

Addex Corporate Presentation

October 2018

Innovative Treatments for Central Nervous System Disorders

SIX: ADXN

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Addex Overview

Swiss Company SIX Listed

- Founded in 2002 & headquartered in Geneva
- Traded on the SIX Swiss Stock Exchange since 2007 – ADXN
- 28.6M shares and market cap of CHF70M
- Cash of CHF43.6m at 30 June 2018
- Runway through 2021

Dipraglurant for Parkinson's Disease

- US PD-LID market estimated at \$4.2B
- FDA Orphan Drug Designation granted in PD-LID
- Positive Phase 2 in PD-LID
- Registration trials scheduled to start H2 2019

Addex Pipeline and Technology Platform



- Validated differentiated pharmacological approach
- Proprietary biological screening assays and chemical library
- Partnership with Indivior PLC on GABAB PAM
- Partnership with J&J on mGluR2 PAM

Experienced Team

- Executive Management:
 - Tim Dyer, CEO / CFO
 - Co-founder of Addex, formerly with PwC
 - Roger Mills, CMO
 - Formerly with Acadia Pharmaceuticals
 - Robert Lutjens, Head of Biology
 - Formerly with Glaxo, The Scripps Res Inst.
 - Jean-Philippe Rocher, Head of Chemistry
 - Formerly with Pierre Fabre, GSK, Mitsubishi
- Team of Experts:
 - Hilde Williams
 - Regulatory Affairs, Former SVP Regulatory Acadia Pharmaceuticals
 - Ron Lawrence
 - CMC; Formerly with GSK
- Clinical Advisors:
 - PD-LID
 - Michael J. Fox Foundation for Parkinson's Research
 - Dr. Erwan Bézard
 - Prof. Chris Goetz
 - Prof. Stuart Isaacson
 - Dystonia
 - Dystonia Medical Research Foundation
 - Prof Hyder Jinnah
 - Prof. Antonio Pisani
 - Dr. Jan Teller
- Board Members:
 - Vincent Lawton, Chairman
 - Former European Head of Merck & Co., MHRA
 - Ray Hill
 - Former Executive Director at Merck & Co.
 - Jake Nunn, New Enterprise Associates
 - Isaac Manke, New Leaf Venture Partners

Clinical Stage Pipeline with Registration Trial-Ready Program










Multiple Orphan Drug Opportunities

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



NAM = Negative Allosteric Modulator
PAM = Positive Allosteric Modulator

Extensive Preclinical Stage Pipeline for Long-Term Growth

Molecule / MoA	Hit to Lead	Lead Optimization	Clinical Candidate	Collaboration Partners
mGluR4 PAM	Parkinson's Disease			        
mGluR2 NAM	Mild Cognitive Impairment			
GABAB PAM	Charcot-Marie-Tooth 1A			
mGluR7 NAM	Psychosomatic Disorders (PTSD)			
mGluR3 PAM	Neurodegen Dis			
TrkB PAM	Neurodegen Dis			

Dipraglurant in Parkinson's Disease

The Dipraglurant Opportunity in Parkinson's Disease

Important Unmet Need in PD-LID

- >1M PD patients in US of which >170,000 have dyskinesia
- Gocovri (reformulated generic amantadine): Approved Aug 2017

Dipraglurant: Unique Mechanism of Action

- First-in-class, selective, oral small molecule mGluR5 NAM
- PK profile mirrors that of L-dopa, making it ideal to treat LID
- Inhibits abnormal glutamate stimulation during L-dopa dosing

Significant Commercial Opportunity

- US LID market estimated at \$4.2B
- Dipraglurant US peak sales estimated at \$1.4B
- Significant recent increase in pricing of PD therapeutics – Nuplazid at \$30K p.a. and Gocovri at \$28.5K p.a.

Development & Regulatory Path

- Manufacturing & planning for registration studies ongoing
- Precedented FDA regulatory path.

Strong IP Position

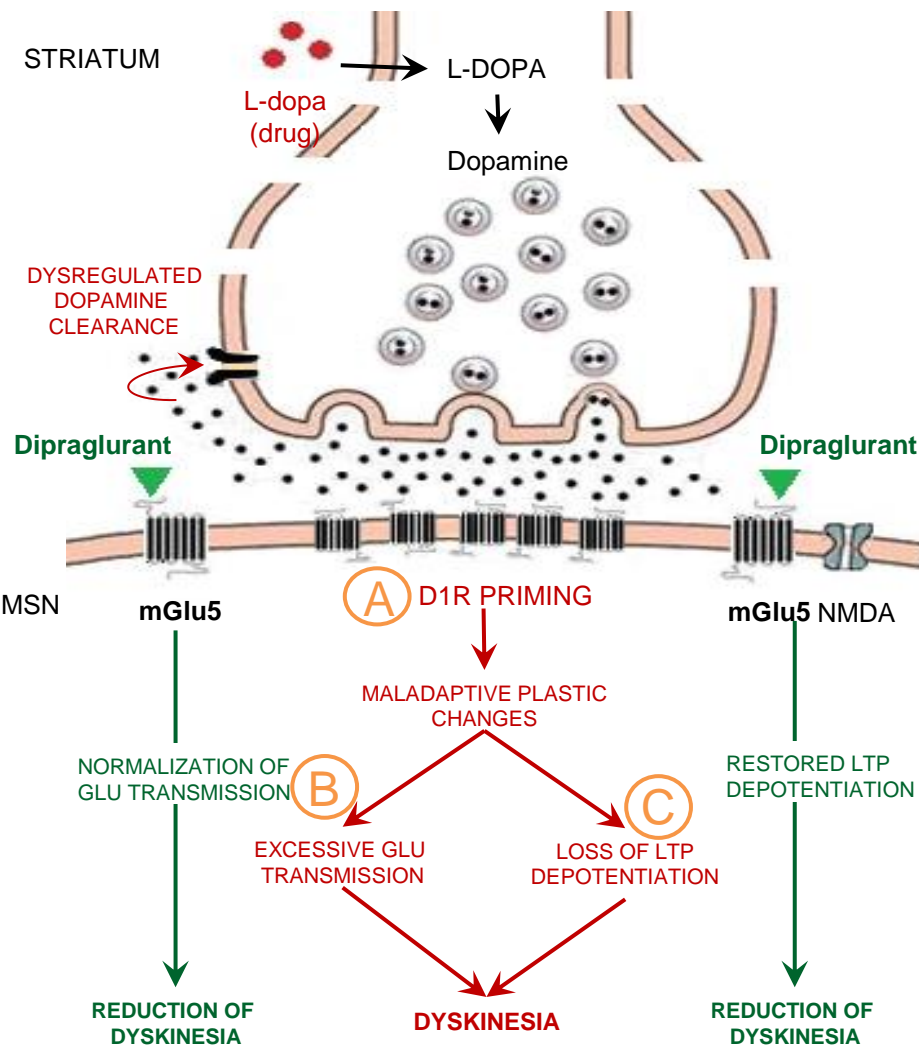
- Composition of matter through June 2025 & strong polymorph patent through 2034 without extensions
- US FDA orphan drug designation in PD-LID

