



Innovative Treatments for Central Nervous System Disorders

April 2019

Allosteric modulators for human health

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Addex Overview

Dipraglurant for dyskinesia in Parkinson's disease

- Pivotal registration program on track to start in Q4 2019
- US PD-LID market estimated at \$4.2B
- FDA Orphan Drug Designation granted in PD-LID

Validating partnerships with industry

- Indivior partnership - \$330m in milestones, tiered royalties up to double digit & funded research program
- J&J deal - €109m in milestones & low double digit royalties

World leading technology platform

- “Allosteric modulators” are a validated & differentiated pharmacological approach to address drug targets
- Proprietary biological screening assays and chemical library

Deep pipeline of first / best in class programs

- Creating future partnership opportunities
- Driving long term growth

Strong balance sheet

- 28.6M shares traded on the SIX Swiss Stock Exchange – ADXN
- Cash of CHF41.7m at 31 December 2018
- Runway through 2021

Experienced Leadership Team



Tim Dyer
CEO / CFO
Co-Founder of Addex
Formerly with PwC
UK Chartered Accountant



Dr Roger Mills
Chief Medical Officer
Developed Nuplazid in
PD Psychosis
30 years in Pharma
industry including Pfizer,
Gilead and Acadia
Pharmaceuticals



Dr Robert Lutjens
Head of Discovery
Biology
Member of Addex
founding team
Formerly with Glaxo &
Scripps Research
Institute



**Dr Jean-Philippe
Rocher**
Head of Discovery
Chemistry
Member of Addex
founding team
Formerly with Pierre
Fabre, GSK and
Mitsubishi

Experienced Board of Directors



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Chairman
Former European Head
of Merck & Co.
Former MHRA Board
member



Ray Hill
Board member
Former Executive
Director Merck & Co.





Jake Nunn
Board member
Partner New Enterprise
Associates



Isaac Manke
Board member
Partner New Leaf Venture
Partners

Pipeline with Lead Program Entering US Pivotal Study

Molecule / MoA	Preclinical	Phase 1	Phase 2	Phase 3
Dipraglurant-IR (<i>mGlu5</i> NAM)	Parkinson's disease levodopa-induced dyskinesia			
Dipraglurant-ER (<i>mGlu5</i> NAM)	Focal cervical dystonia			
ADX71149 (<i>mGlu2</i> PAM)	Epilepsy			
GABA _B PAM	Addiction			

NAM = Negative Allosteric Modulator

PAM = Positive Allosteric Modulator

Multiple orphan drug opportunities

Extensive Discovery Stage Pipeline Driving Long-Term Growth

Molecule / MoA	Hit to Lead	Lead Optimization
GABA _B PAM	Charcot-Marie-Tooth GABA _B PAM	
mGlu7 NAM	Psychiatric Disorders (PTSD & Hearing Loss)	
mGlu2 NAM	Mild Cognitive Impairment	
mGlu4 PAM	Parkinson's Disease	
mGlu3 PAM	Neurodegenerative Disorders	
TrkB PAM	Neurodegenerative Disorders	

NAM = Negative Allosteric Modulator

PAM = Positive Allosteric Modulator

Addex Platform Already Validated – Indivior Partnership Case Study

- **The alliance with Indivior** focusing on discovery of GABA_B Positive Allosteric Modulators (PAMs) for addiction
- 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
- Addex leading funded research effort to deliver drug candidates for preclinical / clinical development
 - 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

Dipraglurant in Parkinson's Disease

The Dipraglurant Opportunity in Dyskinesia Associated with PD

Clear Development & Regulatory Path

- Pivotal studies on track to start in Q4 2019
- Manufacturing and planning ongoing
- Precedented FDA regulatory path

Unmet Need and Significant Commercial Opportunity in PD-LID

- >1M Parkinson's disease patients in US of which >170,000 have dyskinesia
- US LID market estimated at \$4.2B
- Dipraglurant US peak sales estimated at \$1.4B
- Pricing of PD therapeutics – Nuplazid at \$30K p.a. and Gocovri at \$28.5K p.a.

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

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

- Dopamine replacement does not lead to dyskinesia per se, but lowers the triggering threshold for symptoms
- Dyskinesias result from the neurodegenerative process that underlies PD
- LID can become as disabling as the PD symptoms themselves

LID symptoms: irregular migrating uncontrollable contractions or twisting and writhing due to dystonia, chorea, and choreoathetosis

- This can be painful, lead to weight loss, fatigue and exhaustion, with increased risk for falls and injuries
- Leading to withdrawal from social interaction, isolation, frustration, depression, reduced quality of life and increased burden on caregiver

