addex Therapeutics

# Innovative Treatments for Central Nervous System Disorders

**August 2021**

*Allosteric modulators for human health*

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# Addex Overview

| | |
|---|---|
| 3 clinical programs | • Dipraglurant PD-LID study 301 started in June 2021<br>• Dipraglurant blepharospasm Phase 2 study starting Q3 2021<br>• ADX71149 (J&J) epilepsy Phase 2 study started in June 2021 |
| Leading allosteric modulator technology platform | • Allosteric modulation is a validated & differentiated pharmacological approach to address drug targets<br>• Proprietary biological screening assays and chemical library |
| In house discovered pipeline | • Multiple novel drug candidates entering clinical candidate selection<br>• Driving long term growth & future partnership opportunities |
| Partnerships | • J&J - €109M in milestones & double digit royalties<br>• Indivior - $330M in milestones, royalties up to double digit & funded research program |
| Top tier US investors | • Dual listed on SIX Swiss Exchange & US Nasdaq Capital Market<br>• Cash of CHF18.1M at 30 June 2021 |

# Addex Pipeline

| Molecule / MoA | Indication | Partner | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | Milestone |
|---|---|---|---|---|---|---|---|
| Dipraglurant (mGlu5 NAM) | PD-LID | | | | | | Data Q4 2022 |
| | Blepharospasm | | | | | | Data Q4 2021 |
| ADX71149 (mGlu2 PAM) | Epilepsy | Janssen | | | | | Data Q3 2022 |
| $GABA_B$ PAM | Addiction | INDIVIOR | | | | | |
| | CMT1A | | | | | | |
| mGlu7 NAM | PTSD | eurostars™ | | | | | |
| mGlu2 NAM | Mild neurocognitive disorders | | | | | | |
| mGlu4 PAM | Parkinson's disease | | | | | | |
| mGlu3 PAM | Neurodegenerative disorders | | | | | | |

## Lead Program Started US Pivotal Study

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NAM = Negative Allosteric Modulator
PAM = Positive Allosteric Modulator

# Experienced Team

## Leadership Team

| Tim Dyer | Dr Roger Mills | Dr Robert Lutjens | Dr Jean-Philippe Rocher | Dr Mikhail Kalinichev |
|---|---|---|---|---|
| CEO / CFO | Chief Medical Officer | Head of Discovery Biology | Head of Discovery Chemistry | Head of Translational Science |
| Co-Founder of Addex<br>Formerly with PwC<br>UK Chartered Accountant | Developed Nuplazid for PD Psychosis<br>>30 years Pharma industry incl. Pfizer, Gilead and Acadia | Member of Addex founding team<br>Formerly with Glaxo & Scripps Research Institute | Member of Addex founding team<br>Formerly with Pierre Fabre, GSK and Mitsubishi | Neuropharmacologist with >20 years experience<br>Formerly with Ipsen, Lundbeck and GlaxoSmithKline |

## Non-executive Directors

| Vincent Lawton | Ray Hill | Jake Nunn | Isaac Manke |
|---|---|---|---|
| Chairman | Board member | Board member | Board member |
| Former European Head of Merck & Co.<br>Former MHRA Board member | Former Executive Director Merck & Co. | Venture advisor and former Partner at New Enterprise Associates | General Partner at Acorn Bioventures.<br>Formerly Partner at New Leaf Venture Partners |

## Scientific Advisory Board

| Darryle Schoepp | Mark Bear | Peter Bernstein | Benny Bettler |
|---|---|---|---|
| Chairman of SAB | Picower Prof. of Neuroscience at MIT | Principal, PhaRmaB LLC | Biomedicine Prof. at Basel University |
| Former leader of Neuroscience research department at Eli Lilly, and at Merck was Neuroscience research therapeutic area leader | Formerly on faculty of Brown University School of Medicine and an Investigator of the Howard Hughes Medical Institute | Formerly with ICI Astra Zeneca<br>Awarded numerous accolades including Fellow of the American Chemical Society | Formerly at Novartis and discovered allosteric modulators at $GABA_B$ receptor and recipient of the Peter Speiser Award |