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

- Long-term L-dopa use is invariably associated with the development of dyskinesias - as disabling as the PD symptoms themselves
- Prevalence of LID is related to disease duration
 - Within 4-6 years of L-dopa treatment, LID is experienced by >40% of patients
 - By 9 -15 years of L-dopa treatment, LID affects 90% of PD patients
 - Next-generation L-dopa will not negate LID
- Dyskinesias result from the neurodegenerative process that underlies PD.
- Dopamine replacement does not lead to dyskinesia per se, but lowers the triggering threshold for symptoms.
- Patients with LID present with irregular migrating uncontrollable contractions or twisting and writhing due to dystonia, chorea, and choreoathetosis.
- Over time PD drugs become less effective, exacerbated by the emergence of LID, which limits tolerability of the drugs
- The constant dyskinetic movements can be painful, lead to weight loss, fatigue and exhaustion, with increased risk for falls and injuries.
- Patients are embarrassed and withdraw from social interaction leading to isolation, frustration and depression.
- This diminishes the patient's quality of life but it also significantly increases the burden on the caregiver.
- The doctor is faced with a balancing act where drug and dosing regimens must be continually optimized in order to ensure adequate symptom control while minimizing intolerable side effects.

Dipraglurant - Overview & Mechanism of Action

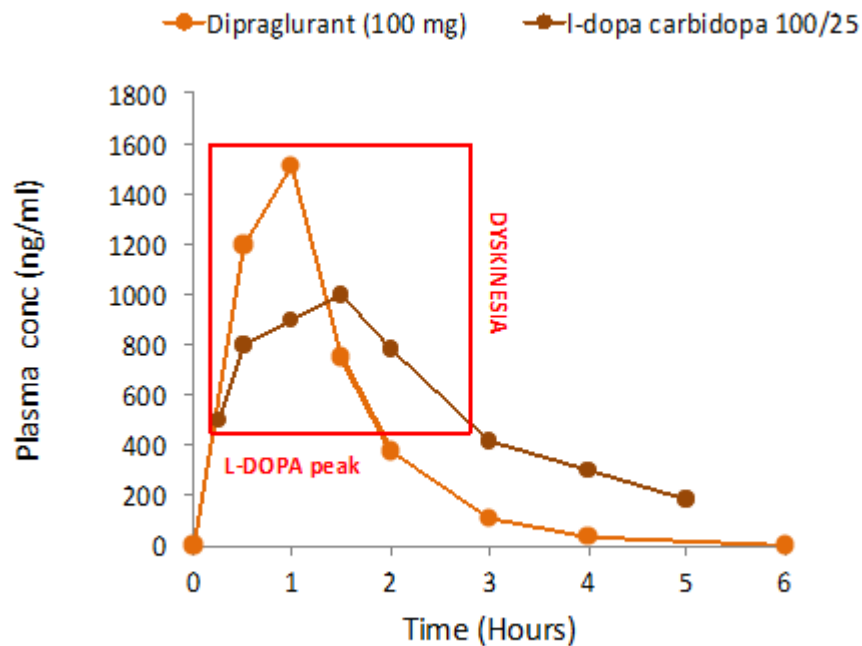
Severe PD
(advanced neuron degeneration)



- Loss of substantia nigra neurons combined with the non-physiological, pulsatile stimulation of dopamine receptors are at the basis of LID development
- In the striatum, **LID is the result of:**
 - (A) *D1 receptor priming*
 - (B) *Abnormal glutamate transmission*
 - (C) *Loss of LTP depotentiation*
- Metabotropic glutamate receptors are attractive drug targets due to their **modulatory** action to normalize glutamatergic activity and restoration of LTP depotentiation
- **mGlu5 receptors are implicated in the control of glutamate transmission**
- Preclinical and clinical data show that mGluR5 blockade controls dyskinesia
- **Dipraglurant is an oral small molecule active as a highly selective negative allosteric modulator at the mGlu5 receptor with the potential to treat LID**

