



Innovative Treatments for Central Nervous System Disorders

January 2020

Allosteric modulators for human health

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Addex Overview

Dipraglurant for dyskinesia in Parkinson's disease

- Pivotal registration program on track to dose patients in Q1 2020
- 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

Leading proprietary technology platform

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

Pipeline of in house discovered programs

- Innovative drug candidates for well validated targets
- Creating future partnership opportunities
- Driving long term growth

Strong balance sheet

- 32.8M shares traded on the SIX Swiss Stock Exchange – ADXN
- Filed registration statement with SEC for Nasdaq listing
- Cash of CHF36.7M at 30 June 2019 - Runway through 2021

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 Pyschosis
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

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In House Discovered Pipeline

Molecule / MoA	Indication	Partner	Pre-clinical	Phase 1	Phase 2	Phase 3	Milestone
Dipraglurant-IR (mGlu5 NAM)	PD-L1D		▶				Top line data Q3 2021
Dipraglurant-ER (mGlu5NAM)	Dystonia		▶				
ADX71149 (mGlu2 PAM)	Epilepsy		▶				
GABA _B PAM	Addiction		▶				
	CMT1A		▶				
mGlu7 NAM	Post-traumatic stress disorder		▶				
mGlu2 NAM	Mild neurocognitive disorders		▶				
mGlu4 PAM	Parkinson's disease		▶				
mGlu3 PAM	Neurodegenerative disorders		▶				

Lead Program Entering US Pivotal Study and Multiple Orphan Drug Opportunities

Dipraglurant in Parkinson's Disease

The Dipraglurant Opportunity in Dyskinesia associated with PD

Clear development & regulatory path

- Pivotal studies on track to dose patients in Q1 2020
- 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

- In house discovered, selective, orally available small molecule mGlu5 NAM
- PK profile mirrors that of L-dopa, making it ideal to treat LID
- Inhibits hyperglutamatergic state 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

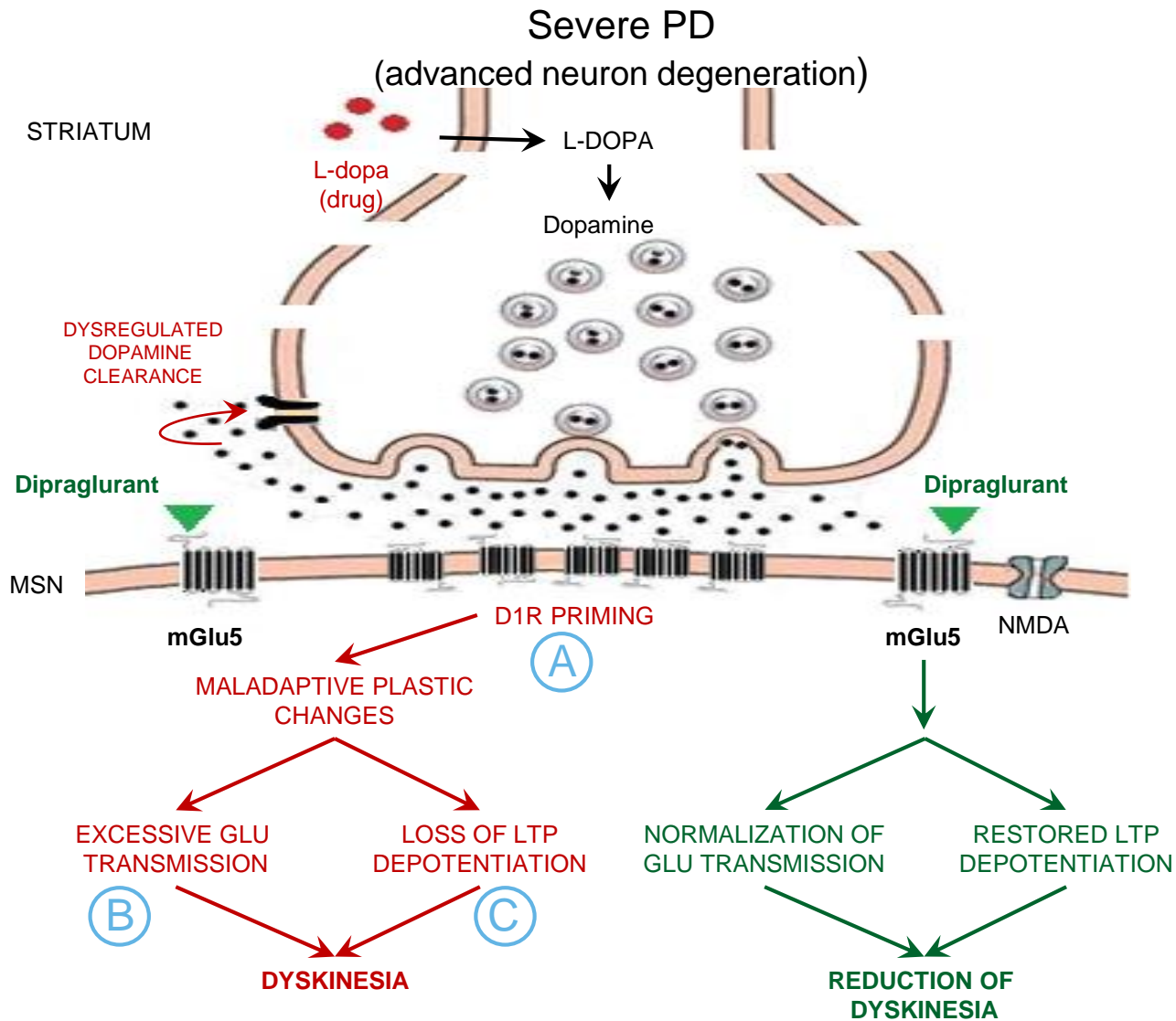
Prevalence of LID is related to disease duration