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

# Compelling Rationale to Develop Dipraglurant for PD-LID

- Large underserved patient population in need of improved treatment options
- Significant commercial opportunity with limited competition
  - 1M Parkinson's disease patients in US of which >170,000 have dyskinesia
  - GOCOVRI® price: $34K p.a., Nuplazid® price: $45K p.a.
  - US LID market estimated at $4B
- Strong mechanistic rationale for blocking mGlu5 to inhibit glutamate signalling
- Supportive pre-clinical data and Phase 2 clinical data
- PK profile ideally suited for treatment of LID
- Dipraglurant is active on same biological pathway as amantadine (inc. GOCOVRI®)
  - Decreases glutamatergic tone
  - Unlike amantadine, dipraglurant:
    - Restores synaptic plasticity to prune aberrant signalling
    - Highly selective with limited off target activity
- Novartis mGlu5 NAM (mavoglurant) data supportive of mGlu5 target & rationale for dipraglurant PK profile

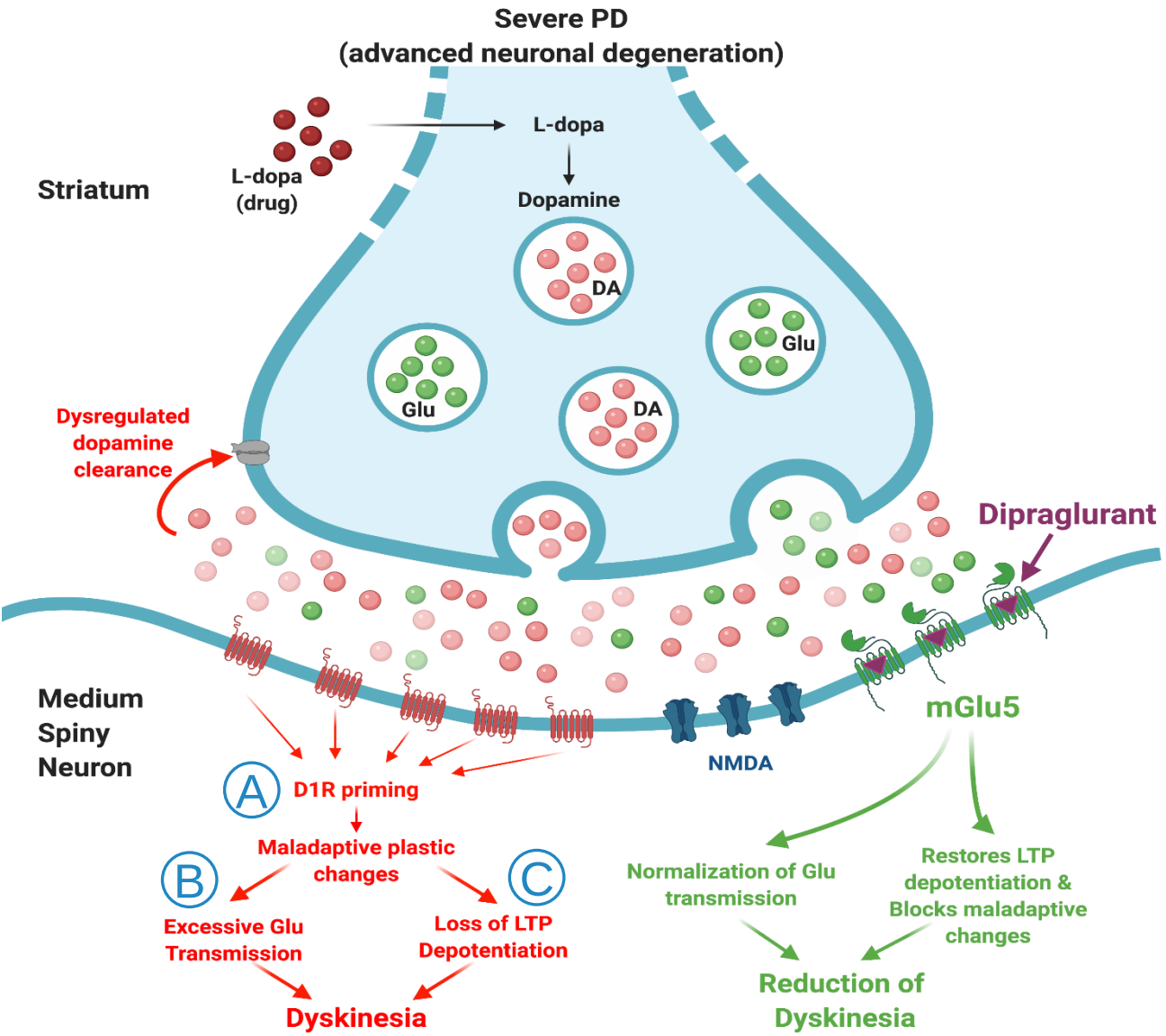


* www.drug.com

# Disability and Impact of PD-LID

| | |