LTP = Long Term Potentiation

Dipraglurant PK is a Key Advantage for Treating LID

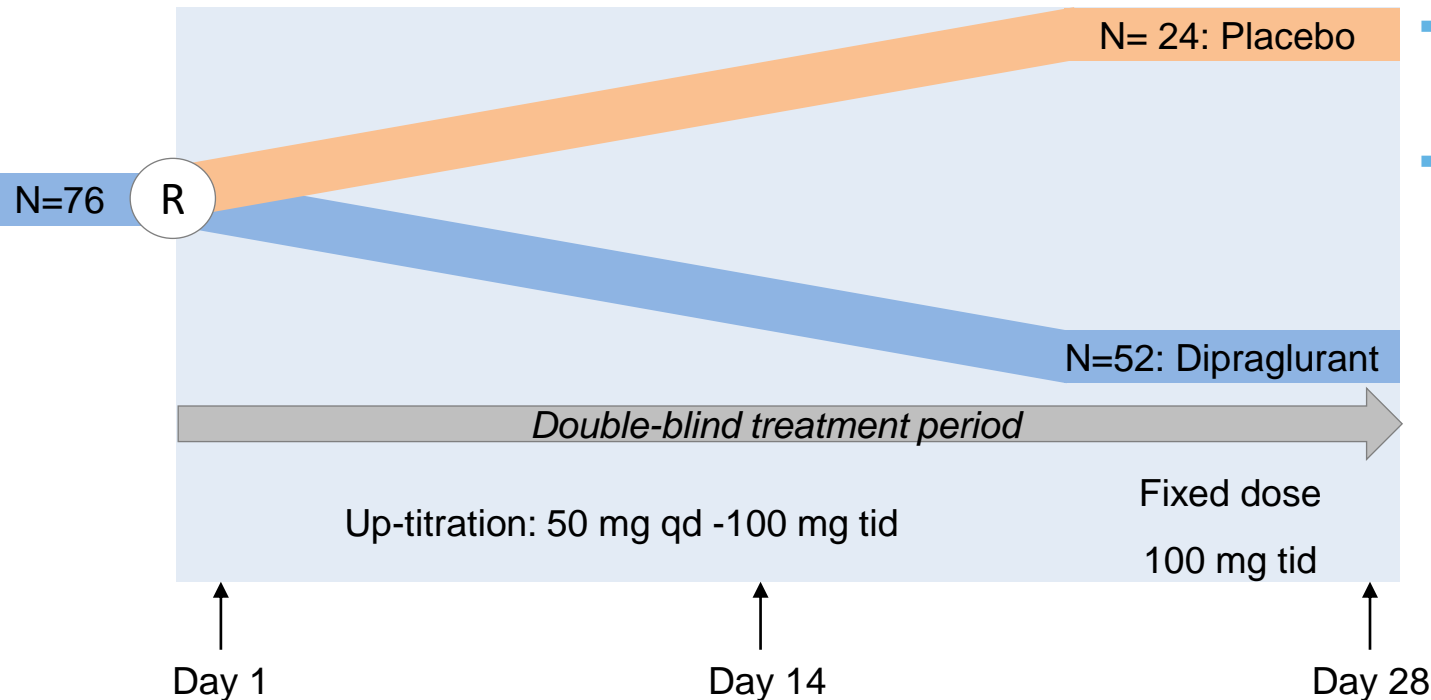


- Dyskinesia symptoms are correlated to peak levels of levodopa therapy
- PK profile of dipraglurant mirrors that of levodopa
- **Dipraglurant inhibits abnormal glutamate stimulation during peak levodopa dose but releases the receptor during normal glutamate activity**

Dipraglurant PK/PD Profile is Ideal for Treating LID

Dipraglurant EU and US Phase 2a Study in LID

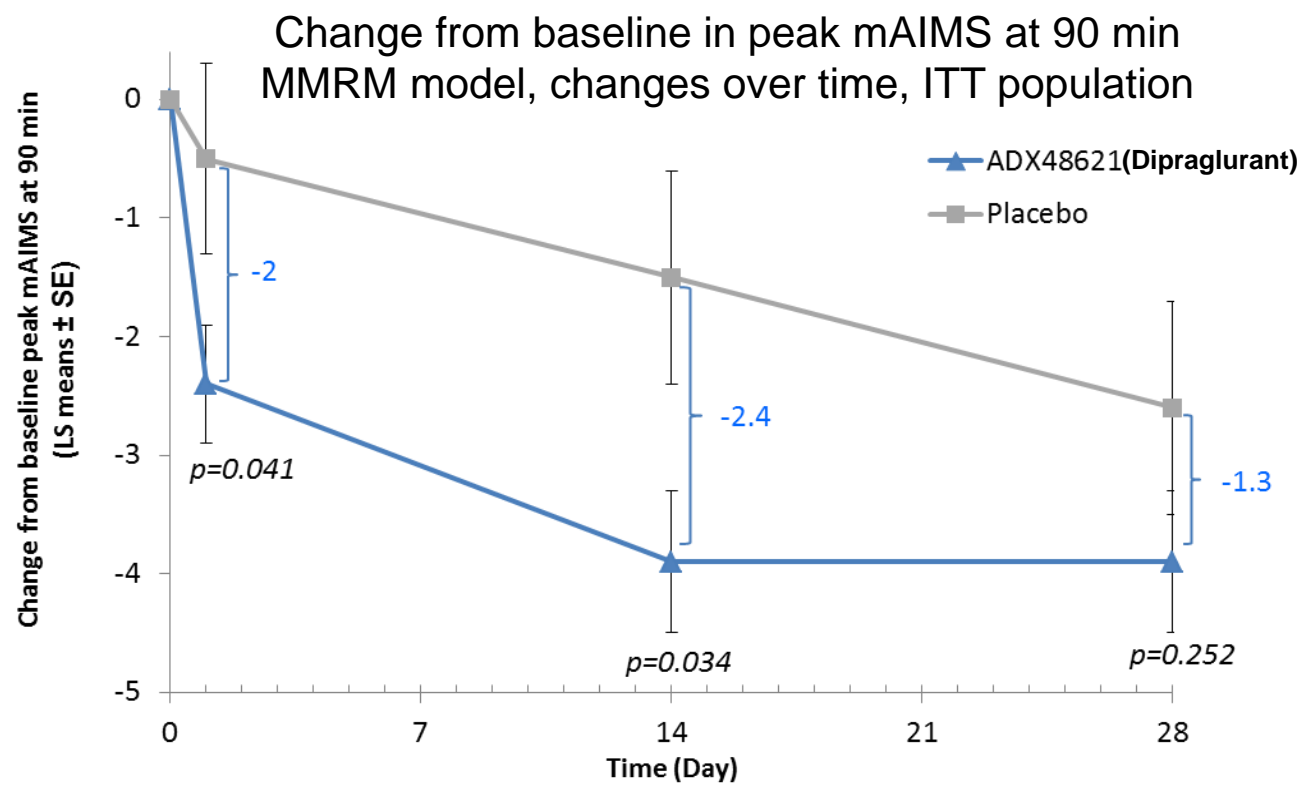
Multicentre study in 25 centres across US and Europe