- 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

Physicians are 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

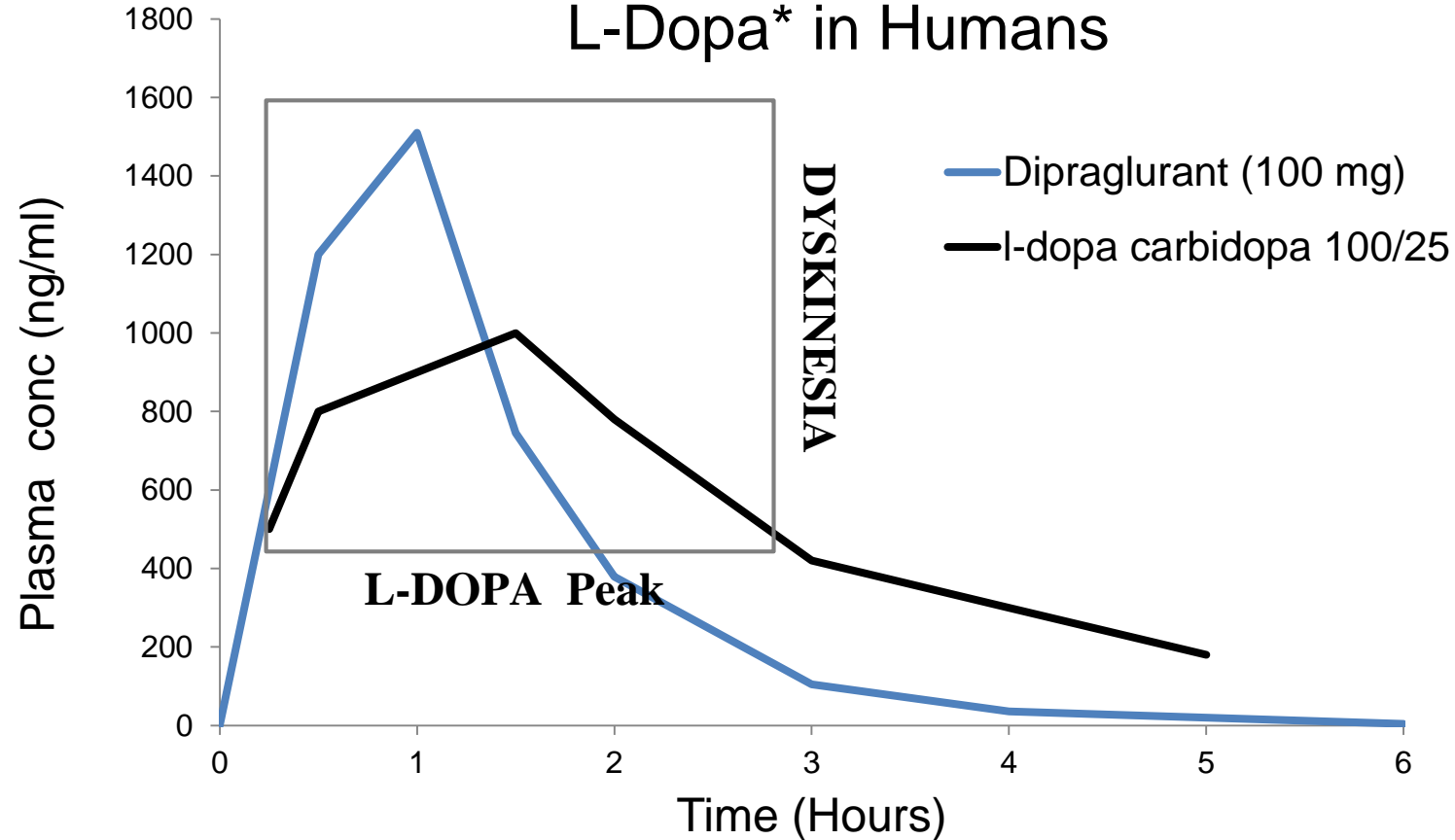
Dipraglurant - Overview and Mechanism of Action



- 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) *Excess 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 mGlu5 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