|---|---|
| Invariably associated with long-term L-dopa use | • Dyskinesias caused by neurodegeneration<br>• Dopamine replacement lowers the triggering threshold for symptoms<br>• LID can become as disabling as the PD symptoms themselves |
| Symptoms include dystonia, chorea, and choreoathetosis | • Uncontrollable muscle contractions, twisting and writhing<br>• Painful and severely disabling<br>• Causes fatigue/exhaustion and increased risk for falls and injuries<br>• Social withdrawal, reduced quality of life and increased burden on caregiver |
| Prevalence related to disease duration | • >40% of patients experience LID within 4-6 years of L-dopa treatment<br>• Increases to 90% after 9 -15 years<br>• Patients treated with next-generation L-dopa will still experience LID |
| PD drug efficacy wanes over time - exacerbated by emergence of LID | **Treatment becomes a balancing act requiring constant adjustments to ensure symptom control & minimize intolerable side effects** |

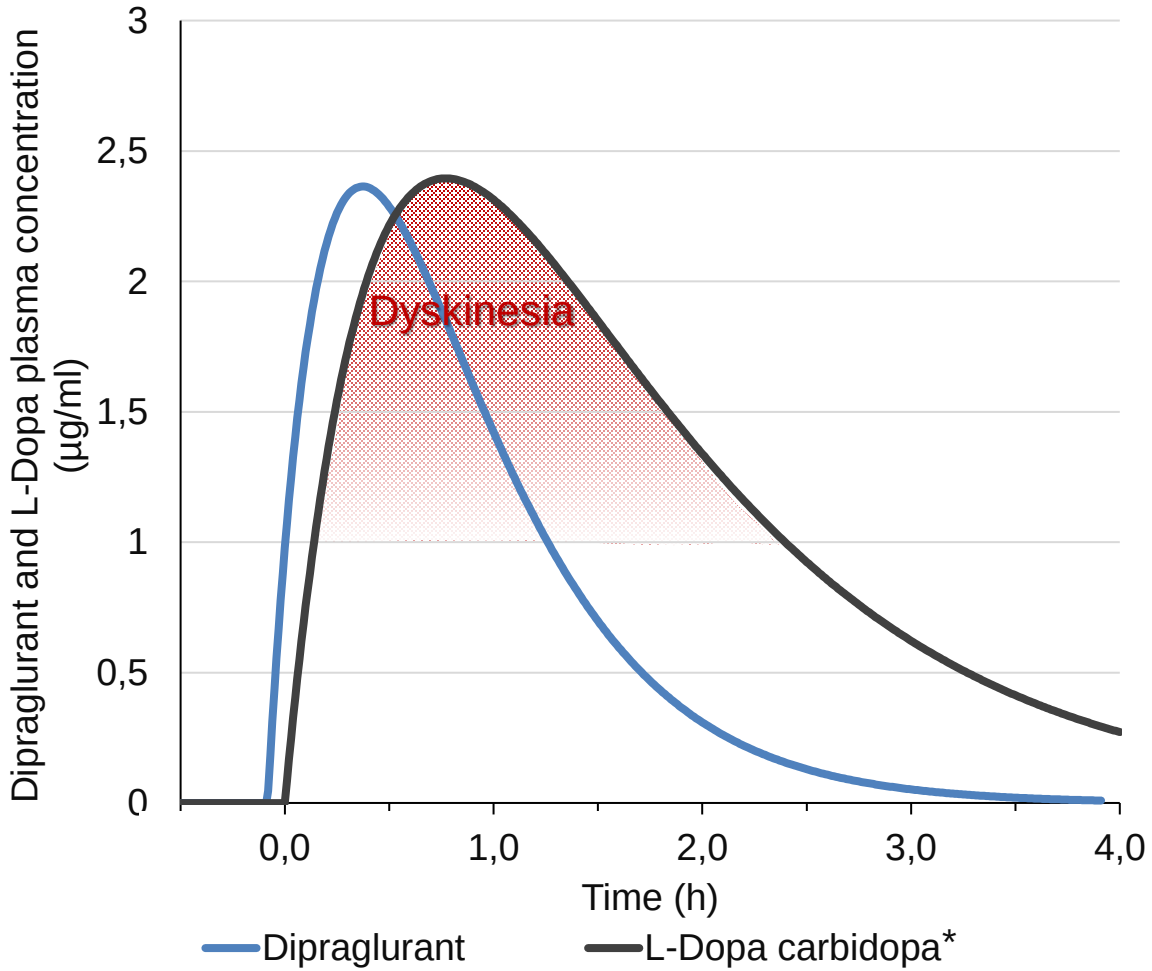
# MoA Rationale for Targeting mGlu5 Inhibition in PD-LID