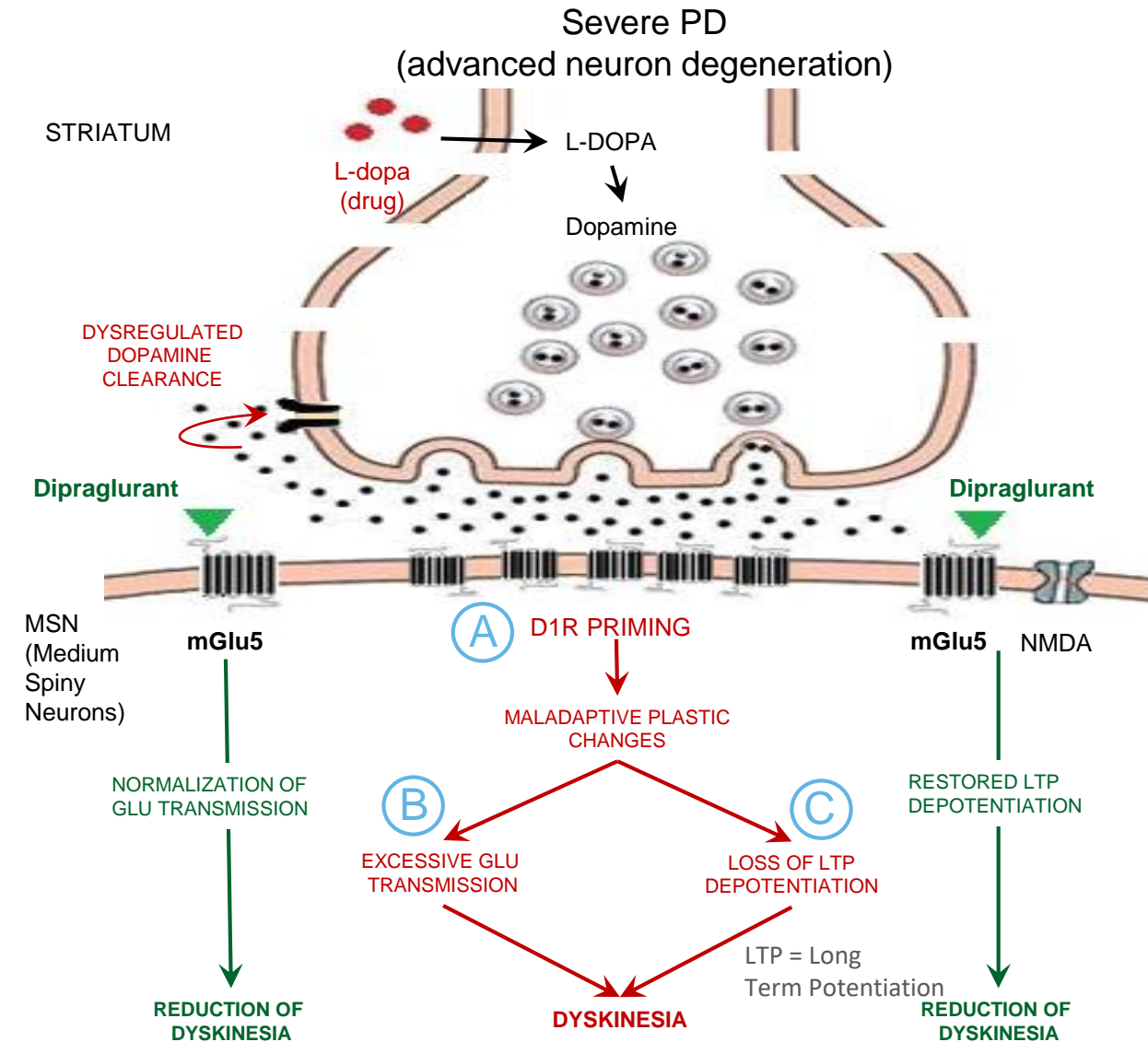
Prevalence of LID is related to disease duration

- 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

Over time PD drugs become less effective, exacerbated by the emergence of LID

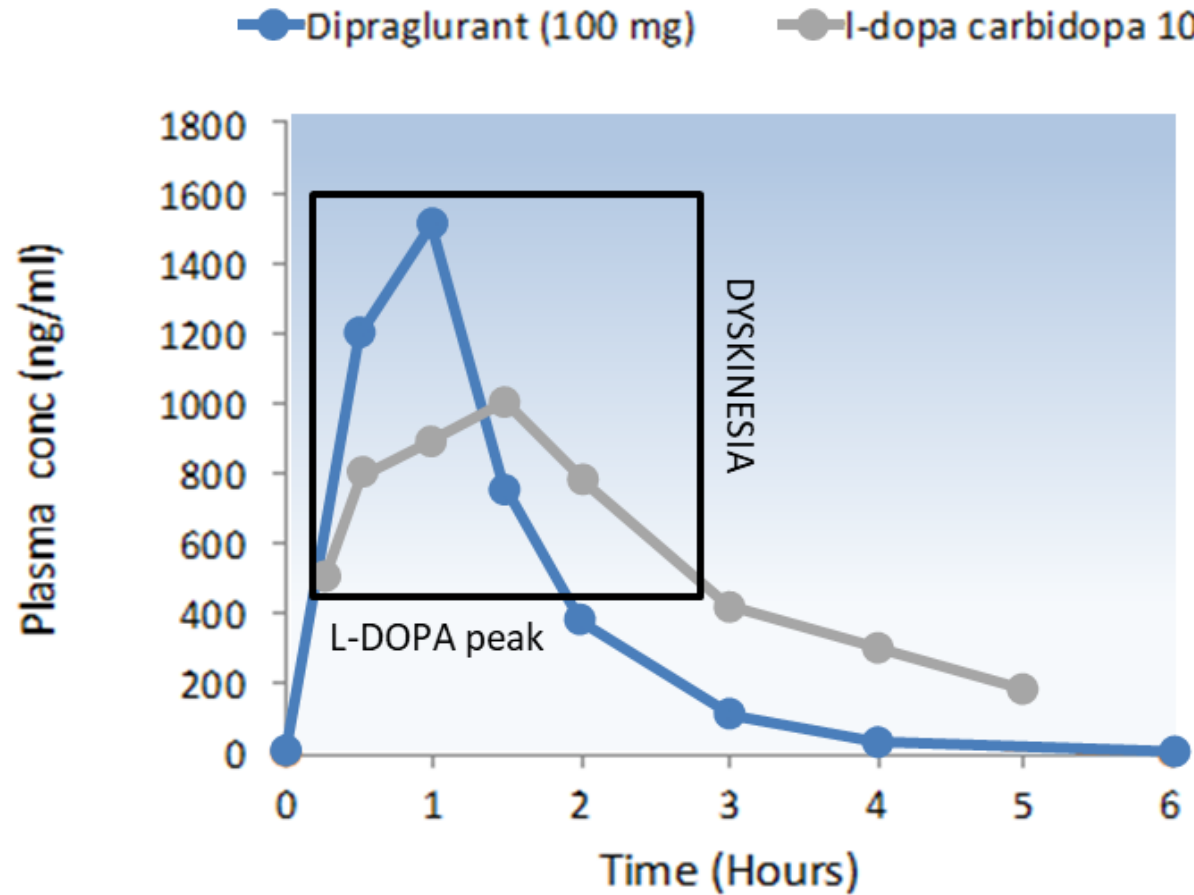
The doctor is faced with a balancing act where drug and dosing regimens must be continually optimized in order to ensure adequate symptom control while minimizing intolerable side effects