Pharmacokinetic Profile of Dipraglurant and L-Dopa* in Humans

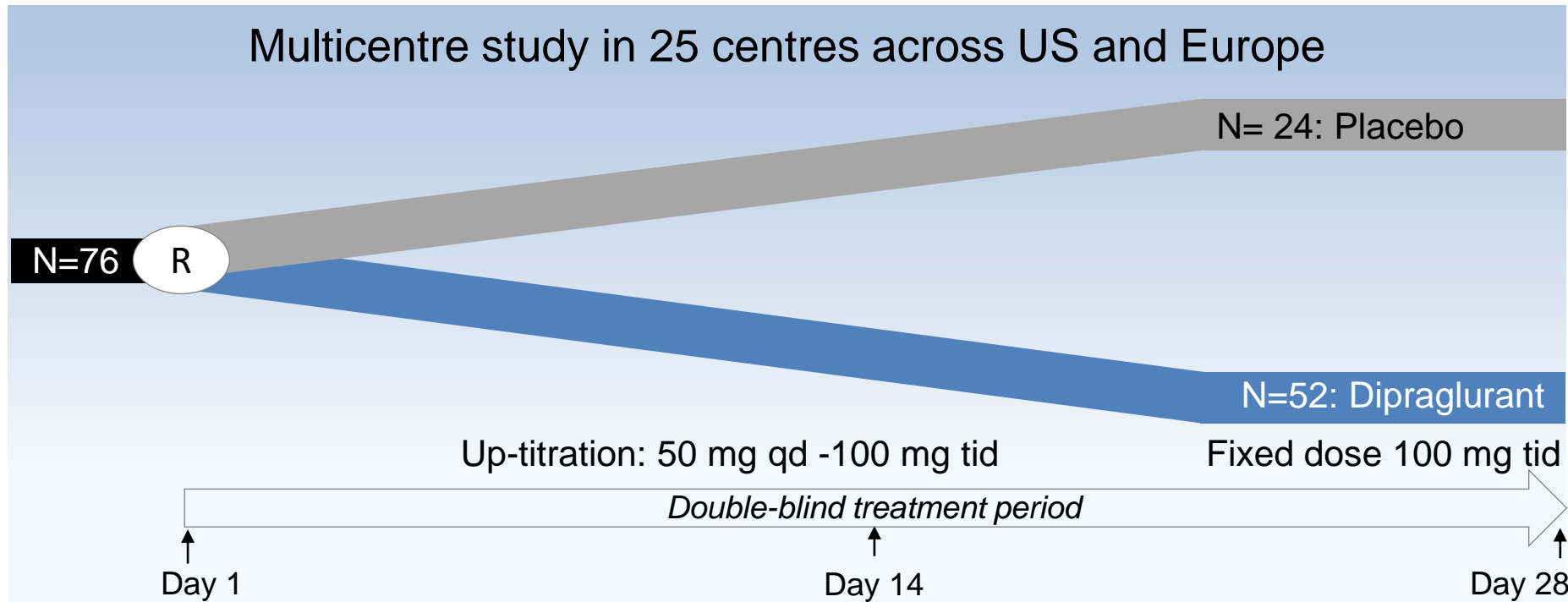


- Dyskinesia symptoms are correlated to peak levels of levodopa therapy
- PK profile of dipraglurant mirrors that of levodopa
- **Dipraglurant inhibits abnormal glutamate stimulation during peak levodopa dose but releases the receptor during normal glutamate activity**

PK profile differentiates dipraglurant from other treatments

Dipraglurant EU and US Phase 2a Study in LID

Multicentre study in 25 centres across US and Europe

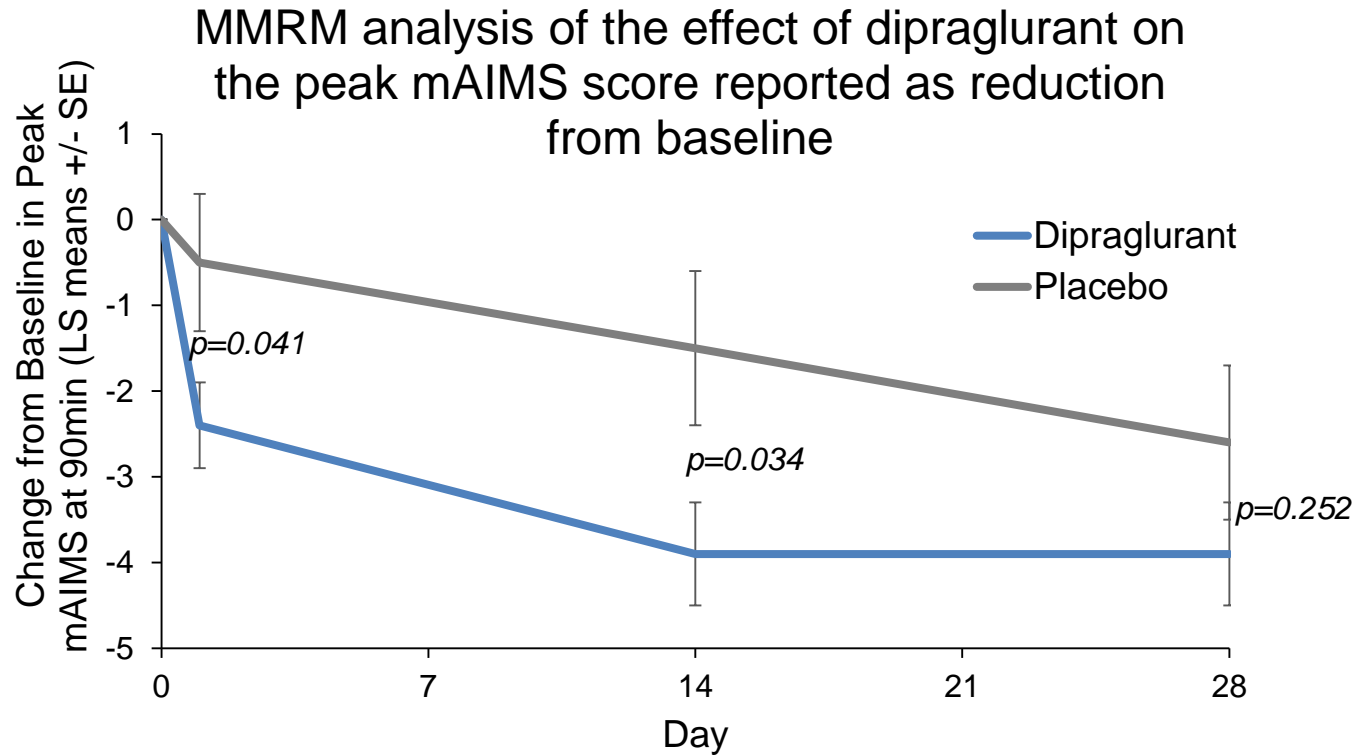


- **Primary objective:** safety & tolerability
- **Secondary objective:** exploratory efficacy:
 - Modified Abnormal Involuntary Movement Scale (mAIMS) on Day 1, 14 and 28
 - Unified Parkinson’s Disease Rating Scale (UPDRS)
 - Clinician and Patient Global Impression of Change (CGIC & PGIC)
 - Pharmacokinetics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

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

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 resulted in significance being lost 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

