addex Therapeutics

Innovative Treatments for Central Nervous System Disorders

February 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	➢ Traded on the SIX Swiss Stock Exchange under ticker ADXN ➢ ADR representing 6 shares traded on Nasdaq under ticker ADXN ➢ Cash of CHF 31.5M at 31 December 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

Board of Directors

Vincent Lawton
Chairman

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

Ray Hill
Board member

Former Executive Director Merck & Co.

Jake Nunn
Board member

Former Partner New Enterprise Associates

Isaac Manke
Board member

Former Partner New Leaf Venture Partners

In House Discovered Pipeline

Molecule / MoA	Indication	Partner	Pre-clinical	Phase 1	Phase 2	Phase 3	Milestone
Dipraglurant-IR (mGlu5 NAM)	PD-LID						Top line data Q3 2021
Dipraglurant-ER (mGlu5 NAM)	Dystonia						
ADX71149 (mGlu2 PAM)	Epilepsy	janssen					
$GABA_B$ PAM	Addiction	INDIVIOR					
	CMT1A						
mGlu7 NAM	Post-traumatic stress disorder	eurostars™					
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

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NAM = Negative Allosteric Modulator
PAM = Positive Allosteric Modulator

IR = Immediate Release
ER = Extended Release

Dipraglurant in Parkinson's Disease

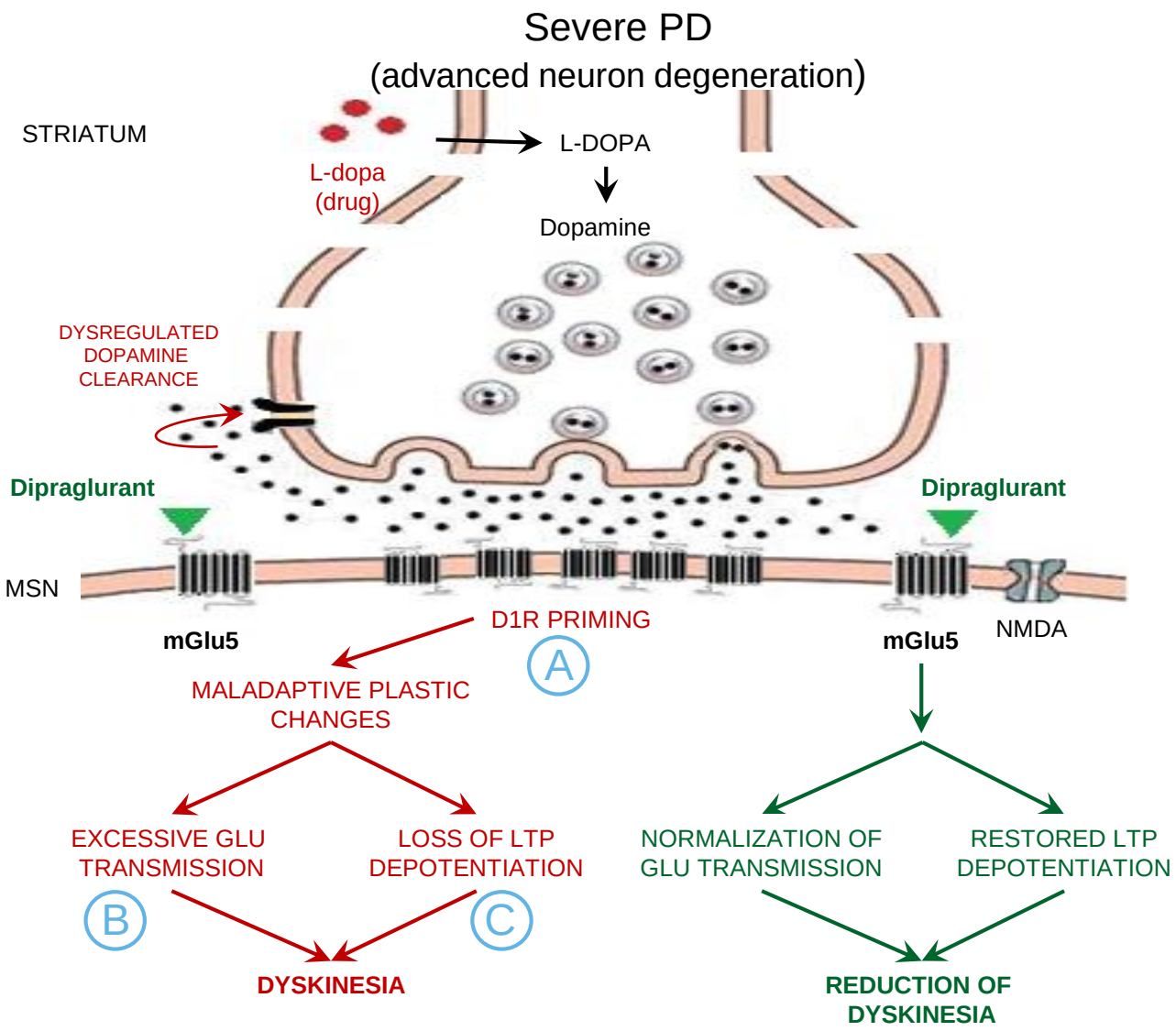
The Dipraglurant Opportunity in Dyskinesia associated with PD

Clear development & regulatory path	➢ Pivotal studies on track to dose patients in Q1 2020 ➢ 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 more than $1.0B ➢ 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 optimized in order to ensure adequate PD symptom control**