Dipraglurant - Overview & Mechanism of Action



- 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 depotentialiation**
- Metabotropic glutamate receptors are attractive drug targets due to their **modulatory** action to normalize glutamatergic activity and restoration of LTP depotentialiation
- **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**

Dipraglurant PK is a Key Advantage for Treating LID



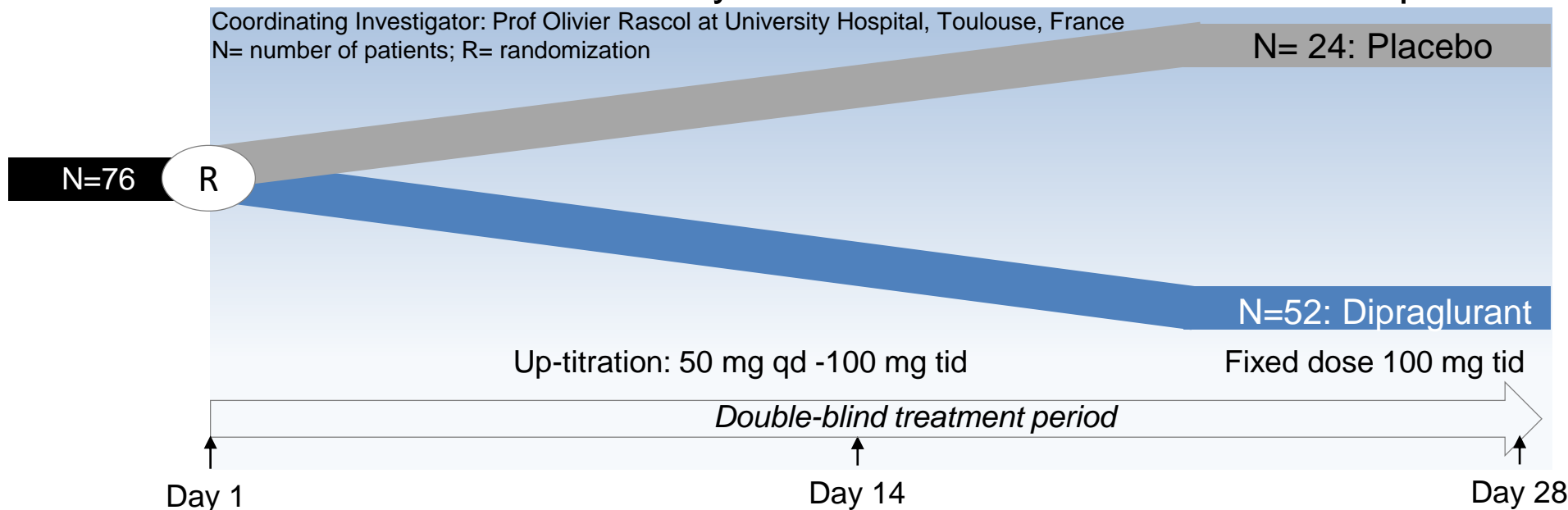
- Dyskinesia symptoms are correlated to peak levels of levodopa therapy
- PK profile of dipraglurant mirrors that of levodopa
- **Dipraglurant inhibits abnormal glutamate stimulation during peak levodopa dose but releases the receptor during normal glutamate activity**

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

Coordinating Investigator: Prof Olivier Rascol at University Hospital, Toulouse, France
 N= number of patients; R= randomization