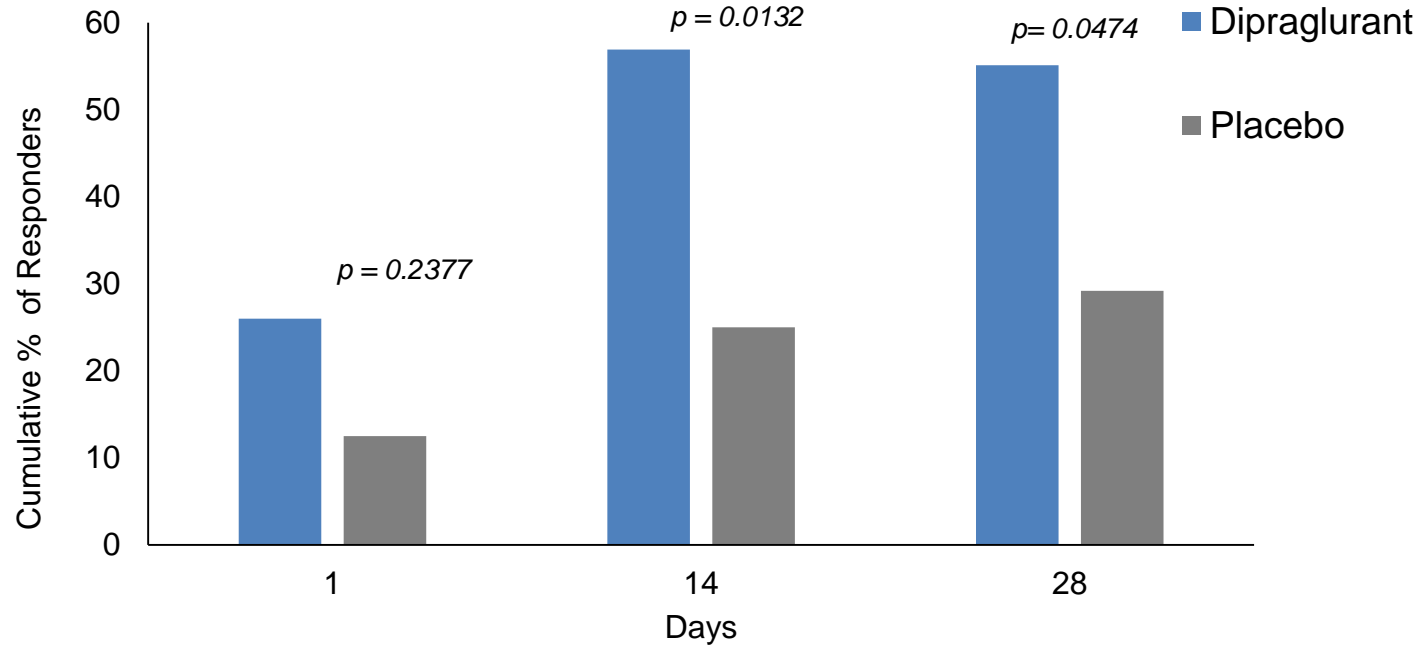
Mean % change of peak mAIMS from baseline

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

Responder Analysis Demonstrates Dipraglurant Significant Benefit

Dipraglurant cumulative % of PD-LID patients showing $\geq 30\%$ change of peak mAIMS from baseline



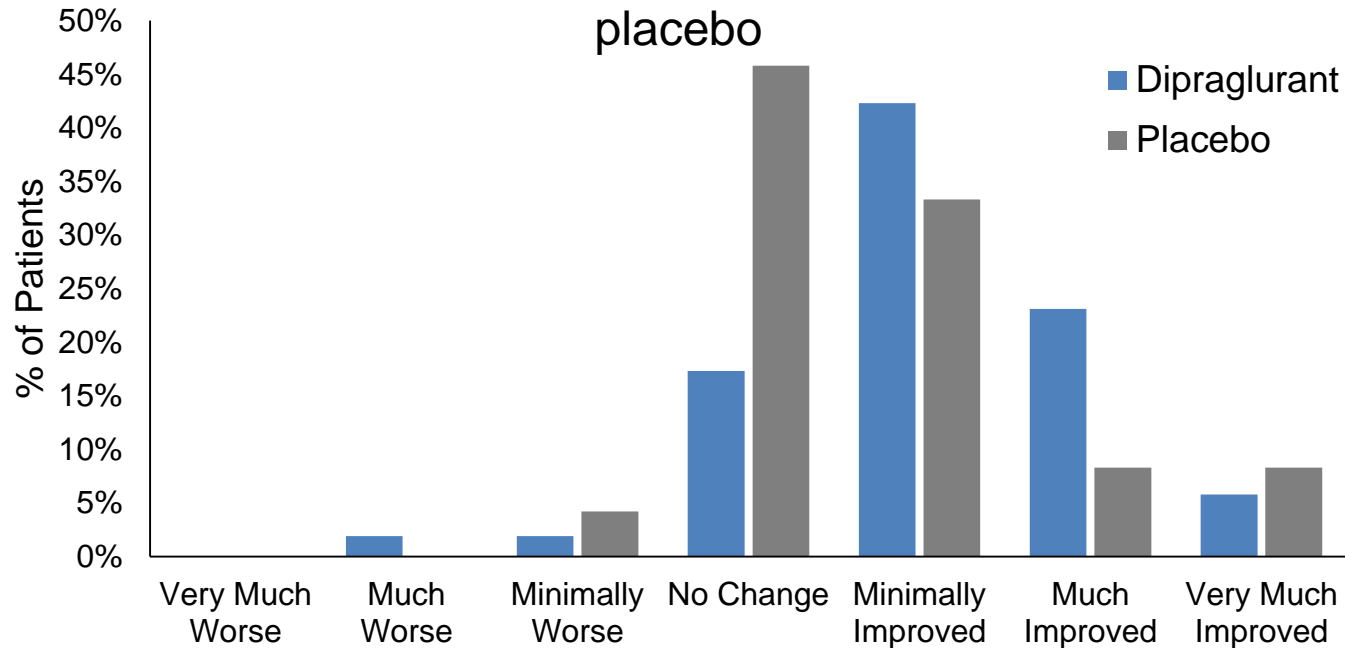
- A 30% reduction in mAIMS
 - One patient was able to hold & read a newspaper for the first time in years
 - Another patient had improved speech and became more easily intelligible

Responder analysis reinforces robustness of dipraglurant anti dyskinetic effect

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	55.1%	n=7	29.2%	0.0474

Clinician Rated Global Impression of Change - Dyskinesia

Clinician rated global impression of change in LID patients after administration of dipraglurant and placebo