- **Primary objective:** safety & tolerability
- **Secondary objective:** exploratory efficacy:
 - ✓ Modified Abnormal Involuntary Movement Scale (**mAIMS**) on Day 1, 14 and 28
 - ✓ Unified Parkinson’s Disease Rating Scale (UPDRS)
 - ✓ Clinician and Patient Global Impression of Change (CGIC & PGIC)
 - ✓ Pharmacokinetics (PK)
 - ✓ Patient diaries of ON & OFF time

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

Dipraglurant Reduces LID Severity by 30%

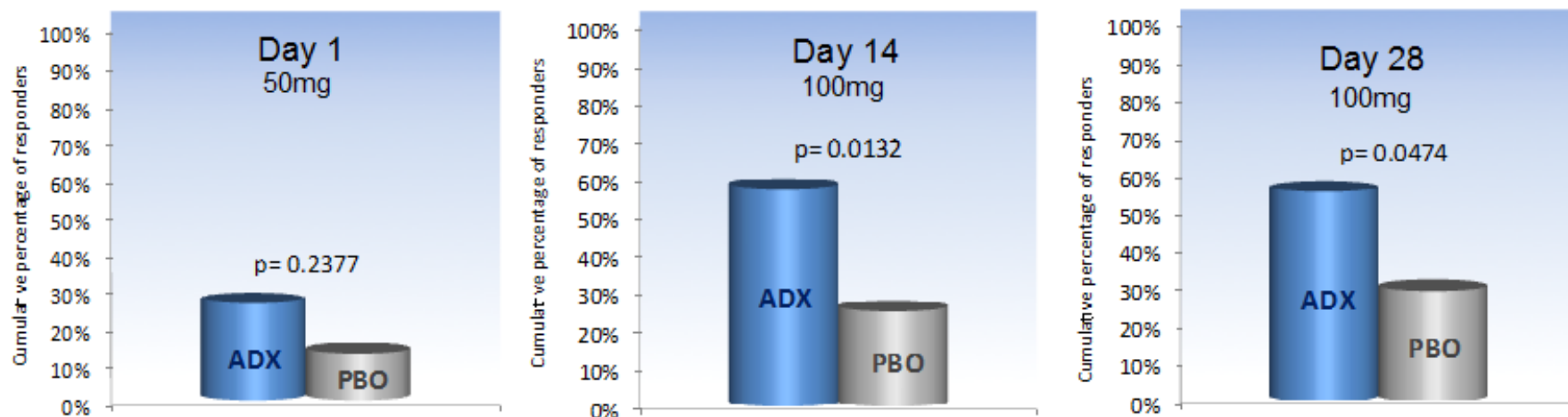


- Dipraglurant had a statistically significant effect on the first day
- Dipraglurant reduced dyskinesia compared to placebo at all visits over the 28 days
- Placebo response confounded significance at day 28
- Dose titration contributed to placebo response (patients only on full dosage for last 7 days)
- No placebo-mitigating techniques deployed in study:
 - No centralized raters
 - No independent raters
 - Rater not blinded to visit number
 - Patients were more moderate than severe

Mean % change of peak mAIMS from baseline		
Midday dose	Dipraglurant	Placebo
Day 1 (50 mg)	19.9%	4.1%
Day 14 (100 mg)	32.3%	12.6%
Day 28 (100 mg)	31.4%	21.5%