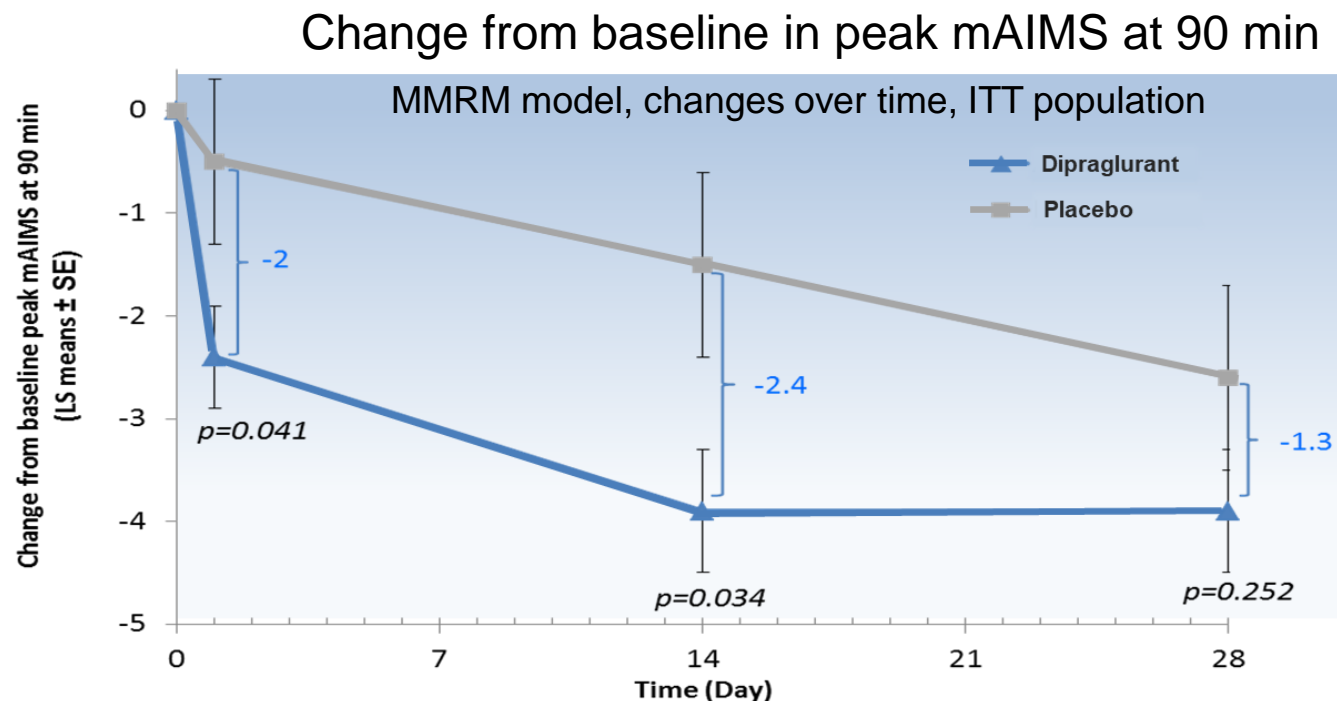


Days		1-3	4-7	8-13	14-16	17-21	22-28
Dose/mg	AM			50	50	50	100
	Noon	50	50	50	100	100	100
	PM		50	50	50	100	100
	Daily	50	100	150	200	250	300

- **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

Measuring acute effect of mid day dose on days 1, 14 and 28

Dipraglurant Reduces LID Severity by 30%



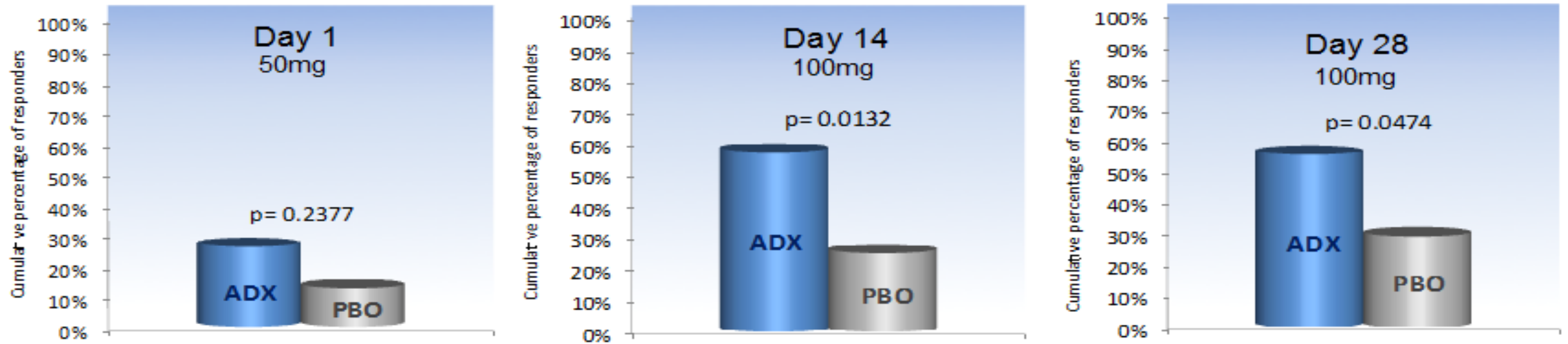
Mean % change of peak mAIMS from baseline		
Midday dose	Dipraglurant	Placebo
Day 1 (50 mg)	19.9%	4.1%
Day 14 (100 mg)	32.3%	12.6%
Day 28 (100 mg)	31.4%	21.5%

