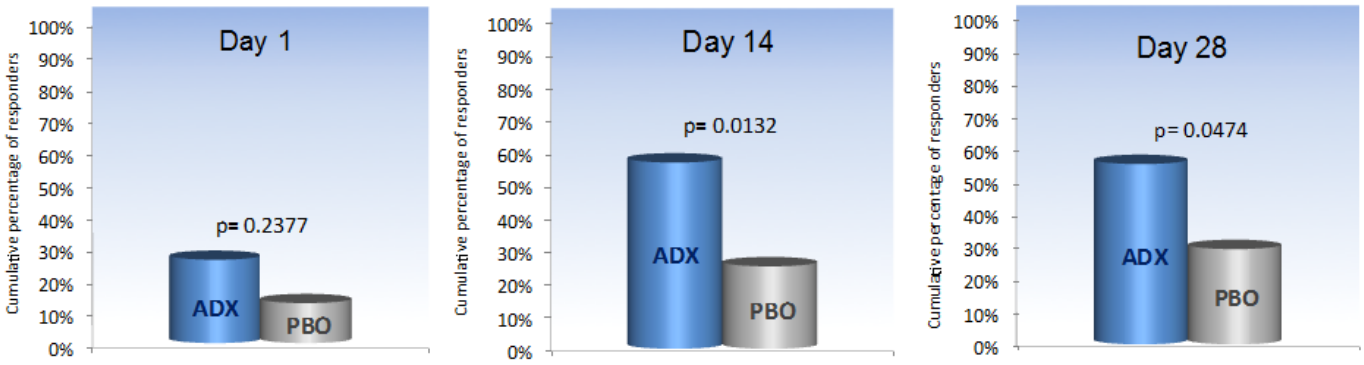
Figure 1. Improvement in On Time without Dyskinesia Following Dipraglurant Treatment



Source: Corporate Presentation

The Company has also reported additional data on the proportion of responders in the Phase IIa study, shown in **Figure 2**. Responders were defined as a mAIMS reduction of at least 30%, which is considered to be clinically meaningful. When examining the data in this manner, the treatment difference was statistically significant at day 14 (p=0.0132) and day 28 (p=0.0474). At the end of the study, 55% (27/52) of dipraglurant-treated patients were considered responders, compared with a 29% (7/24) responder rate in the placebo group. Results were similar at day 14. While a responder analysis is not likely to be a key endpoint in the Phase IIb study, this analysis provides further validation of dipraglurant's clinically meaningful effect and suggests that an improved trial design to minimize placebo response may assist in teasing out a statistically significant difference in subsequent studies.

Figure 2. Improvement in On Time without Dyskinesia Following Dipraglurant Treatment



Source: Corporate Presentation

- **Safety Profile of Dipraglurant Supportive of Continued Development**. 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. The most common adverse events, which are shown in **Figure 3**, included worsening 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.

Figure 3. Most Common AEs in the Phase IIa Trial

Adverse Event	Dipraglurant	Placebo
Worsening dyskinesia	15.3%	12.5%
Dizziness	19%	12.5%
Nausea	19%	0%
Fatigue	15%	4%

Source: Corporate Presentation

- **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. On average, the onset of LID is typically 6.8 years after receiving a PD diagnosis. 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, the PD patient population 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 approved drug for psychosis associated with PD, at $30,700 per year may provide a suitable reference point for the pricing that may be possible for dipraglurant. *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. The pricing of Adamas Pharmaceuticals' (NasdaqGS: ADMS) *Nurelin* (amantadine ER), if it is approved, will also factor into the pricing potential for dipraglurant.

- **Dipraglurant's Mechanism of Action Represents a Sensible Strategy for Reducing Dyskinesia**. 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 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.

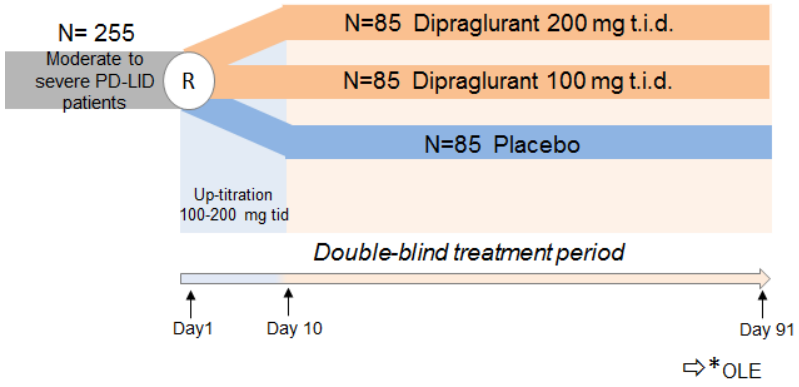
  Abnormal glutamate signaling in the basal ganglia is thought to play a key role in the manifestation of LID in PD patients.[ref, ref] The primary input into the basal ganglia circuit is glutamatergic projections from the cortex to the striatum, and dopamine plays an important role in modulating this 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).