Responder Analysis Demonstrates Dipraglurant Significant Benefit

Cumulative % of Patients Showing $\geq 30\%$ Change of Peak mAIMS from Baseline



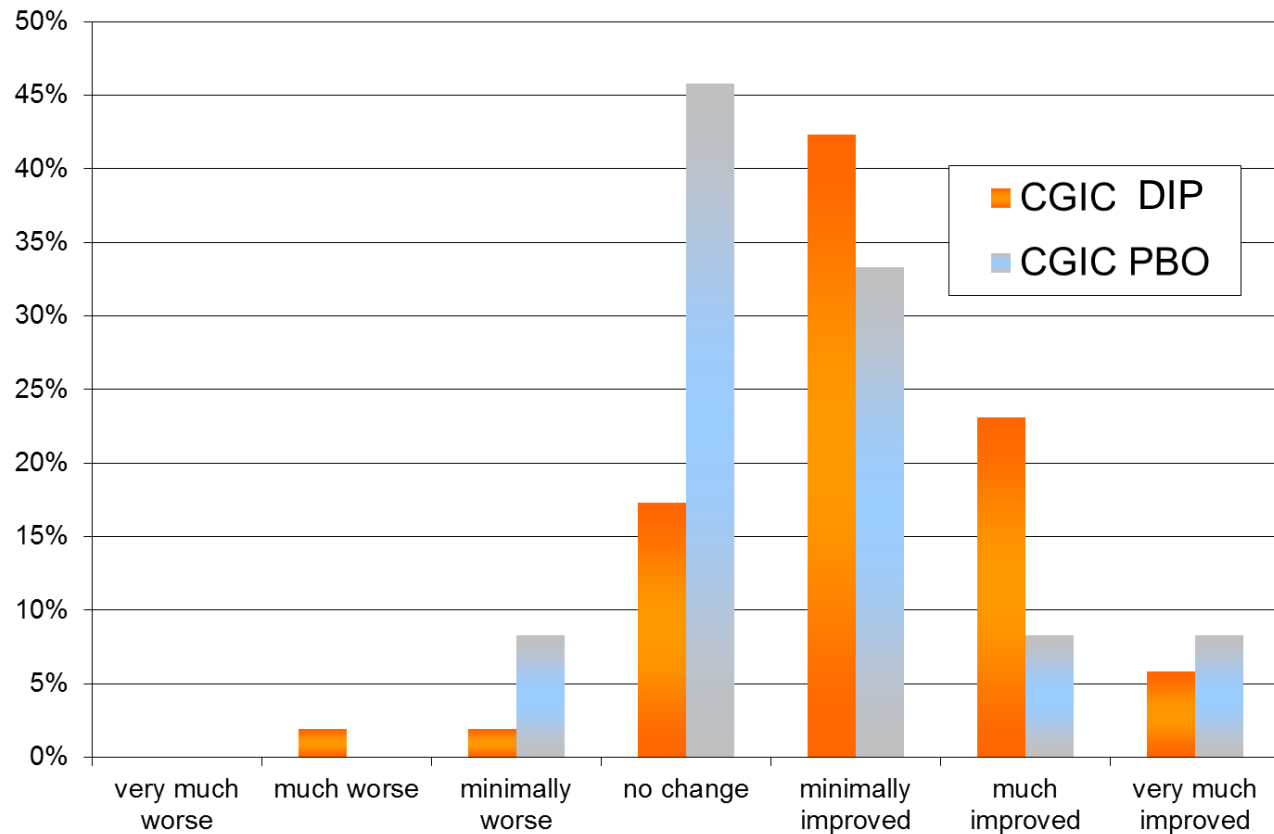
Responder analysis ($\geq 30\%$ change of peak mAIMS from baseline)

Midday dose	Dipraglurant		Placebo		p-value
Day 1 (50 mg)	n=13	26.0%	n=3	12.5%	0.2377
Day 14 (100 mg)	n=29	56.9%	n=6	25.0%	0.0132
Day 28 (100 mg)	n=27	55.3%	n=7	29.2%	0.0474

- A 30% reduction in mAIMS is clinically meaningful
 - One patient was able to hold & read a newspaper for the first time in years
 - Another patient had improved speech and became more easily intelligible

Responder analysis reinforces robustness of dipraglurant anti-dyskinetic effect

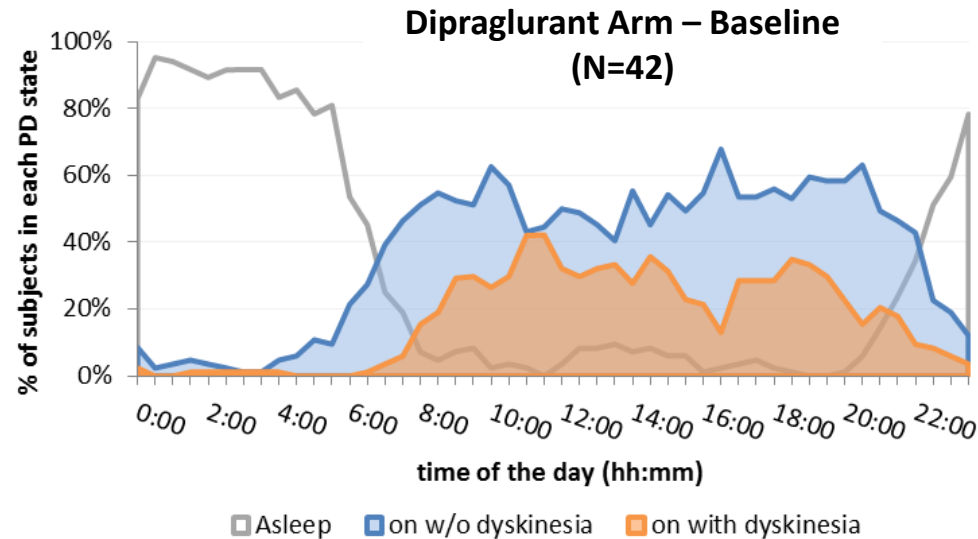
Clinician Rated Global Impression of Change - Dyskinesia



- Relatively simple scale that reflects everyday clinical practice
- Assessment by treating physician and thus is a more objective assessment than the more subjective mAIMS
- Assessment performed at end of study compared to baseline
- **Greater improvement in dyskinesia with dipraglurant according to clinicians ($p < 0.05$)**

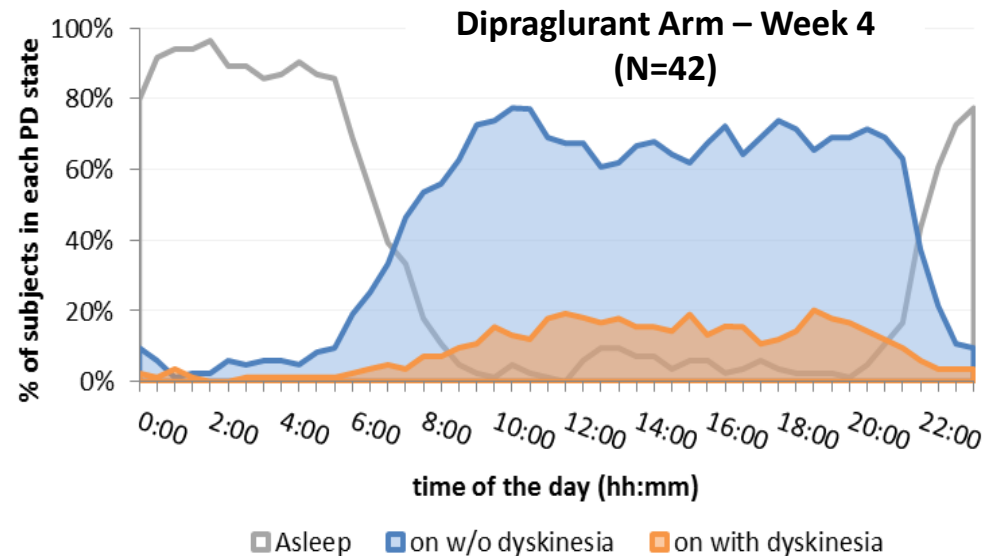
	Dipraglurant	Placebo
Improved ($p < 0.05$)	71.2%	49.9%
No change	17.3%	45.8%