Clear dose response but need to manage placebo

- 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

Responder Analysis Demonstrates Dipraglurant Significant Benefit

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

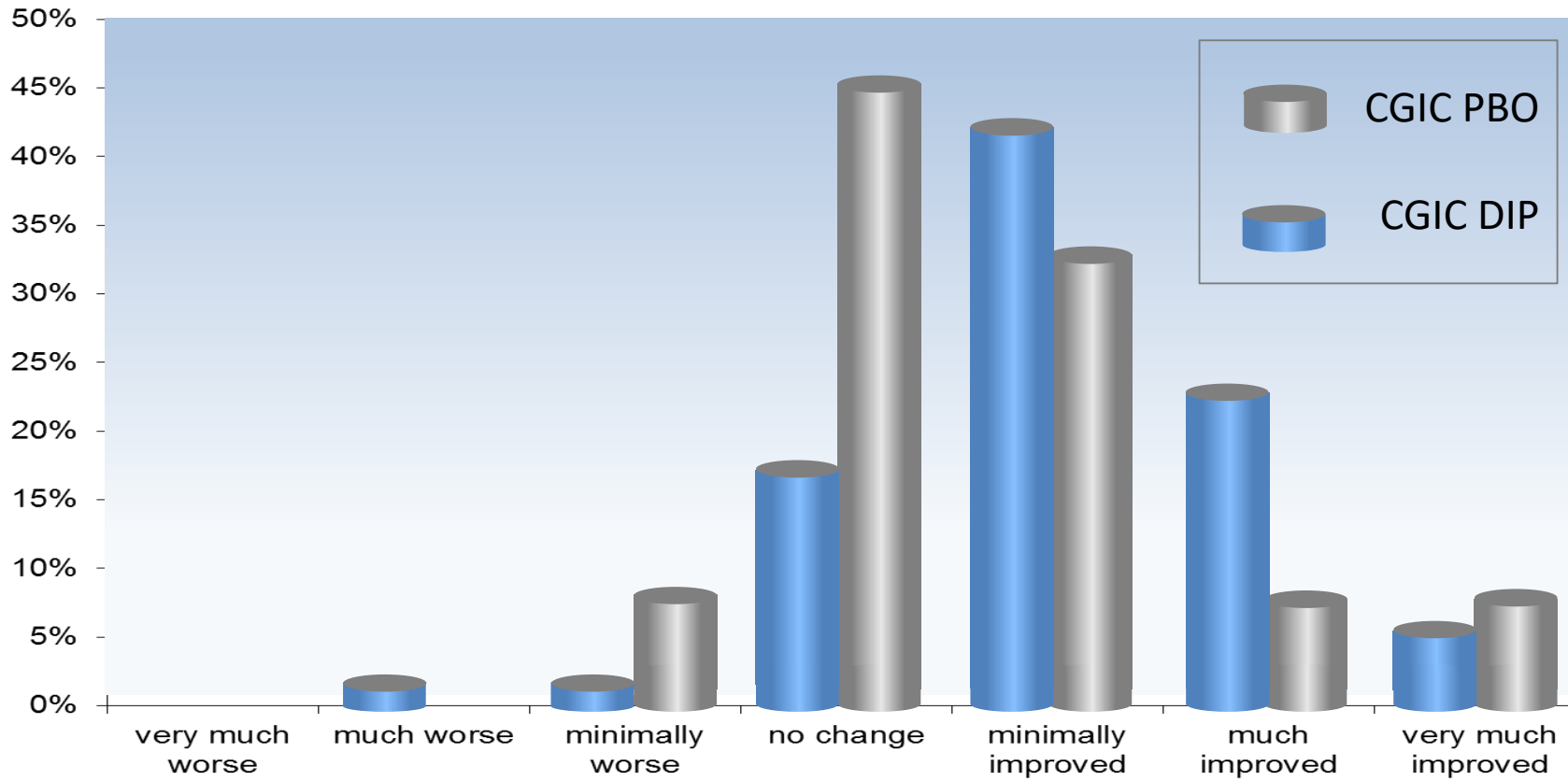


Responder analysis ($\geq 30\%$ change of peak mAIMS from baseline)					
Midday dose	Dipraglurant		Placebo		p-value
Day 1 (50 mg)	n=13	26.0%	n=3	12.5%	0.2377
Day 14 (100 mg)	n=29	56.9%	n=6	25.0%	0.0132
Day 28 (100 mg)	n=27	55.3%	n=7	29.2%	0.0474

- 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

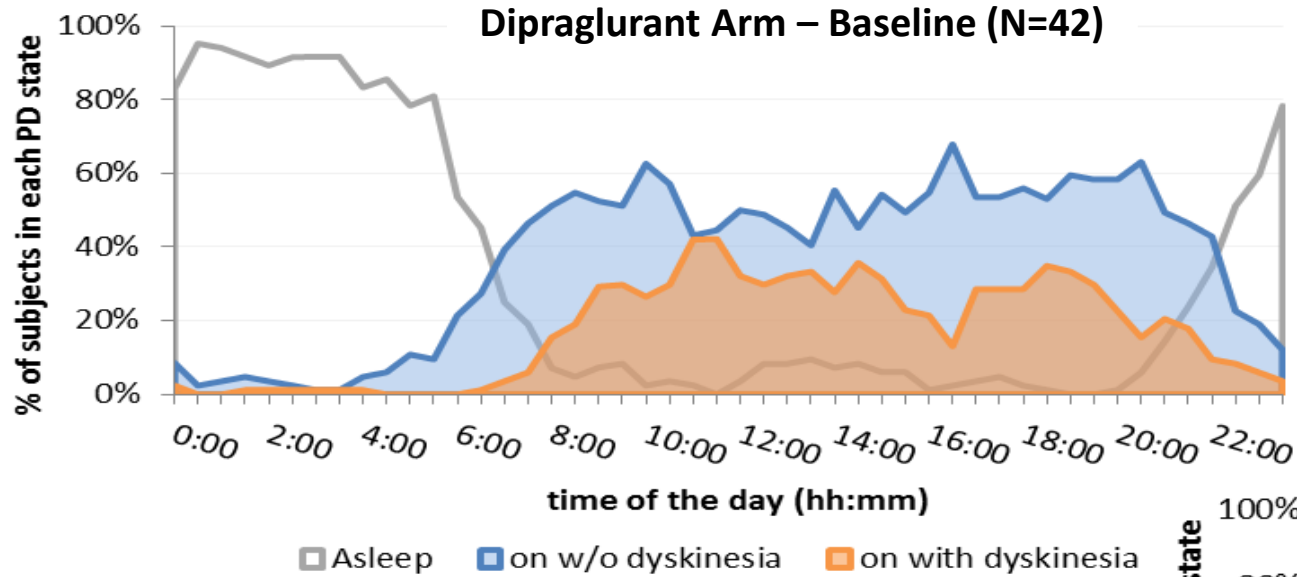
Clinician Rated Global Impression of Change - Dyskinesia