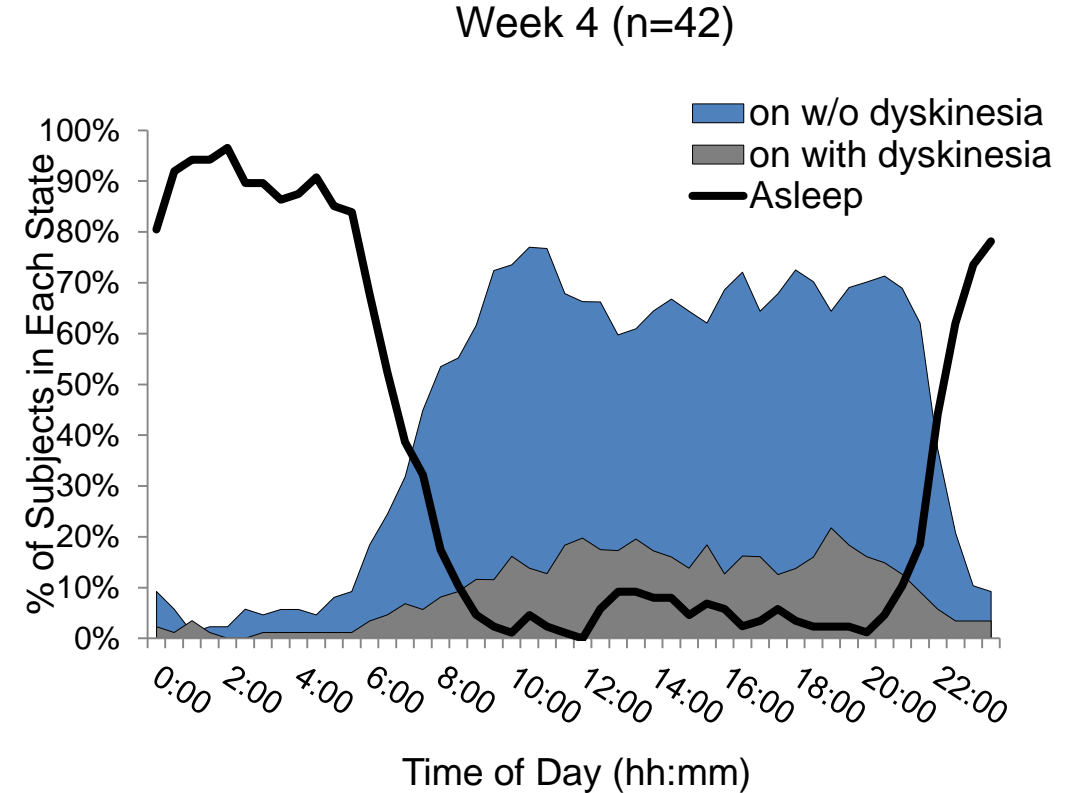
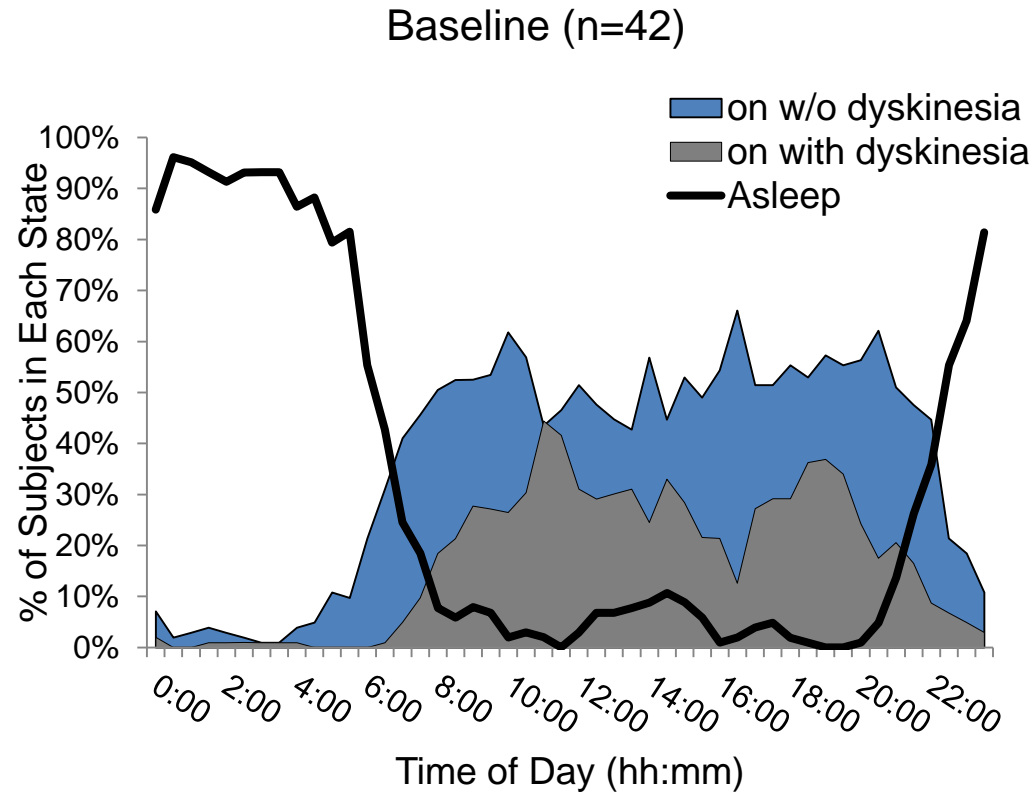
- Relatively simple scale that reflects everyday clinical practice
- Assessment by treating physician and thus is a more objective assessment than the more subjective mAIMS
- Assessment performed at end of study compared to baseline

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

Improvement in dyskinesia with dipraglurant according to clinicians (p<0.05)

Patient Diaries – Improvement Throughout the Waking Day

Pattern of motor complications of dipraglurant patients over the course of a day, as reported in patients' diaries



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 Demonstrated Good Safety and Tolerability in PD Patients

- Adverse events were common in both treatment groups (dipraglurant 88.5%, placebo 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)