- 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:
  - Ⓐ *D1 receptor priming*
  - Ⓑ *Excess glutamate transmission*
  - Ⓒ *Loss of LTP depotentiation*
- mGlu5 receptor is an attractive target due to its modulatory action - normalizing glutamatergic activity and restoring LTP depotentiation
- Inhibiting mGlu5 decreases excess glutamatergic tone thereby controlling dyskinesia
- Dipraglurant is an oral, highly selective NAM of the mGlu5 receptor

LTP = Long Term Potentiation
D1R = D1 dopamine receptor
Glu = glutamate DA = dopamine

# Dipraglurant PK is a Key Advantage for Treating LID



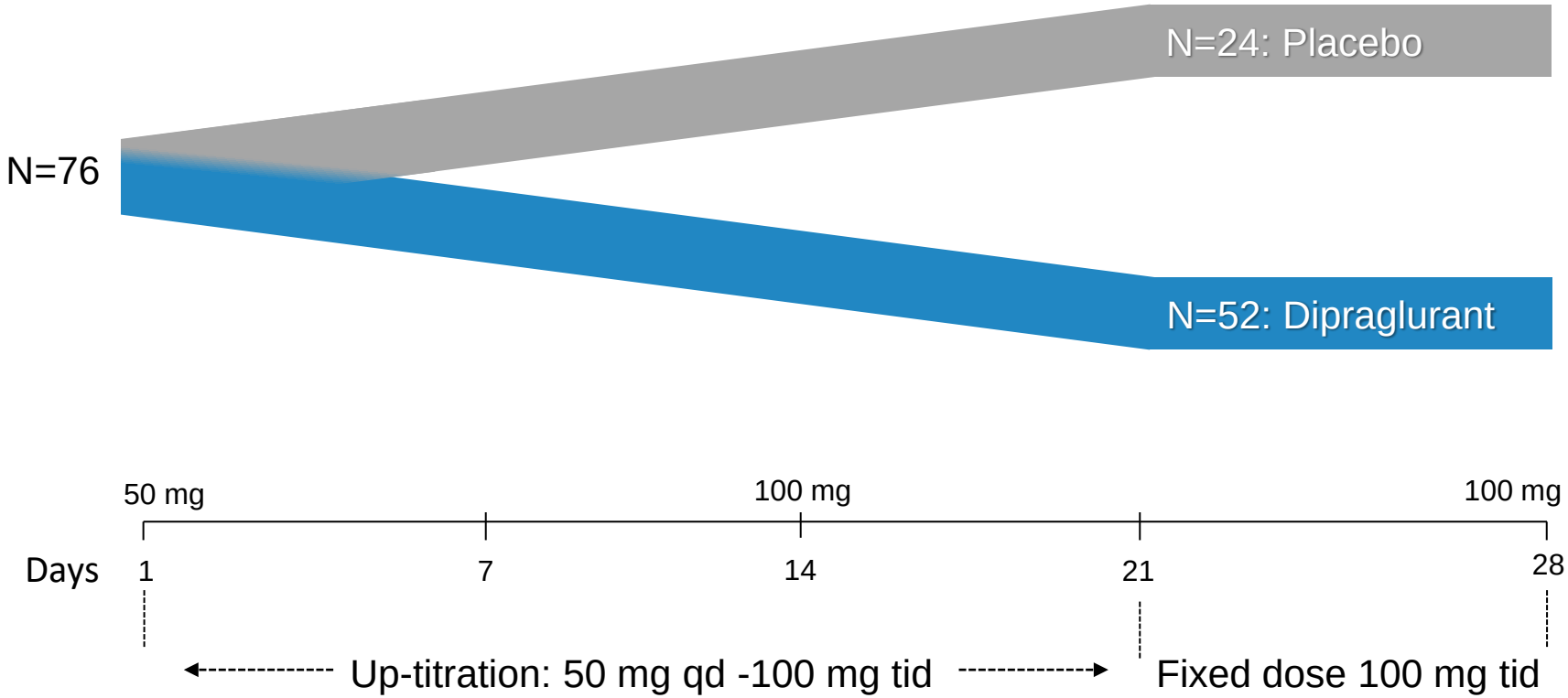

- Dyskinesia symptoms are correlated to peak levels of L-dopa
- PK of dipraglurant allows control of glutamatergic tone ahead of L-dopa Cmax