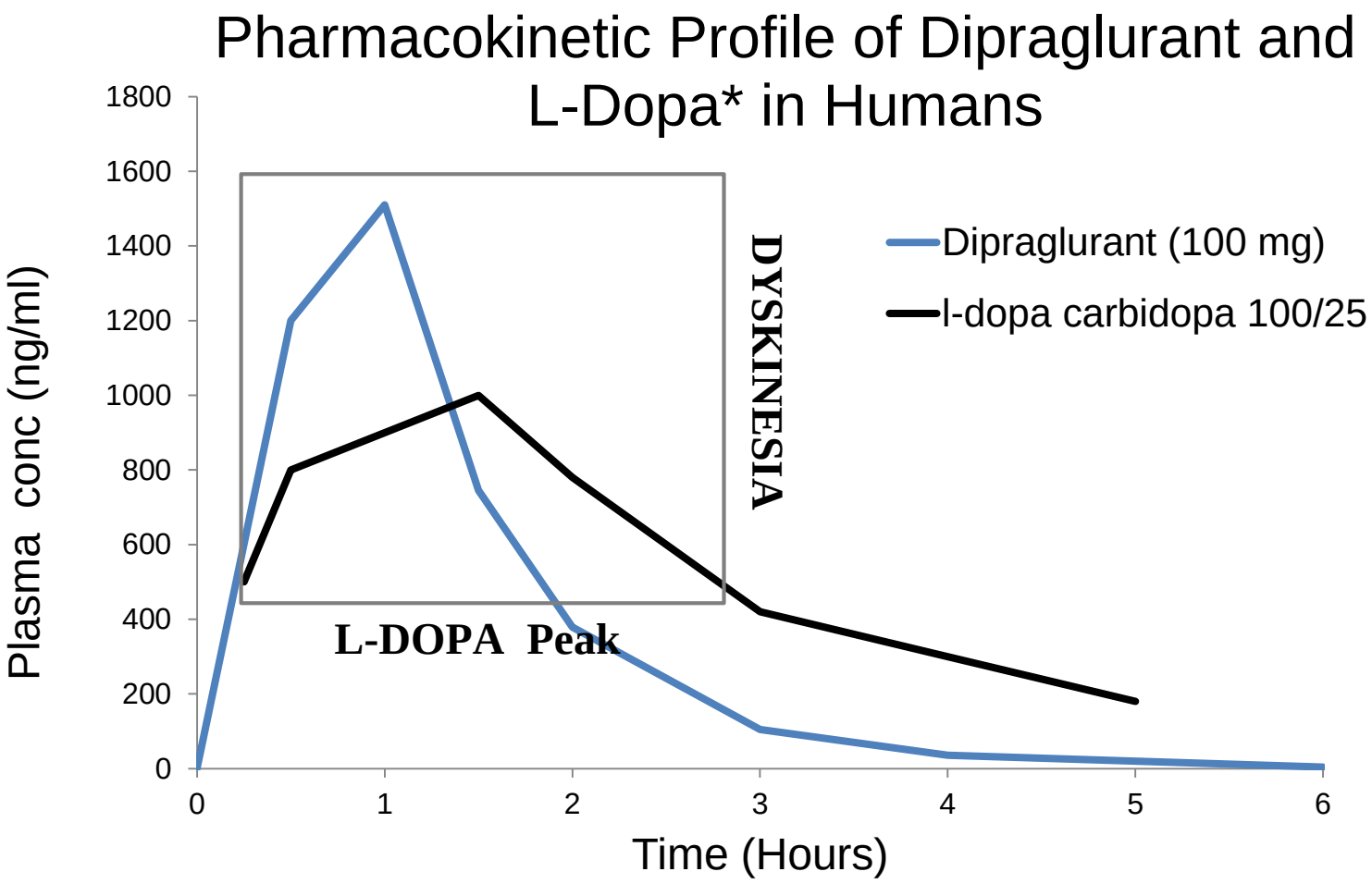
Dipraglurant - Overview and Mechanism of Action



- Loss of substantia nigra neurons combined with the non-physiological, pulsatile stimulation of dopamine receptors with L-Dopa 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**