Patient Diaries – Improvement Throughout the Waking Day



After 4-week treatment with dipraglurant:

- ON time with dyskinesia **reduced** during the day
- ON time without dyskinesia **increased** and maintained during the day



Dipraglurant 50 and 100 mg Doses Demonstrated Safety and Satisfactory Tolerability in PD Patients

- Adverse events were common in both treatment groups (dipraglurant 88.5%, pbo 75%)
- The majority of patients completed the dose escalation regimen
- Most common AEs:

	Dipraglurant	Placebo
Worsening Dyskinesia	21% (15.3%*)	12.5%
Dizziness	19%	12.5%
Nausea	19%	0%
Fatigue	15%	4%

* 3 of the 11 patients who reported “worsening dyskinesia” did so only in the follow up period (i.e. when not taking the drug). Thus the dyskinesia recurred only after therapy had stopped. Therefore the adjusted AE% is 15.3% for dipraglurant arm vs. 12.5% for placebo arm.

- AEs caused discontinuation in 2 patients taking dipraglurant 100 mg
- AEs at the 50 mg dose level (wk 1 and 2) were less frequent – 53% vs 58% pbo than at the 100 mg dose level (wk 3 and 4) – 73% vs 63% pbo
- No treatment effects on any safety monitoring variables (ECG, HR, BP, haematology and biochemistry)

Safety profile suitable for continued development in PD (KOLs and DSMB)

Summary of Efficacy Data

- Dipraglurant showed a clinical meaningful improvement of dyskinesia
 - Significant improvement of mAIMS on Days 1 and 14
 - Trial design exacerbated placebo response – confounding significance at Day 28
 - Responder analysis ($\geq 30\%$ improvement) demonstrates clinically meaningful and statistically significant benefit on Days 14 and 28
 - Investigator assessed CGIC shows dipraglurant significantly improved dyskinesia over placebo during the study ($p < 0.05$)
- Did not impair motor function (UPDRS) – important consideration for FDA
- Dipraglurant effects in patient-reported outcomes:
 - 50-minute reduction in “OFF time” by week 4
 - 2.3 hours more “ON time” without dyskinesia by week 4

Clinical Development Plan

- Pivotal trials:
 - Two studies required for registration
 - Primary endpoint: UDysRS - more sensitive to treatment effect than mAIMS and less prone to placebo response (Goetz 2013)
 - Pivotal Study 1 (301) – 13 weeks – data H2 2020
 - Pivotal Study 2 (302) – 26 weeks (primary endpoint at 13 weeks) – data H2 2021
 - Open label extension: 100 patients exposed for 1 year
- Toxicology:
 - 6 and 9 month toxicology
 - 3 month combination toxicology study in one species before large studies start
- Regulatory:
 - Continue to interact with regulatory bodies in 2018
 - Consider fast-track / breakthrough applications after first pivotal study
 - NDA submission projected for mid 2022