**Dipraglurant normalizes abnormal glutamate stimulation during peak levodopa dose**

## Dipraglurant peaks ahead of L-dopa for optimal LID control

* Pharm Sci (www.cspsCanada.org) 20, 226 - 238, 2017

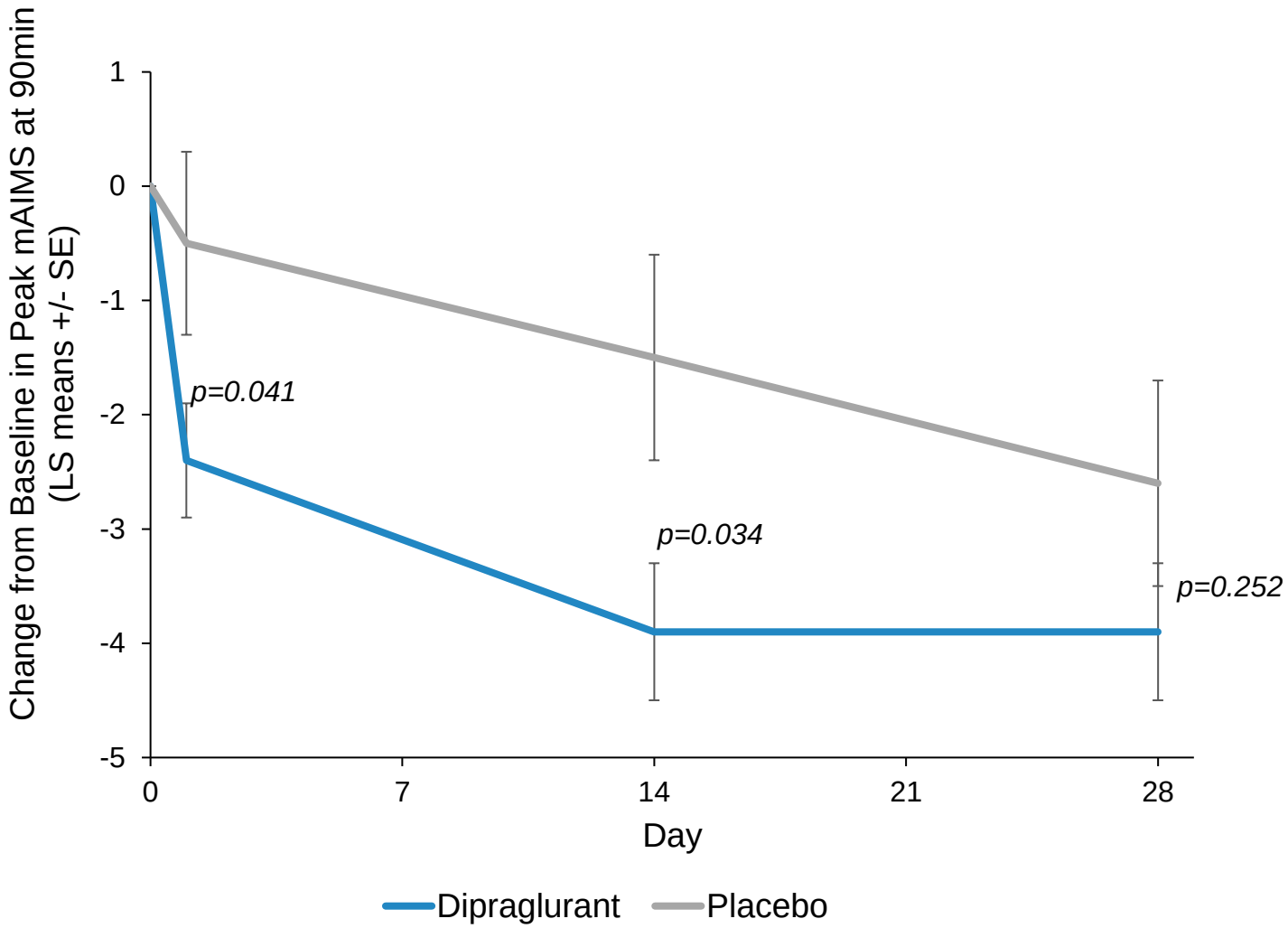
# Dipraglurant Phase 2a Study in LID (in US and Europe)