- 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)**

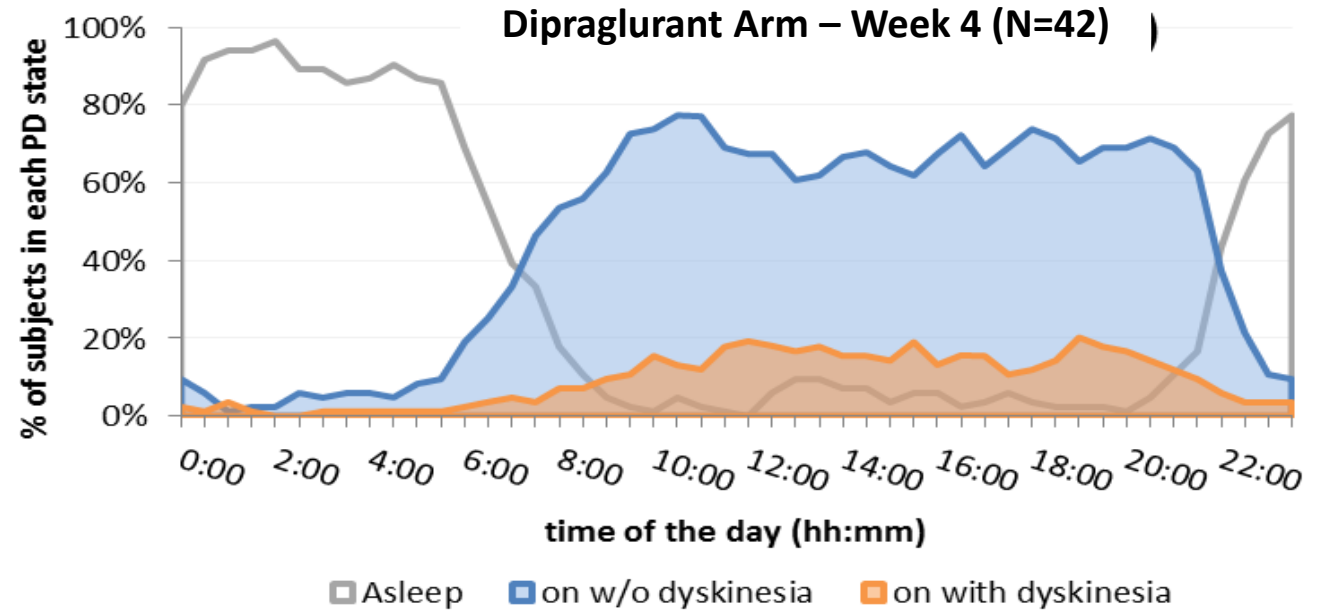
	Dipraglurant	Placebo
Improved (p<0.05)	71.2%	49.9%
No change	17.3%	45.8%

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)

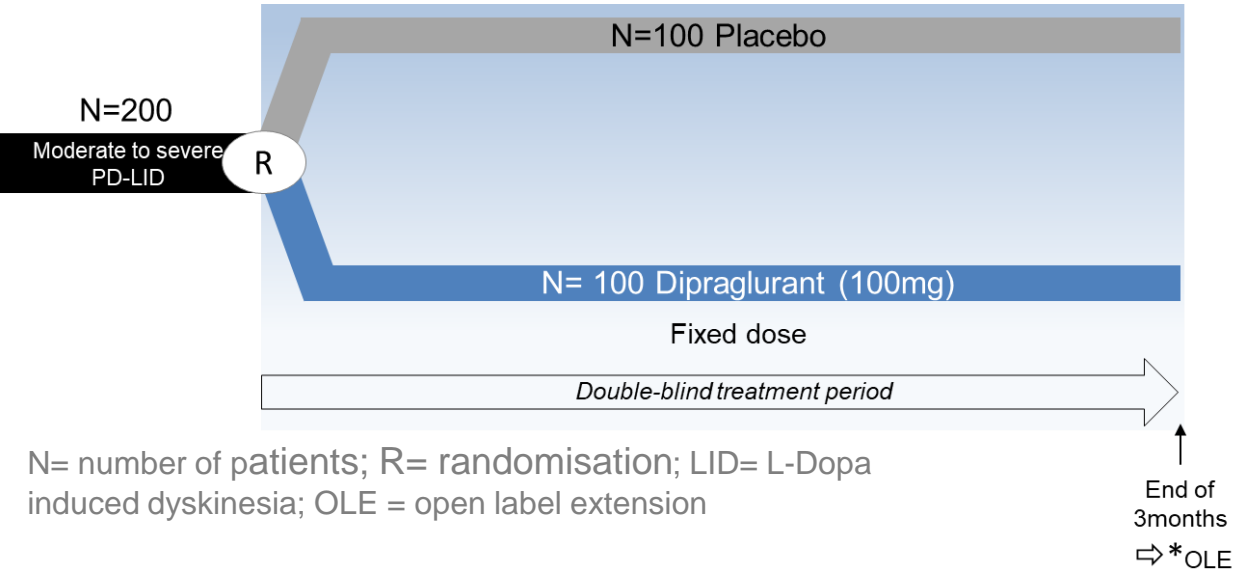
Phase 3 Trial on track to start q4 2019

- The Phase 3 trial is fully funded and expected to report out in Q3 2021
- Considering Fast-Track and/or Breakthrough Therapy applications after first pivotal study readout
- Management of placebo response is a priority:

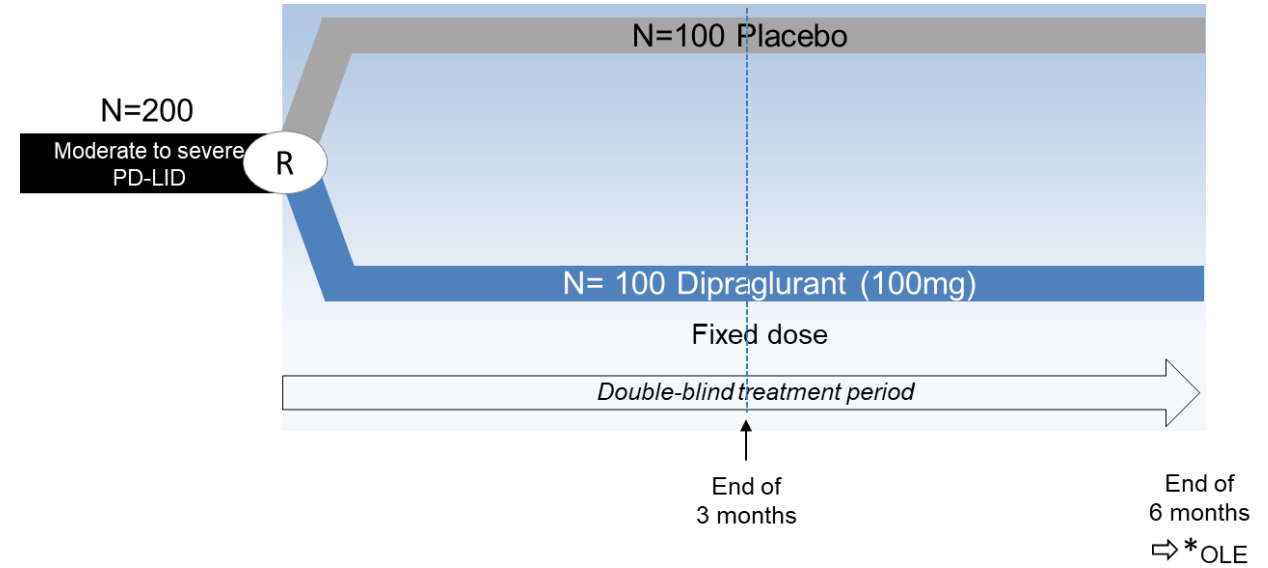
Objective	Strategy
Minimize rater variability (across and within sites)	➤ Use independent (centralized) raters
Reduce expectancy bias	➤ Raters blinded to visit and do not rate the same patient at baseline and study endpoint
Exclude patients with minimal symptoms (as more likely to respond to placebo)	➤ Ensure that symptom score reflects moderate to severe symptoms that warrant therapy ➤ Ensure occur frequently enough for scale sensitivity
Exclude potential investigator rating inflation	➤ Independent oversight of screening and use of centralized rater baseline visit score as study entry gate
Draw placebo response ahead of randomization	➤ Consider non-pharmacologic intervention during screening period
Ensure no geographic bias	➤ Only include countries / sites where centralized rating is feasible

Dipraglurant pivotal registration studies

1st Pivotal LID Study (301)



2nd Pivotal LID Study (302)



The Primary and Secondary endpoints for both trials are the same:

■ Primary objective

efficacy in reducing LID

- ✓ Change over time in UDysRS (wk13 from baseline)

■ Secondary objectives

(Safety & tolerability, additional efficacy parameters, PK)

- ✓ Change over time in MDS-UPDRS Part III (Clinician-scored monitored motor evaluation)
- ✓ Patient diaries, on & off time
- ✓ CGI-S
- ✓ Pharmacokinetics (PK)
- ✓ Safety and tolerability

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 with 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

Exciting Preclinical Pipeline

GABA_B PAM Program for Charcot-Marie-Tooth 1A Neuropathy

- Rationale :
 - 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)
 - Clinical efficacy in Charcot-Marie-Tooth type 1A (CMT1A)
 - Positive Allosteric Modulator (PAM) is a differentiated pharmacological approach
 - Preclinical validation of efficacy of ADX71441 in rodent model of CMT1A
 - Potential safety and efficacy advantages – lack of tolerance and less side effects
- Status:
 - Lead optimization ongoing – progressing towards IND-enabling studies
 - Novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds
 - Significant novel IP in the field

mGlu7 PAM Program for PTSD & Hearing Loss

- Rationale :
 - Based on mGlu7 receptor knockout mice phenotype & mGlu7 receptor pharmacological inhibition studies, negative allosteric modulators show strong potential for anxiety related disorders such as PTSD
 - In addition, other potential indications include pain, neuroprotection, schizophrenia, ADHD, age-related hearing impairment, tinnitus...
- Status:
 - Late lead optimization – progressing towards IND-enabling studies
 - Two main chemical series with potent, selective, orally bioavailable and brain penetrant compounds
 - Preclinical proof-of-concept efficacy in rodent PTSD model; inner ear studies ongoing
 - Significant novel IP in the field

mGlu2 NAM Program for Mild Cognitive Impairment

- Rationale :
 - Potential to treat medical conditions linked to lowered glutamate levels in the brain via restoration of a normalized glutamatergic tone
 - Alzheimer's Disease (AD) : cognitive deficits and possible disease-modifying effect (slowing disease progression via reduction of build-up of amyloid β induced by mGluR2 activation (Kim et al) and reducing chromogranin A-induced microglial neurotoxicity (Taylor et al)
 - Major Depressive Disorder: ketamine-like antidepressant efficacy in depressed patients whilst avoiding the NMDA associated negative effects of ketamine.
- Status:
 - Late lead optimization – 12 month program leading to IND-enabling studies
 - Several novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds
 - Significant novel IP in the field

mGlu4 PAM Program for Parkinson's Disease

- Rationale :
 - Novel non-dopaminergic approach to treat Parkinson's disease with potential to treat both motor and non-motor symptoms, disease modifying neuroprotective potential:
 - Motor functions: in acute and chronic preclinical models of PD, mGluR4 PAM demonstrated improvement
 - Neuroprotection: effect in MPTP mice model demonstrated with mGluR4 PAM
 - Non-motor (anxiety): mGluR4 activators demonstrated anxiolytic-like response in preclinical rodent models
 - Potential to treat a broad range of debilitating autoimmune disorders linked to aberrant TH17 responses, including rheumatoid arthritis, psoriasis, inflammatory bowel disease and uveitis
 - Raised interest in field following recent acquisition of Prexton Therapeutics by Lundbeck
- Status:
 - Late lead optimization – progressing towards IND-enabling studies
 - Several novel chemical series with potent, selective, orally bioavailable and brain penetrant compounds with significant novel IP potential