- **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 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.[ref]

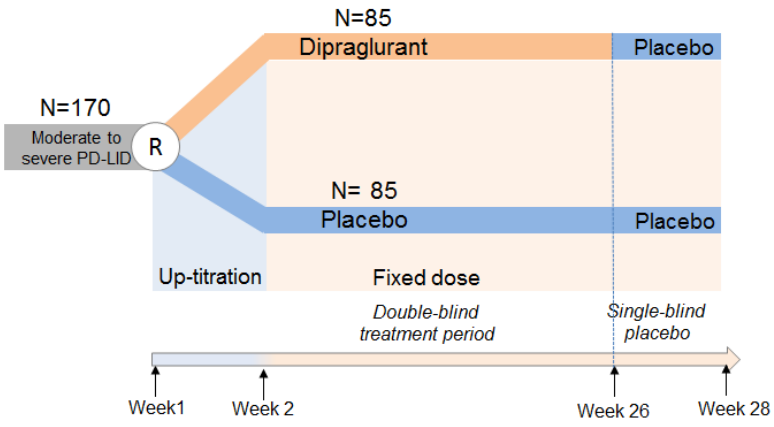
- **Phase IIb and Phase III Trial Designs**. The Phase IIb study is designed to randomize 255 moderate-to-severe PD patients into one of three treatment arms to receive 100 mg or 200 mg of dipraglurant or placebo three times per day. The Phase III trial is intended to enroll 170 patients who will be randomized to receive either dipraglurant at a dose determined in the Phase IIb study or placebo three times per day. The primary endpoint of both studies is expected to be the change in the Unified Dyskinesia Rating Scale (UDysRS) at 13 weeks. The Phase III study will continue treatment for a total of 26 weeks followed by a two-week single-blind placebo treatment period before having the option to enter into an open-label extension period. The trials are intended to incorporate several strategies to minimize placebo response, including the use of centralized raters that are blinded to visit number, and excluding patients showing minimal symptoms. The designs of these trials are highlighted in **Figure 4**.

Figure 4. Phase IIb and Phase III Trial Designs

Phase IIb Trial



Phase III Trial



Source: Corporate Presentation

Risk to Invesment

We consider an investment in Addex to be a high-risk investment. While Addex has generated proof-of-concept data, these 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 registration-directed Phase IIb 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.

Analyst Certification

The research analyst denoted by an "AC" on the cover of this report certifies (or, where multiple research analysts are primarily responsible for this report, the research analyst denoted by an "AC" on the cover or within the document individually certifies), with respect to each security or subject company that the research analyst covers in this research, that: (1) all of the views expressed in this report accurately reflect his or her personal views about any and all of the subject securities or subject companies, and (2) no part of any of the research analyst's compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst(s) in this report.

DISCLOSURES

This research contains the views, opinions and recommendations of LifeSci Capital, LLC ("LSC") research analysts. LSC (or an affiliate) has received compensation from the subject company for producing this research report. Additionally, LSC expects to receive or intends to seek compensation for investment banking services from the subject company in the next three months. LSC (or an affiliate) has also provided non-investment banking securities-related services, non-securities services, and other products or services other than investment banking services to the subject company and received compensation for such services within the past 12 months. LSC does not make a market in the securities of the subject company.

Neither the research analyst(s), a member of the research analyst's household, nor any individual directly involved in the preparation of this report, has a financial interest in the securities of the subject company. Neither LSC nor any of its affiliates beneficially own 1% or more of any class of common equity securities of the subject company.

LSC is a member of FINRA and SIPC. Information has been obtained from sources believed to be reliable but LSC or its affiliates (LifeSci Advisors, LLC) do not warrant its completeness or accuracy except with respect to any disclosures relative to LSC and/or its affiliates and the analyst's involvement with the company that is the subject of the research. Any pricing is as of the close of market for the securities discussed, unless otherwise stated. Opinions and estimates constitute LSC's judgment as of the date of this report and are subject to change without notice. Past performance is not indicative of future results. This material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The opinions and recommendations herein do not take into account individual client circumstances, objectives, or needs and are not intended as recommendations of particular securities, companies, financial instruments or strategies to particular clients. The recipient of this report must make his/her/its own independent decisions regarding any securities or financial instruments mentioned herein. Periodic updates may be provided on companies/industries based on company specific developments or announcements, market conditions or any other publicly available information. Additional information is available upon request.