LTP = Long Term Potentiation
MSN = Medium Spiny Neurons

Dipraglurant PK is a Key Advantage for Treating LID

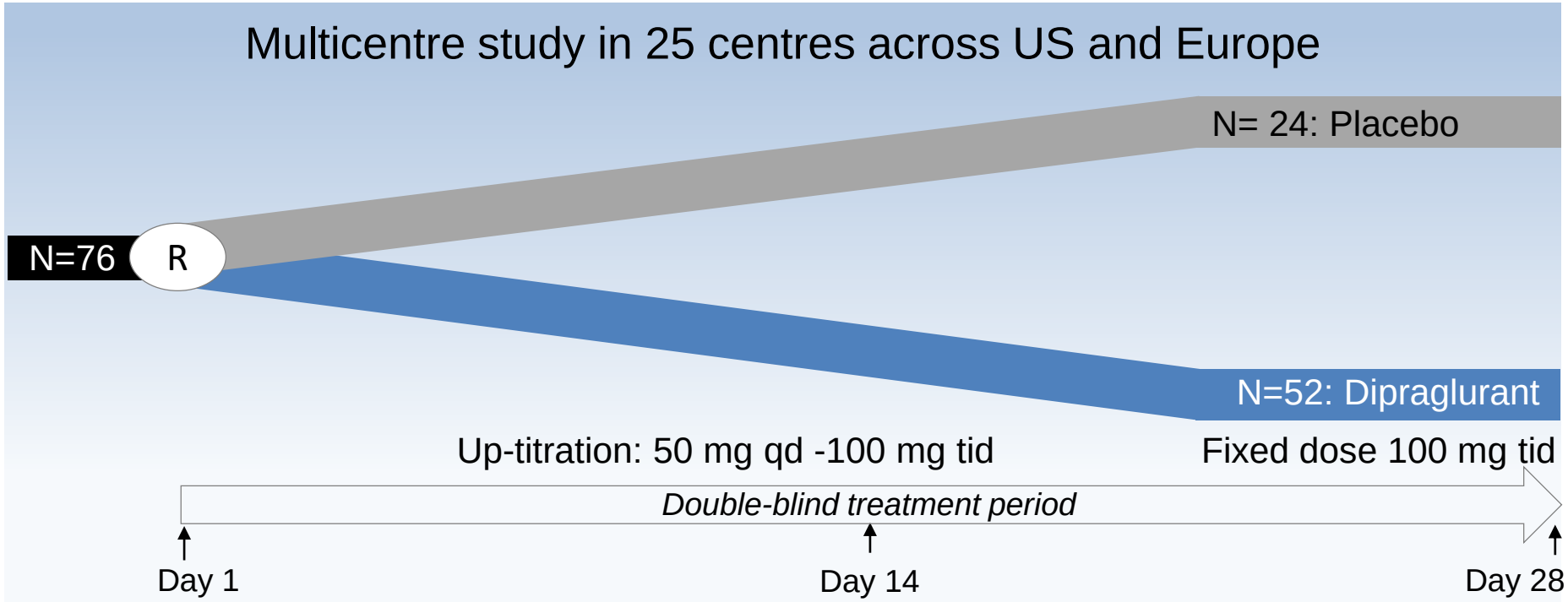


- Dyskinesia symptoms are correlated to peak levels of levodopa therapy
- PK profile of dipraglurant mirrors that of levodopa
- **Dipraglurant inhibits abnormal glutamate stimulation during peak levodopa dose but releases the receptor during normal glutamate activity**

PK profile differentiates dipraglurant from other treatments

* Clinical Neuropharmacology Vol 22 No.1 pp.24-29

Dipraglurant EU and US Phase 2a Study in LID



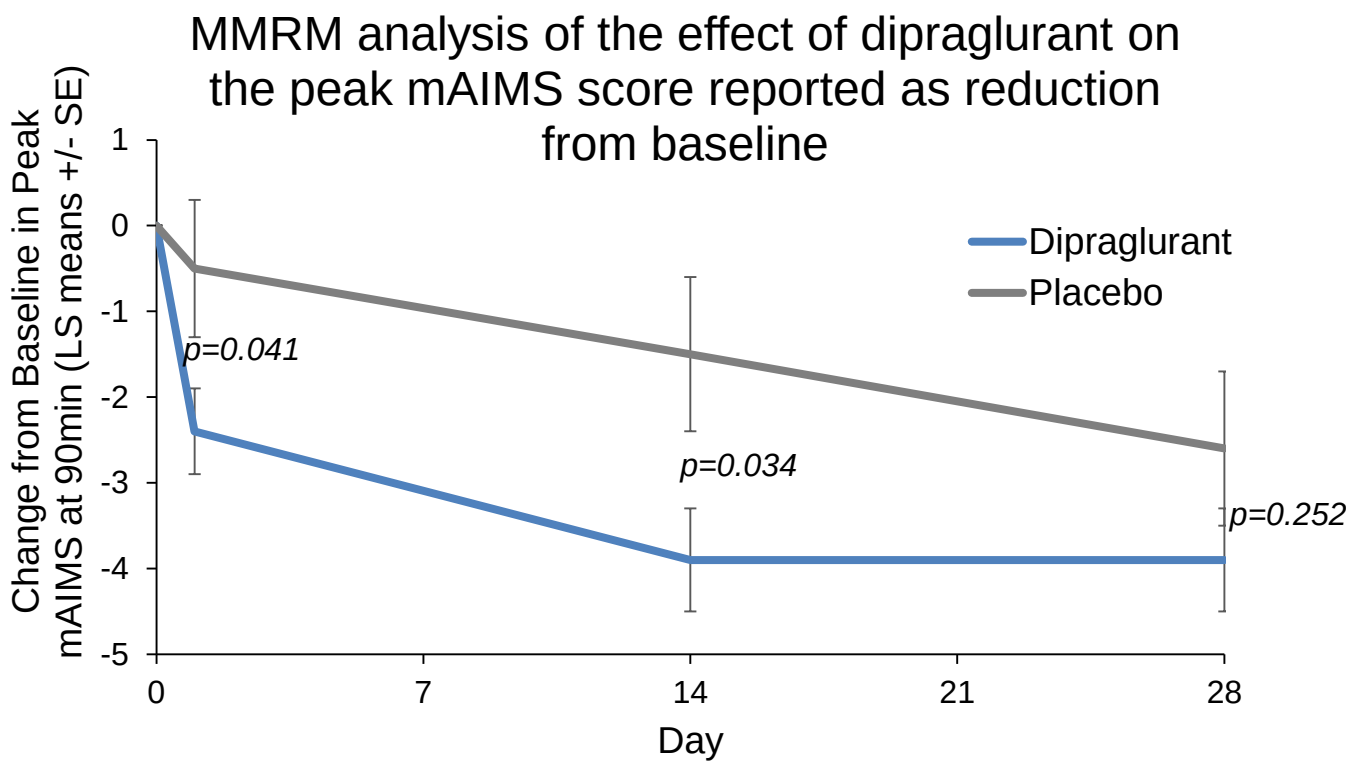
Days		1-3	4-7	8-13	14-16	17-21	22-28
Dose/mg	AM			50	50	50	100
	Noon	50	50	50	100	100	100
	PM		50	50	50	100	100
	Daily	50	100	150	200	250	300

- **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 Global Impression of Change (CGIC)
  - Pharmacokinetics (PK)
  - Patient diaries of "On" & "Off" time