mGlu3 PAM Program for Neurodegenerative Diseases

- Rationale :
 - Novel mechanism of action for treatment of neurodegenerative disorders & schizophrenia
 - Strong rational and preclinical validation through:
 - Schizophrenia: studies demonstrate GRM3 gene variants association; mGlu3 receptor KO mice exhibit a “schizophrenia-like” phenotype
 - Neurodegenerative diseases: demonstrated neuroprotective effects, with “dual” action: reduction of glutamate release, potentially lowering excitotoxic insult; and stimulation of production of growth factors such as GDNF & TGF β 1
- Status:
 - Lead generation stage
 - Several novel chemical series identified from internal screening of corporate library with proprietary screening tools – two series prioritized
 - Most potent and selective mGlu3 PAMs ever described – first in class potential
 - Significant novel IP in the field

TrkB PAM Program for Neurodegenerative Diseases

- Overview :
 - TrkB is the receptor for BDNF (brain-derived neurotrophic factor)
 - TrkB activation is 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

Financials

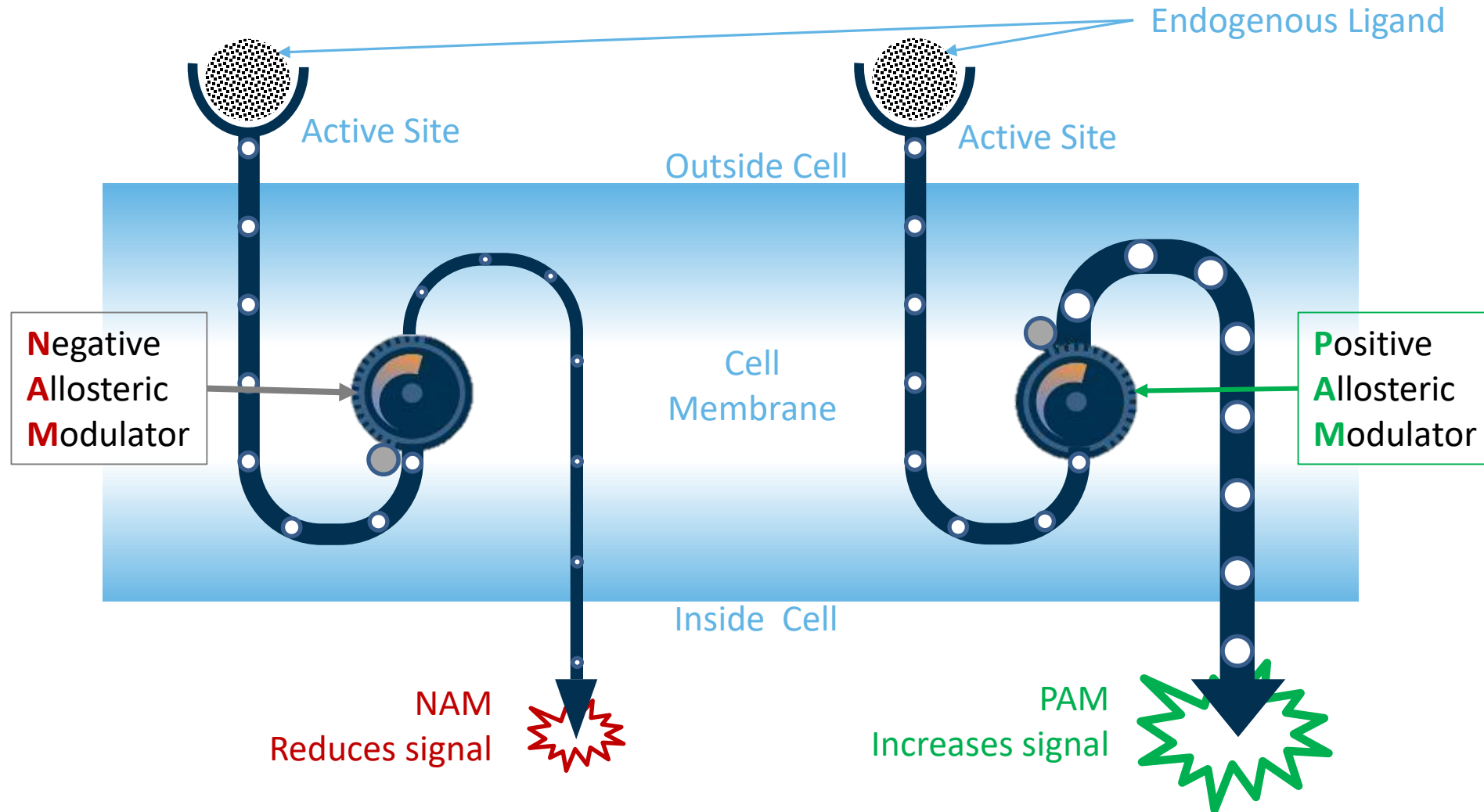
Financials and Stock

- Cash runway through 2021
 - Cash of CHF41.7M at 31 December 2018
 - Fully funded through dipraglurant study 301 readout
- 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
- Market capitalization: approx. CHF50M
- No debt

Upcoming Major Development Milestones

Milestone	Timing
Dipraglurant – LID Phase 3 Registration Program	
Complete manufacturing of Drug Product	Q3 2019
Study 301 – start dosing	Q4 2019
Study 301 – Top line data	Q3 2021

What are Allosteric Modulators?



Addex is based on a world leading technology platform



ALLOSTERIC MODULATORS FOR HUMAN HEALTH

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