Management of Placebo Response

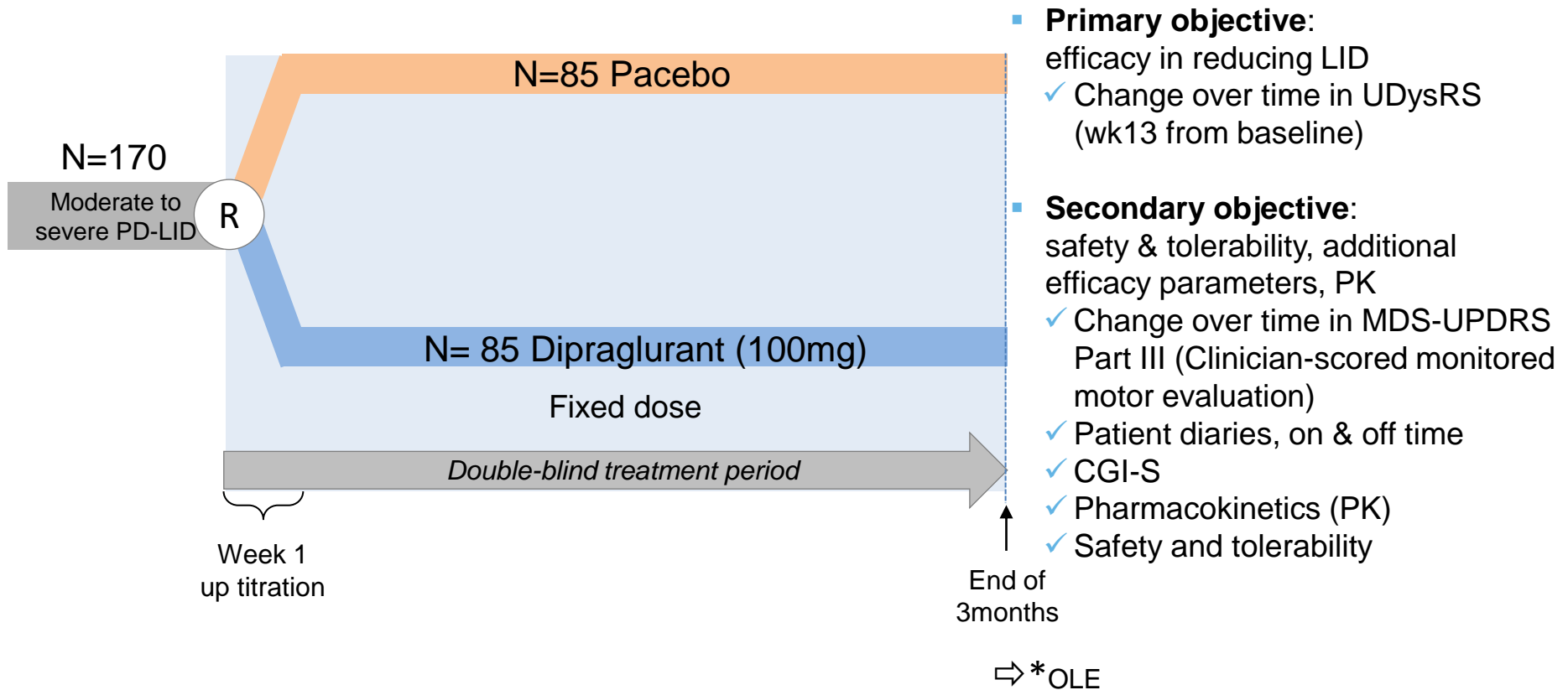
Objective	Strategy
<ul style="list-style-type: none">Minimize rater variability (across and within sites)	<ul style="list-style-type: none">Use independent (centralized) raters
<ul style="list-style-type: none">Reduce expectancy bias	<ul style="list-style-type: none">Raters blinded to visit and do not rate the same patient at baseline and study endpoint
<ul style="list-style-type: none">Exclude patients with minimal symptoms (as more likely to respond to placebo)	<ul style="list-style-type: none">Ensure that symptom score reflects moderate to severe symptoms that warrant therapyEnsure occur frequently enough for scale sensitivity
<ul style="list-style-type: none">Exclude potential investigator rating inflation	<ul style="list-style-type: none">Independent oversight of screening and use of centralized rater baseline visit score as study entry gate
<ul style="list-style-type: none">Draw placebo response ahead of randomization	<ul style="list-style-type: none">Consider non-pharmacologic intervention during screening period
<ul style="list-style-type: none">Ensure no geographic bias	<ul style="list-style-type: none">Only include countries / sites where centralized rating is feasible

Dyskinesia Rating Scales: UDysRS verses mAIMS

	UDysRS	mAIMS
Characteristics	<ul style="list-style-type: none"> • Recommended scale by Movement Disorder Society • FDA regulatory NDA precedent (Adamas - Gocovri) • Contains anchored objective clinician evaluated measures of dyskinesia • UDysRS has both patient-based perceptions of disability and physician assessments of impairment and disability embedded in the single scale • Less prone to placebo effect 	<ul style="list-style-type: none"> • mAIMS alone was identified as suboptimal in detecting treatment-related changes • mAIMS patient driven • More prone to placebo effect
Clinimetric properties	<ul style="list-style-type: none"> • Validated 	<ul style="list-style-type: none"> • Only the original version has been validated
History	<ul style="list-style-type: none"> • Developed in 2009 specifically for dyskinesia in PD patients 	<ul style="list-style-type: none"> • Developed in 1970 to assess tardive dyskinesia in psychiatric patients