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

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

Dipraglurant Reduces LID Severity by 30%

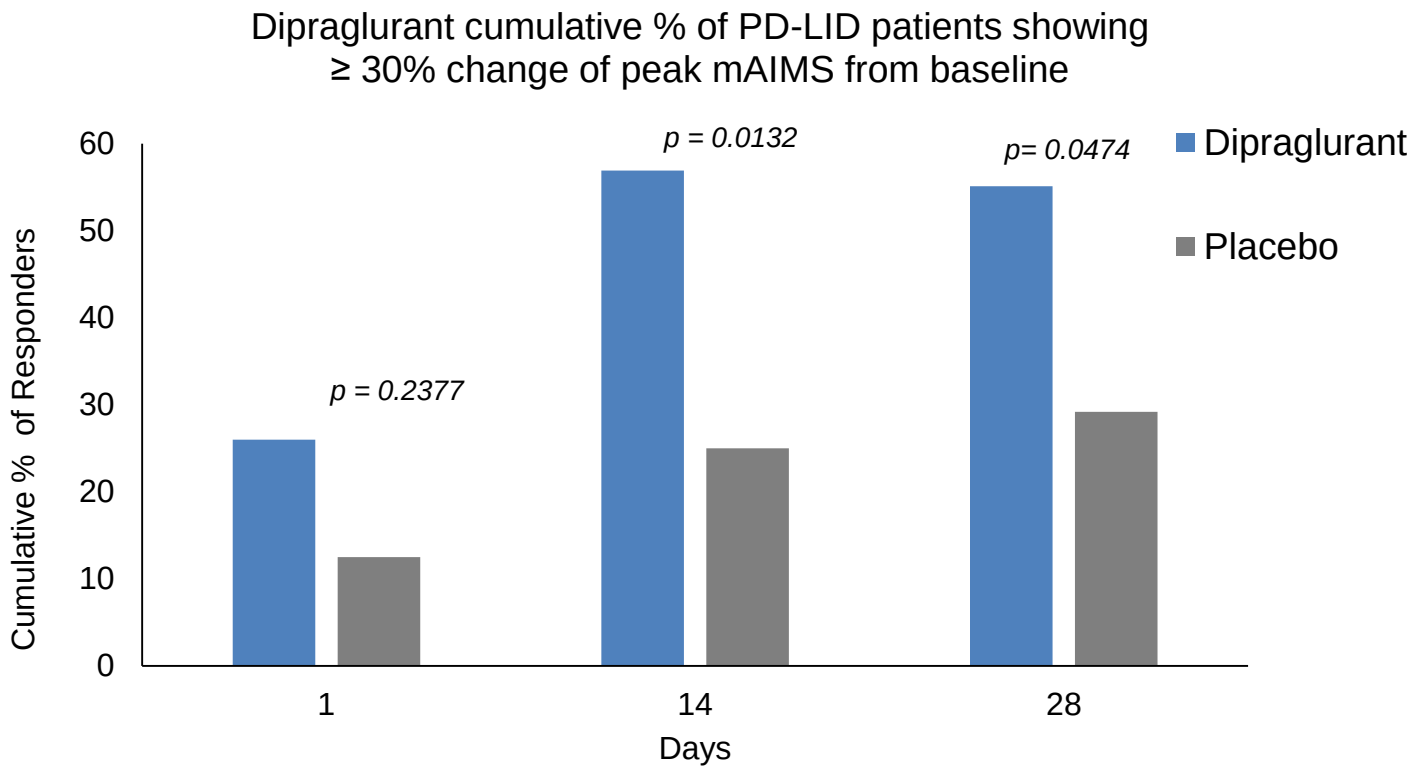


Mean % change of peak mAIMS from baseline		
Midday dose	Dipraglurant	Placebo
Day 1 (50 mg)	19.9%	4.1%
Day 14 (100 mg)	32.3%	12.6%
Day 28 (100 mg)	31.4%	21.5%

- 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

Clear dose response but need to manage placebo

Responder Analysis Demonstrates Dipraglurant Significant Benefit



Responder analysis (≥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

- 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

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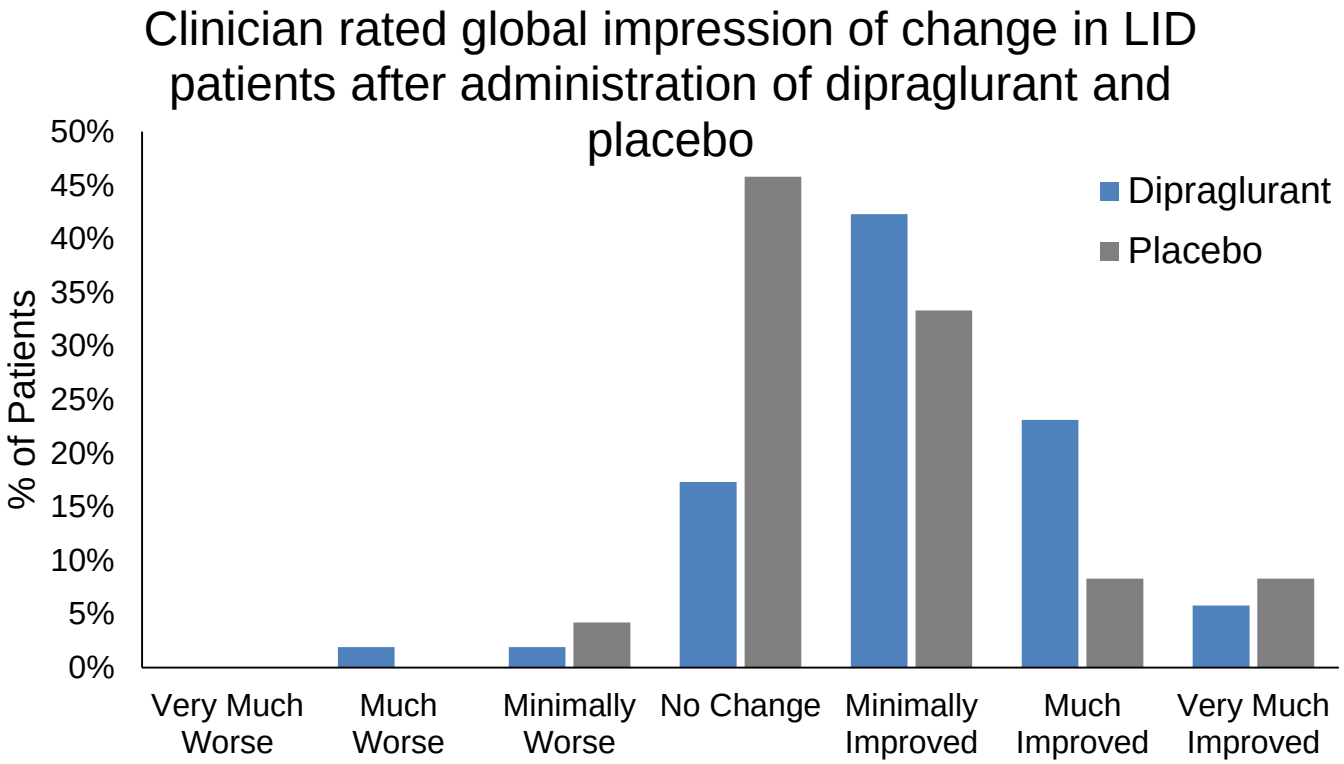
Clinician Rated Global Impression of Change - Dyskinesia