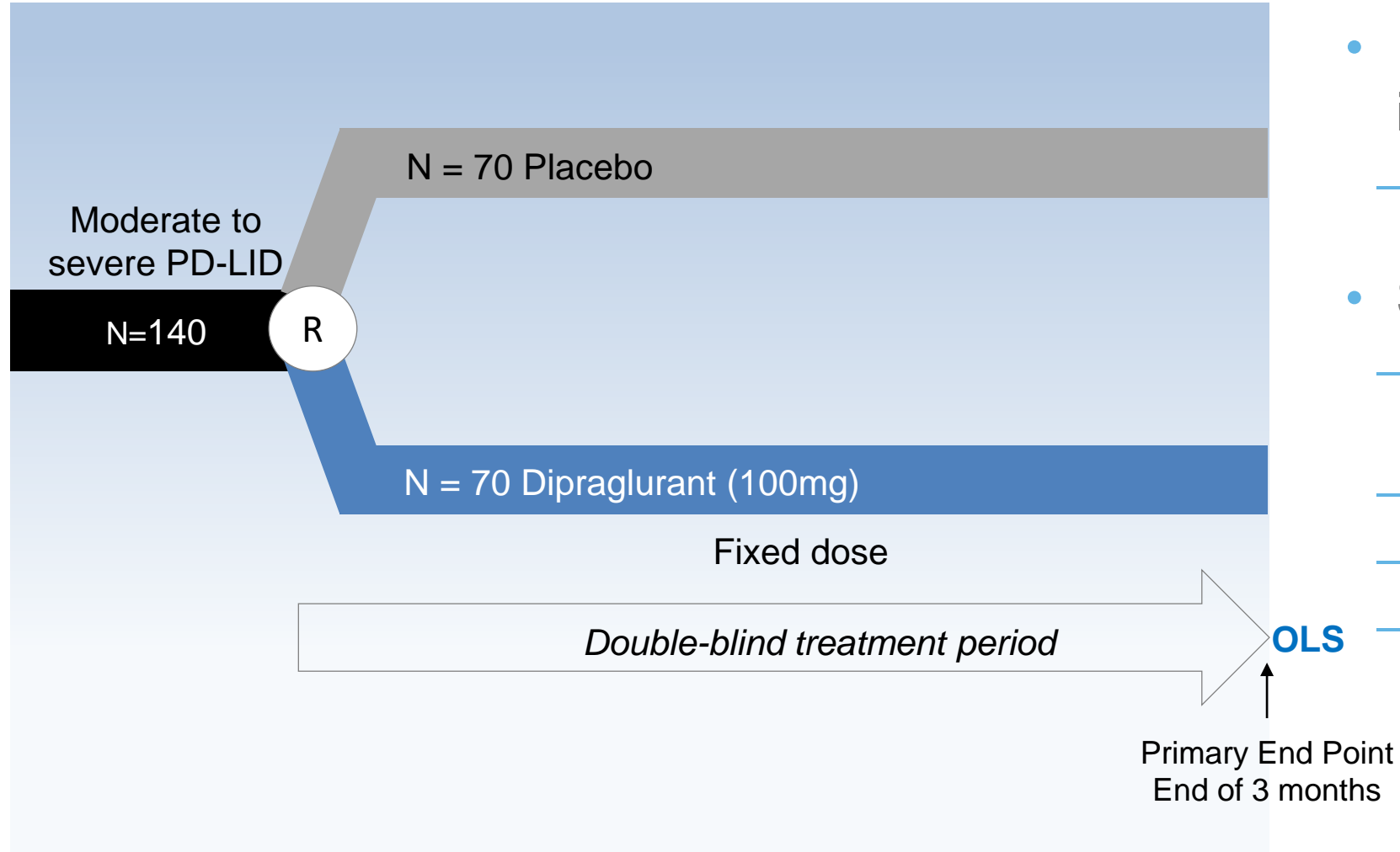
Safety profile suitable for continued development in PD (KOLs and DSMB)

Dipraglurant PD-L1D Registration Program Started

- Manufacturing of drug product completed
- First pivotal registration trial on track to start dosing patients in Q1 2020
 - Fully funded and expected to report out in Q3 2021
- Primary endpoint: UDysRS – more sensitive to treatment effect than mAIMS (Goetz, 2008) and less prone to placebo response (Goetz, 2013)
- Implementing measures to manage placebo response is a priority
- Considering Fast-Track and/or Breakthrough Therapy applications after first pivotal study readout

Dipraglurant First Pivotal PD-LID Study (301)