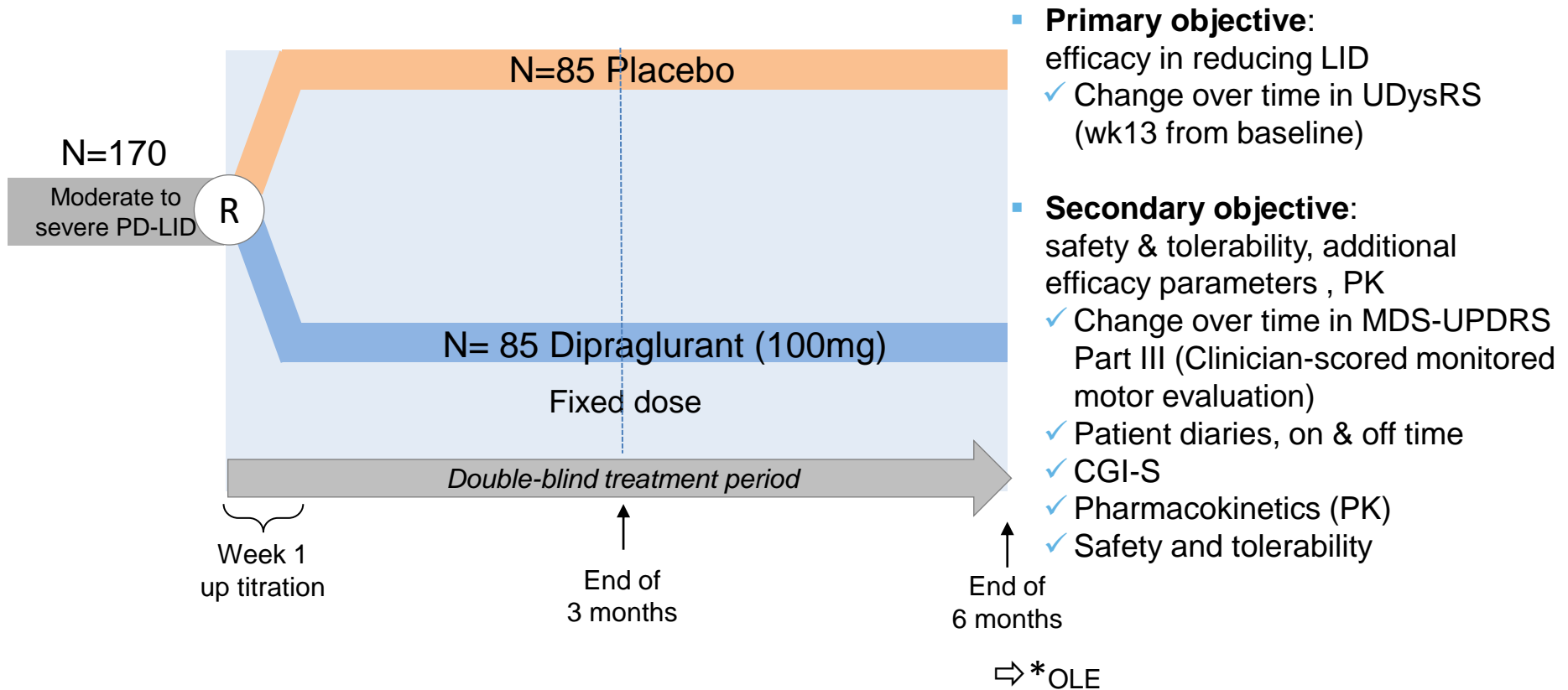
UDysRS= Unified Dyskinesia Rating Scale

Dipraglurant 1st Pivotal LID Study (301)



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

Dipraglurant 2nd Pivotal LID Study (302)



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

Dipraglurant LID Opportunity

- LID has a large unmet need and market opportunity
 - > 170K LID patients in US
 - ~\$1.4bn US market opportunity for dipraglurant
- Limited competition – only one FDA approved medicine
 - Gocovri (reformulation of generic amantadine): Approved on 24th August 17 – safety profile similar to generic
 - Dipraglurant 1st in class highly selective oral monotherapy – improved safety profile
- Development plan defined
- Precedented regulatory path paved by Gocovri (Adamas)
 - Two registration trials
 - Ideal PK profile mirrors levodopa – recognized by KOLs as key advantage
- Strong patent and market exclusivity
 - NCE and polymorph patent provide protection through 2034 without extensions and data exclusivity
 - Orphan Drug Designation – 7 years of market exclusivity

Preclinical Programs

Indivior Partnership on GABA_B PAM

- GABA_B is the metabotropic receptor for GABA, main inhibitory neurotransmitter
- Activation of GABA_B is validated through the use of baclofen (GABA_B orthosteric agonist)
 - Approved for the treatment of spasticity
 - Clinical efficacy in alcoholism and Charcot-Marie-Tooth type 1A (CMT1A)
- Positive Allosteric Modulator (PAM) is a differentiated pharmacological approach
 - Potential safety and efficacy advantages – lack of tolerance and less side effects
- Worldwide license and collaboration on GABA_B PAM
- Indivior leading development of ADX71441 in addiction
- Addex leading funded research effort to deliver back up compounds
 - Addex has right to select back up compounds at clinical candidate stage for development in retained indications including CMT1A neuropathy
- Financial terms:
 - Upfront of USD 5 million & USD 4 million research funding over 2 years
 - USD 330 million of development, regulatory and commercial milestones
 - Tiered royalties up to double-digit royalties

Addex mGlu4 PAM Program

- Overview :
 - novel non-dopaminergic approach to treat Parkinson's disease with potential to treat both motor and non-motor symptoms
 - Significant preclinical validation
 - Raised interest in field following recent acquisition of Prexton Therapeutics by Lundbeck
- Status:
 - Late lead optimization - IND-enabling studies planned for 2020
 - Several novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds
 - Significant novel IP in the field

Addex TrkB PAM Program

- Overview :
 - TrkB is the receptor for BDNF (brain-derived neurotrophic factor)
 - Preclinically validated
 - neurodegenerative diseases - Alzheimer's, Parkinson's, or Huntington's disease
 - potential for both disease-modifying and symptomatic treatment
 - PAM approach enabled identification of novel chemistry
- Status:
 - Lead generation stage
 - Supported with grants from Michael J Fox Foundation and InnoSuisse
 - Collaboration with University of Geneva access to complex *in vitro*, *ex vivo* and *in vivo* models to probe neuroprotective and neurogenesis potential of TrkB PAMs

World Leading Allosteric Modulator Discovery Platform

Allosteric Modulation Drug Discovery Platform

- Proven track record
 - Pipeline of in house discovered drug candidates
 - mGluR5 NAM & mGluR2 PAM in clinical studies
 - Novel chemistry for GABAB, mGluR4, mGluR3, mGluR7 and TrKB
 - Proprietary biological tools for screening and medicinal chemistry support
 - Drug like allosteric biased chemical library
 - Significant in house expertise
- Platform & preclinical strategy
 - Continue to invest in allosteric modulation expertise
 - Leverage platform through collaboration with industry and non-dilutive sources of expertise and funding
 - Focus on advancing preclinical portfolio to clinical candidate selection

Financials

Financials and Stock

- Cash runway through 2021
 - Cash of CHF43.6M at 30 June 2018
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- 28,564,031 shares outstanding 37.7M fully diluted)
 - New Enterprise Associated – 16%
 - New Leaf Venture Partners – 5.6%
 - CAM Capital – 5.6%
 - Credit Suisse Asset Management – 5.5%
 - Management & board holds - 15% (fully diluted basis)
- Analyst coverage:
 - Van Leeuwenhoek – Marcel Wijma
 - valuationLAB – Bob Pooler
- Market capitalization: approx. CHF70M
- Tax losses carried forward: CHF190M
- No debt

Upcoming Development Milestones

Milestone	Timing
Dipraglurant – LID Phase 3 Registration Program	
Study 301 – start dosing	H2 2019
ADX71441 – Addiction (Partnered with Indivior)	
Phase 1 (NIDA sponsored study) – start dosing	H1 2019

Allosteric modulators for human health

www.addextherapeutics.com