- 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

	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)

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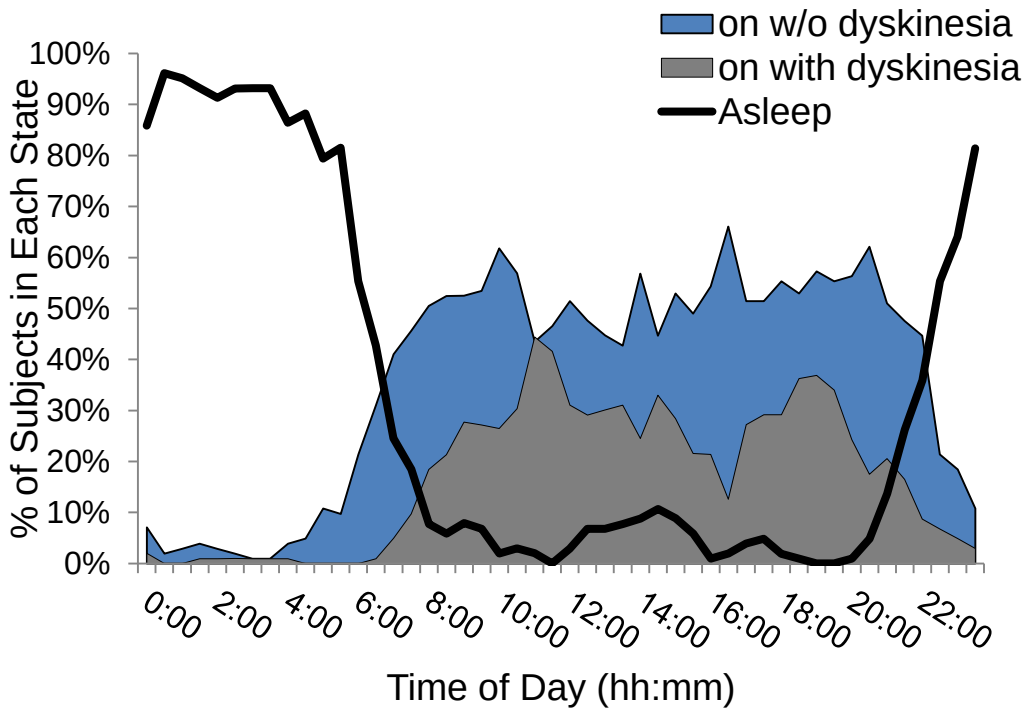
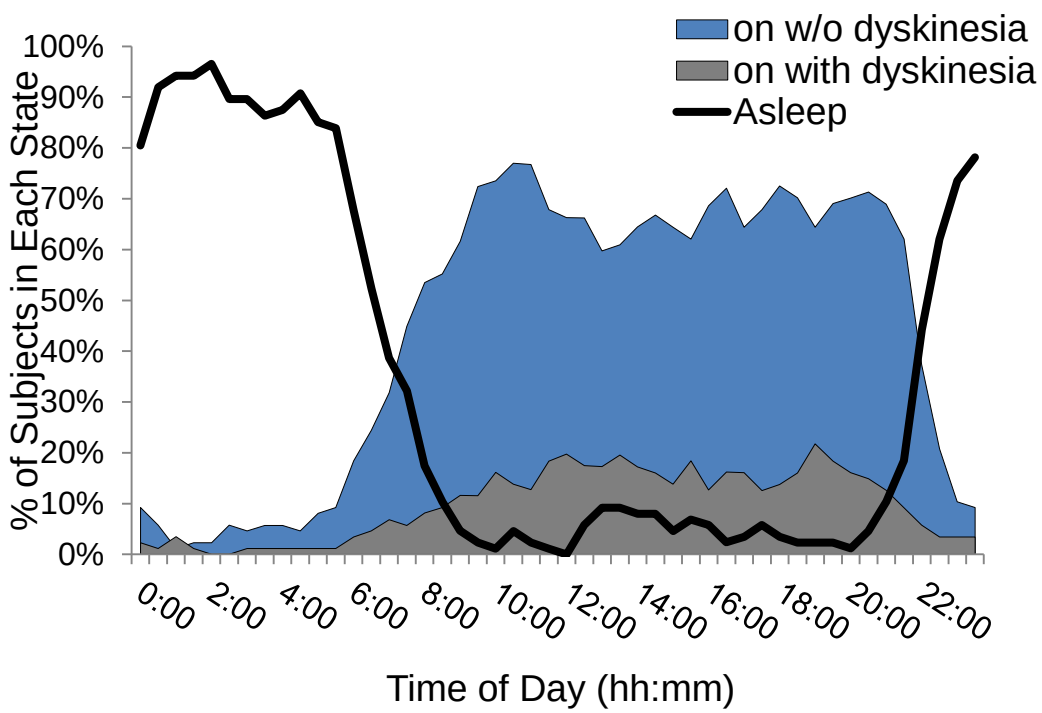
Patient Diaries – Improvement Throughout the Waking Day

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

Baseline (n=42)



Week 4 (n=42)



After 4-week treatment with dipraglurant:

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

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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.