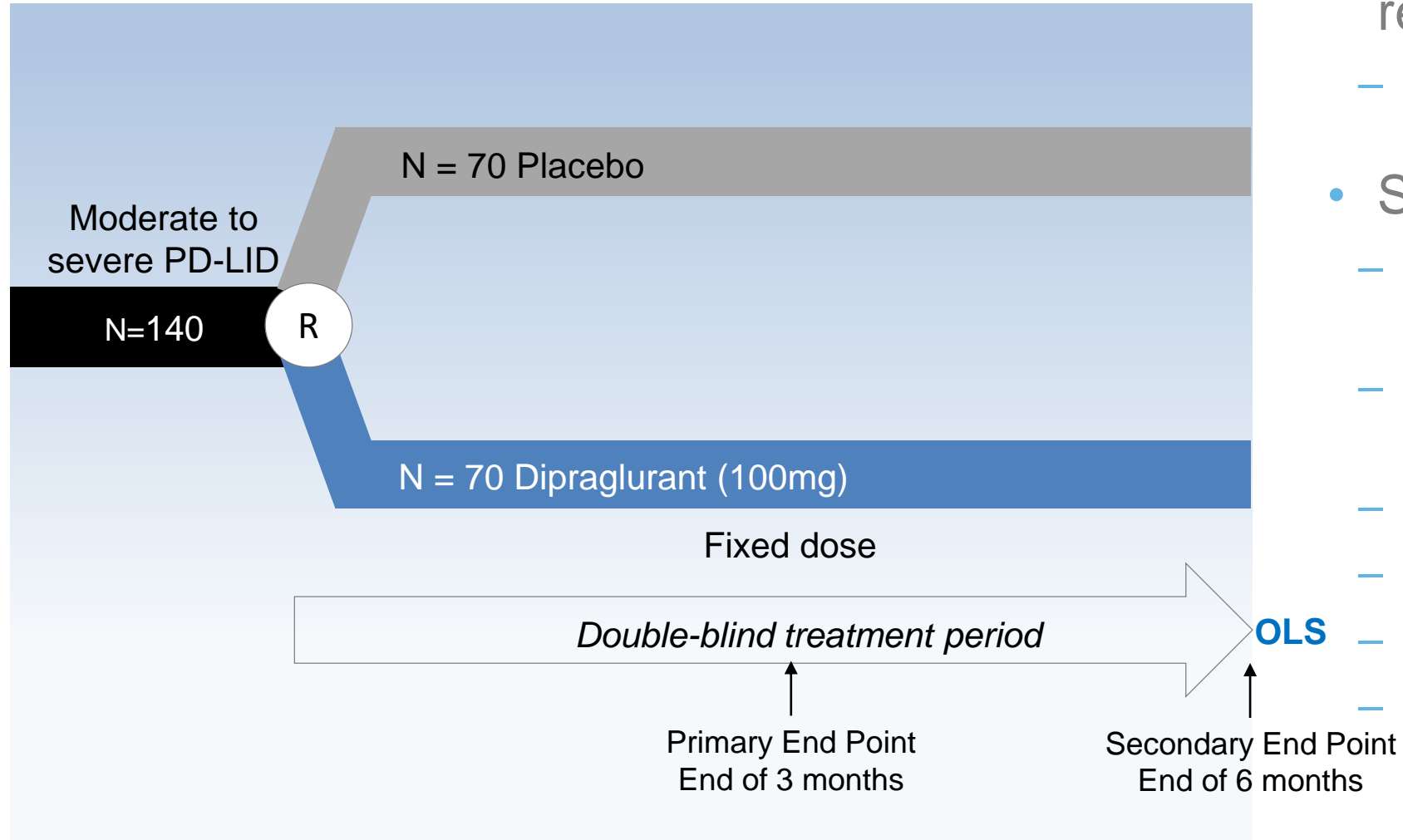
Study Design



- Primary objective is efficacy in reducing LID
 - Change over time in UDysRS at 3 months
- Secondary objectives
 - Change over time in MDS-UPDRS Part III
 - Patient diaries, on & off time
 - CGI-S
 - Safety and tolerability

Dipraglurant Confirmatory Phase 3 PD-LID Study (303)

Study Design



- Primary objective efficacy in reducing LID
 - Change over time in UDysRS at 3 months
- Secondary objectives
 - Change over time in UDysRS at 6 months
 - Change over time in MDS-UPDRS Part III
 - Patient diaries, on & off time
 - CGI-S
 - Pharmacokinetics (PK)
 - Safety and tolerability

Dipraglurant LID Opportunity

Limited competition – only one FDA approved medicine

- > 170K LID patients in US
- ~\$1.4bn US market opportunity for dipraglurant

LID has a large unmet need and market opportunity

- >Gocovri (reformulation of generic amantadine)
 - Approved on 24th August 17, safety profile similar to generic
- Dipraglurant is a highly selective orally available mGlu5NAM
- Improved safety profile & Ideal PK profile mirrors levodopa

Clear development plan with precedented regulatory path

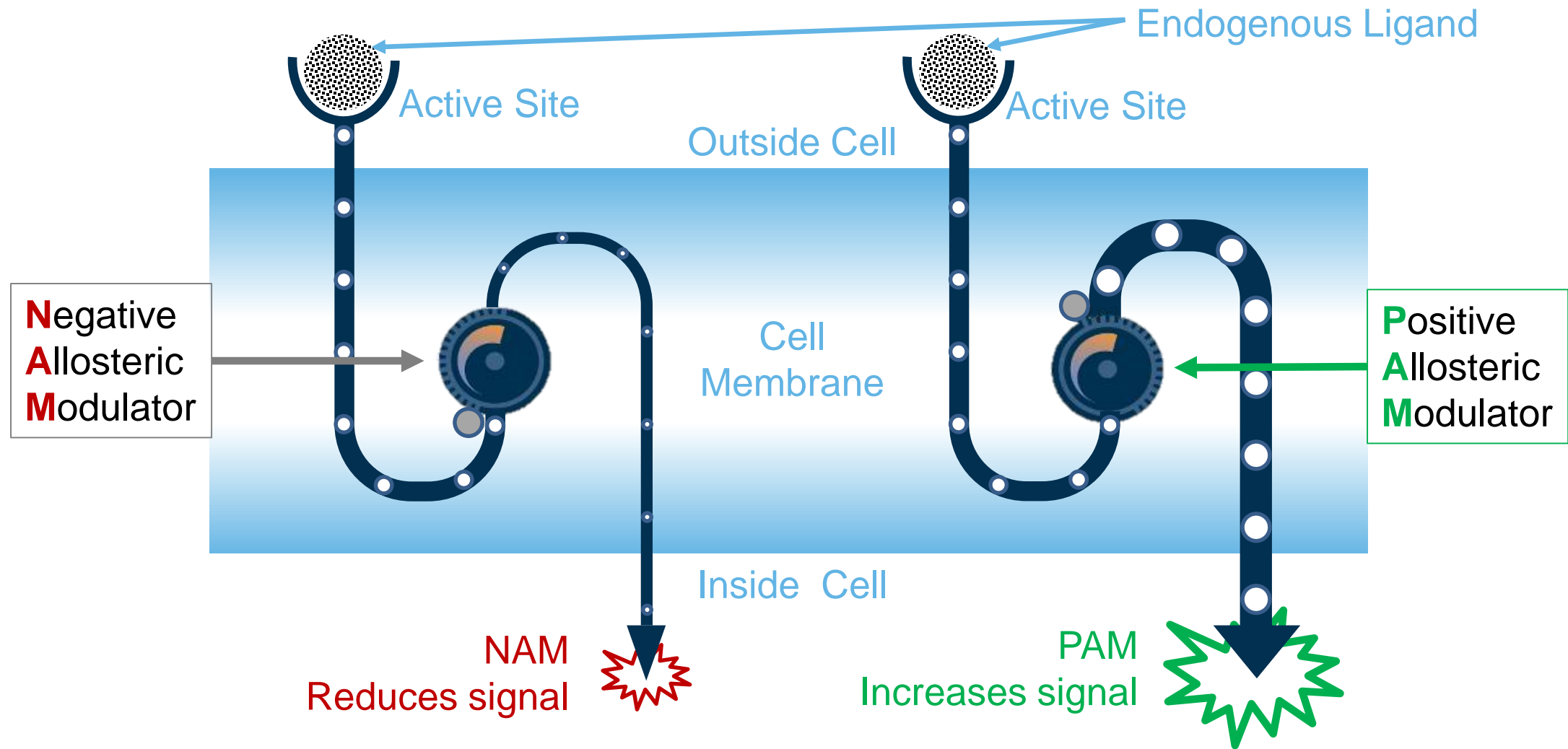
- Precedented regulatory path paved by Gocovri (Adamas)
- Two registration trials (301 and 303) with Open Label Study (302)
- Managing placebo response in registration trials is key for success:
 - UDysRS is more sensitive to treatment effect & less prone to placebo response (Goetz 2013)
 - Implementing measures to manage placebo response in registration program