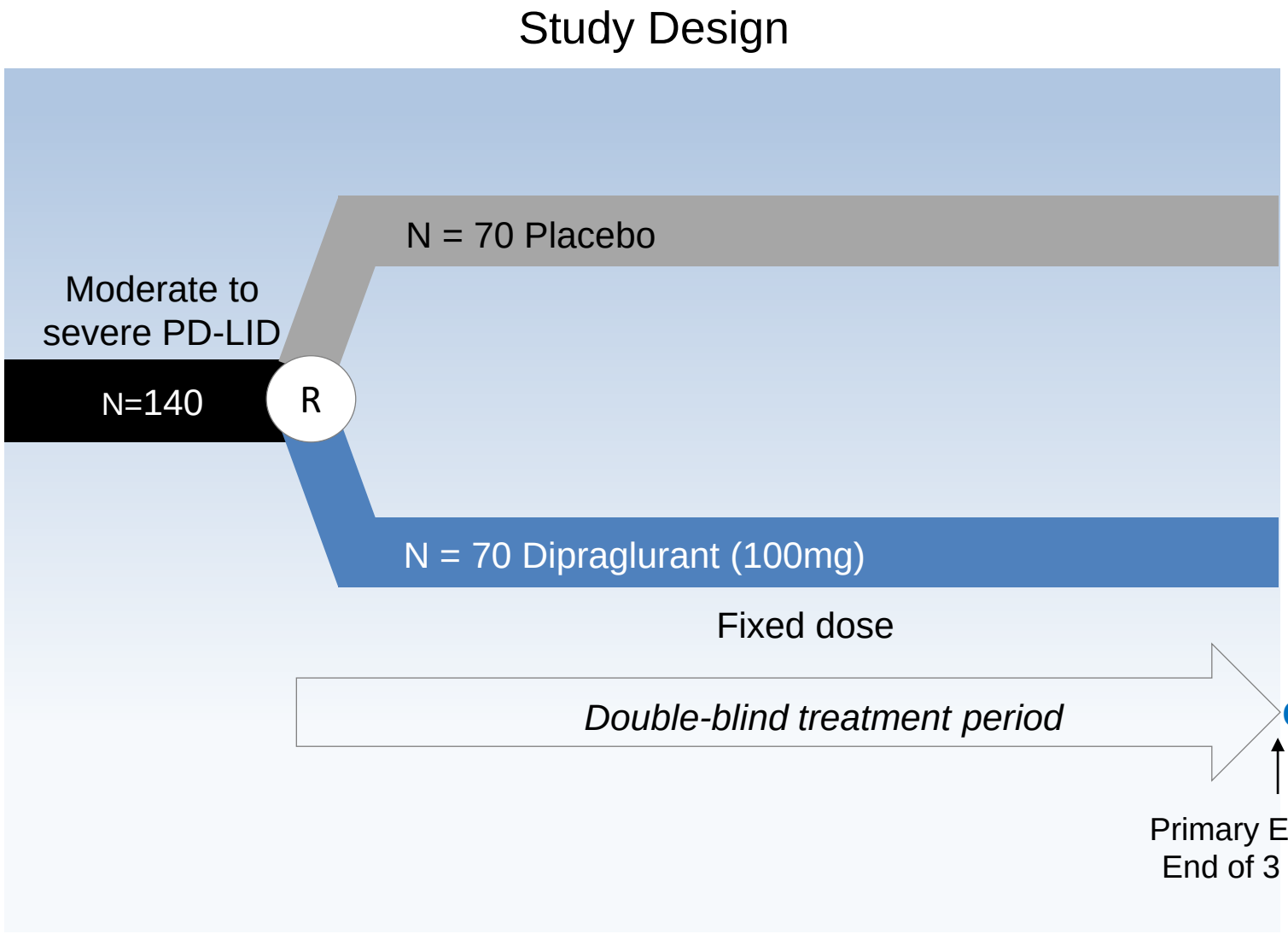
- AEs caused discontinuation in 2 patients taking dipraglurant 100 mg
- AEs at the 50 mg dose level (wk 1 and 2) were less frequent – 53% vs 58% pbo than at the 100 mg dose level (wk 3 and 4) – 73% vs 63% pbo
- No treatment effects on any safety monitoring variables (ECG, HR, BP, haematology and biochemistry)

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

Dipraglurant PD-LID Registration Program Started

- First pivotal registration trial (301) on track to start dosing patients in Q1 2020
  - Fully funded and expected to report out in Q3 2021
- Open label study (302) starting in parallel
  - 6 and 12 month safety data
- 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

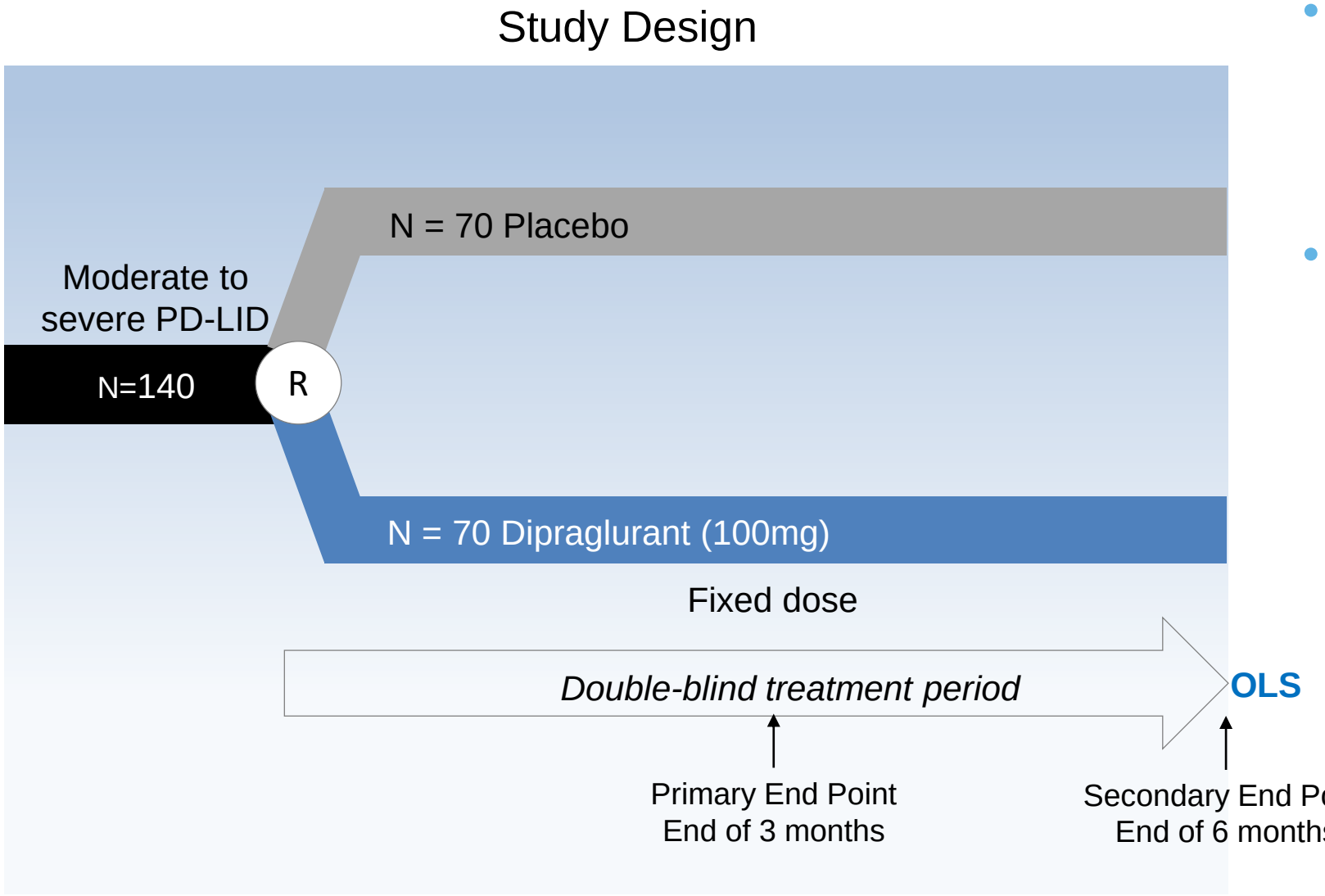
Dipraglurant First Pivotal PD-LID Study (301)



- 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

N= Number of patients
LID= L-Dopa induced dyskinesia
R= Randomisation
OLS = Open label study

Dipraglurant Confirmatory Phase 3 PD-LID Study (303)



- 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

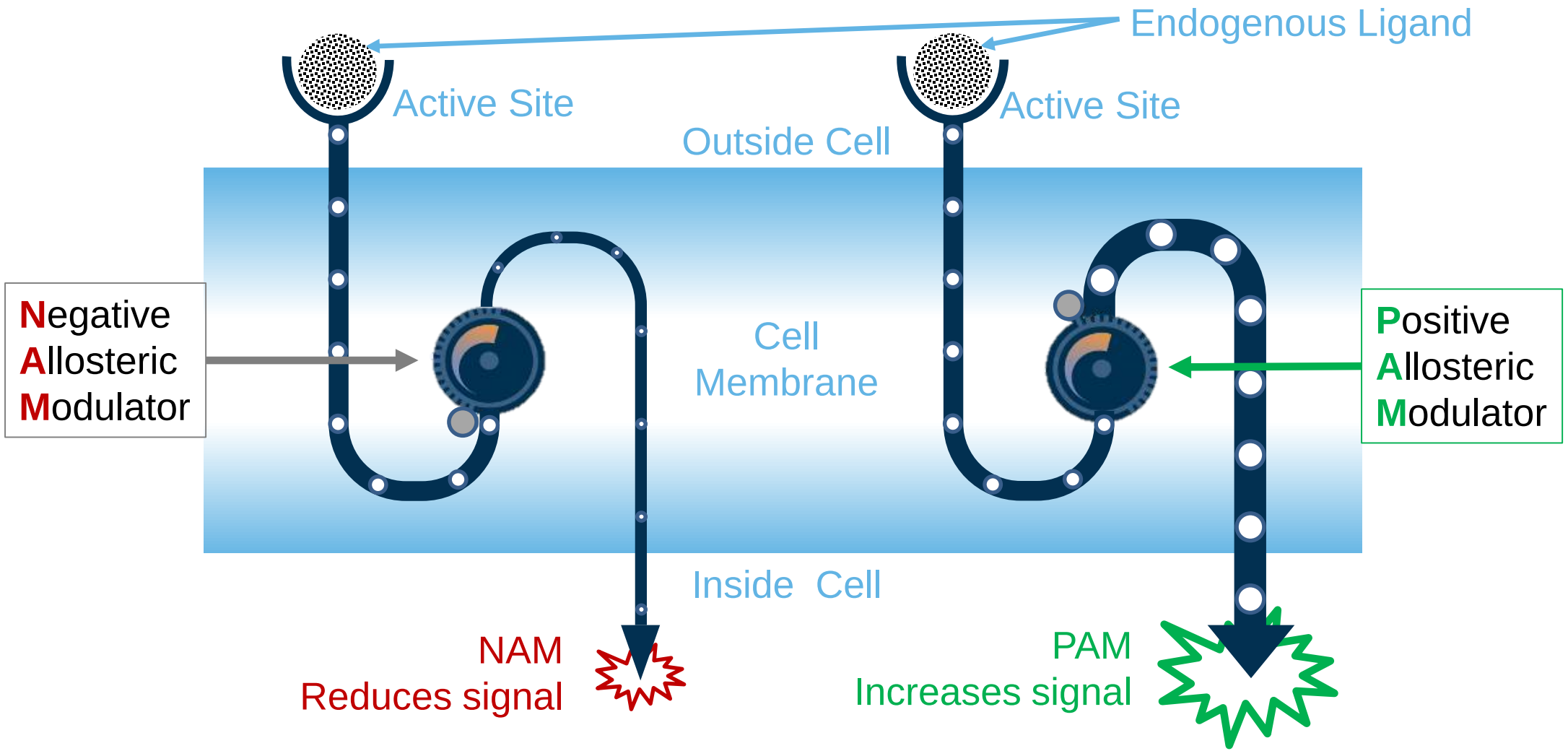
N= Number of patients
LID= L-Dopa induced dyskinesia
R= Randomisation
OLS = Open label study