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

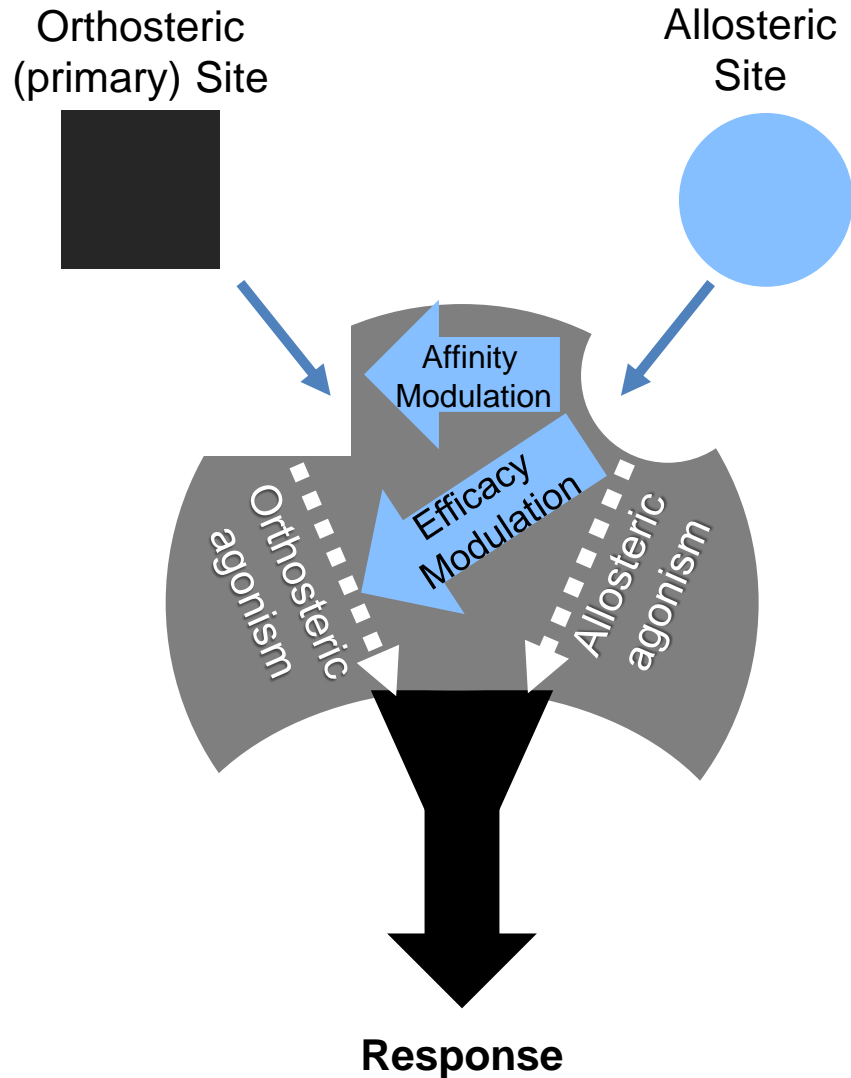
Addex Allosteric Modulation Technology Platform Becoming an Exciting Space

What are Allosteric Modulators?



Addex is based on a leading technology platform

Using Allosteric Modulation to Discover Novel CNS Drug Candidates



Potential benefits

- Novel, orally available drug class
- Superior receptor sub-type selectivity
- Bind to non-competitive sites and therefore potential to address intractable targets
- Re-address well characterized and clinically validated GPCR targets
- Potentially improved safety due to selectivity and modulatory pharmacology
- Potentially superior efficacy over long term due to lack of tolerance from more modulatory pharmacology
- Clinical use in combination with competitive agonists

Addex Platform Already Validated – Indivior Partnership Case Study

The alliance with Indivior focusing on discovery of GABA_B Positive Allosteric Modulators (PAMs) for addiction

- Positive Allosteric Modulator (PAM) is a differentiated pharmacological approach
 - Potential safety and efficacy advantages – lack of tolerance and less side effects
- 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
- Worldwide license and collaboration 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)
- Financial terms:
 - Upfront of USD5 million & USD5.6 million research funding over 2 years
 - USD 330 million of development, regulatory and commercial milestones
 - Tiered royalties up to double-digit

Financials

Financials and Stock

- Cash runway through 2021
 - Cash of CHF36.7M at 30 June 2019
 - Fully funded through dipraglurant study 301 readout
- Market capitalization: approx. CHF45M
- No debt
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- 32,848,635 shares outstanding 44.6M (fully diluted)
 - New Enterprise Associated - 13.91%
 - New Leaf Venture Partners - 4.86%
 - CAM Capital – 4.86%
 - Credit Suisse Asset Management - 4.87%
 - Management & board holds -14% (fully diluted basis)
- Analyst coverage:
 - Van Leeuwenhoek - Marcel Wijma
 - valuationLab - Bob Pooler
 - ZKB - Dr. Michael Nawrath



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