Dipraglurant LID Opportunity

Limited competition – only one FDA approved medicine	➢ > 170K LID patients in US ➢ ~ $1B US peak sales potential 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 mGlu5 NAM ➢ 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

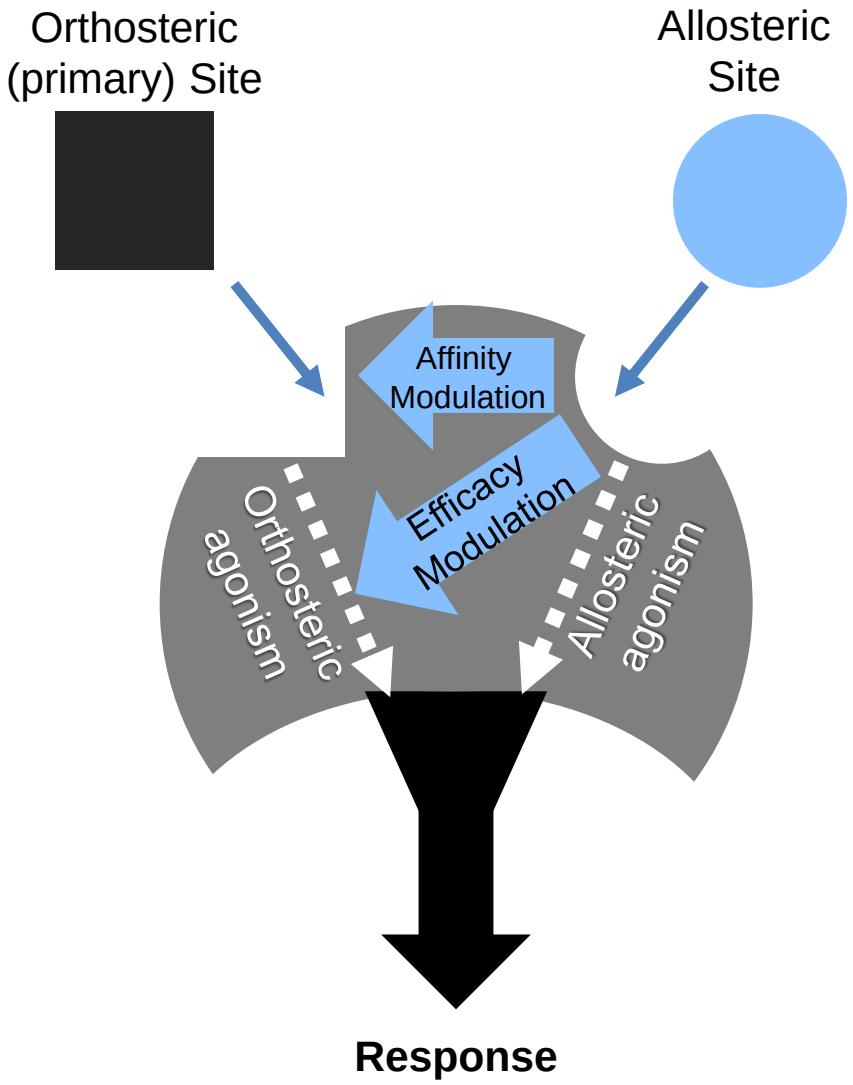
Addex Allosteric Modulation Technology Platform Becoming an Exciting Space

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 compared to orthosteric ligands
- 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

*Modified from : Nat Rev Drug Discov."*Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders". Jeffrey Conn, et al

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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 USD 5.0M & USD 5.6M research funding over 2 years
  - USD 330M of development, regulatory and commercial milestones
  - Tiered royalties up to double-digit

Financials

Financials and Stock

- Cash runway through 2021
  - Cash of CHF 31.5M at 31 December 2019
  - Fully funded through dipraglurant study 301 readout
- Market capitalization: approx. CHF 55M
- No debt
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- ADR representing 6 shares traded on Nasdaq: ADXN (ISIN: US00654J107 CUSIP: 00654J107)
- 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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ALLOSTERIC MODULATORS FOR HUMAN HEALTH

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