- **Primary objective**: safety & tolerability
- **Secondary objective**: exploratory efficacy:
  - Modified Abnormal Involuntary Movement Scale (mAIMS) on days 1, 14 and 28
  - Clinician Global Impression of Change (CGIC)
  - Patient diaries of “On” & “Off” time

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

# Dipraglurant Improves LID by 30%




- Statistically significant effects: Day 1 (50mg) and Day 14 (100mg)
- Improvement maintained through Day 28
- Increasing placebo response caused significance to be lost at Day 28
- No placebo mitigation 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% |

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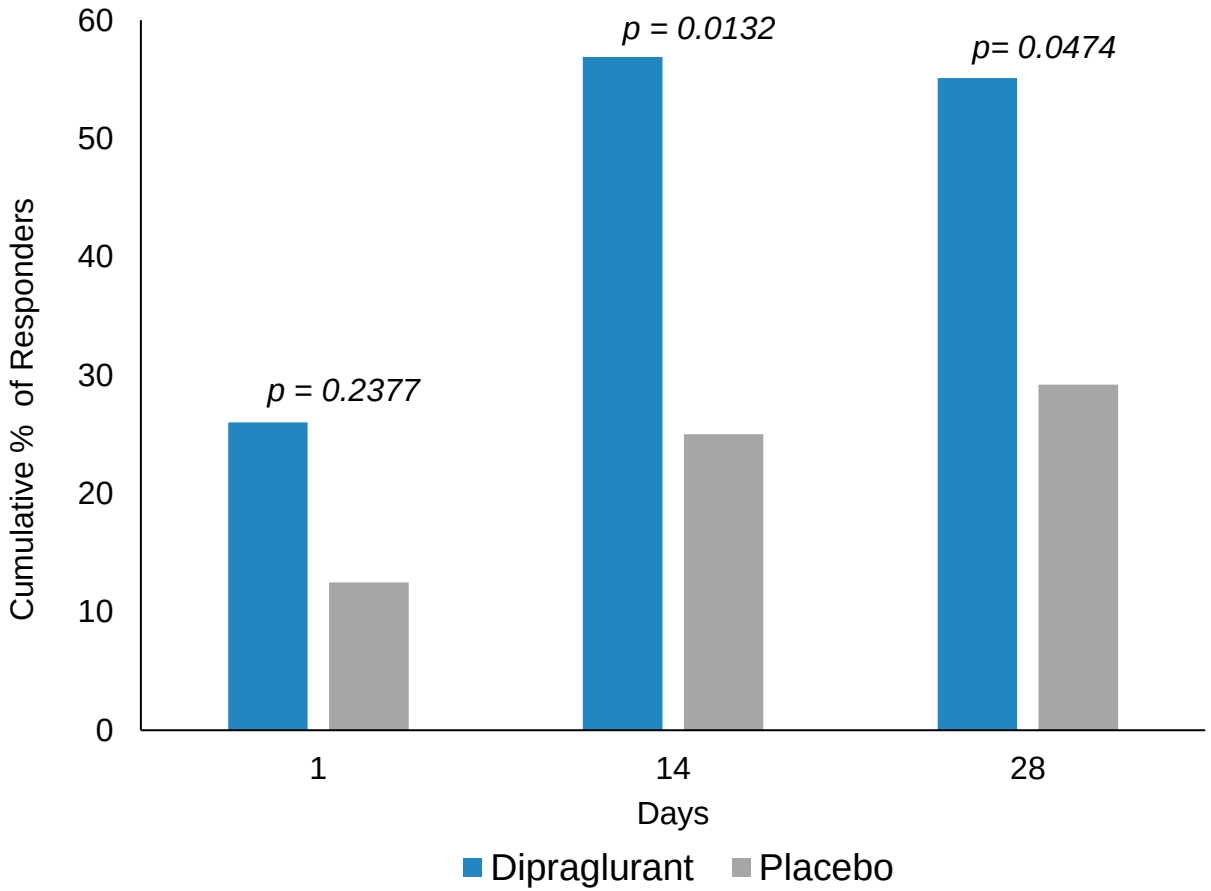
# Responder Analysis Demonstrates Dipraglurant Significant Benefit

## Percent of patients with ≥ 30% improvement on mAIMS

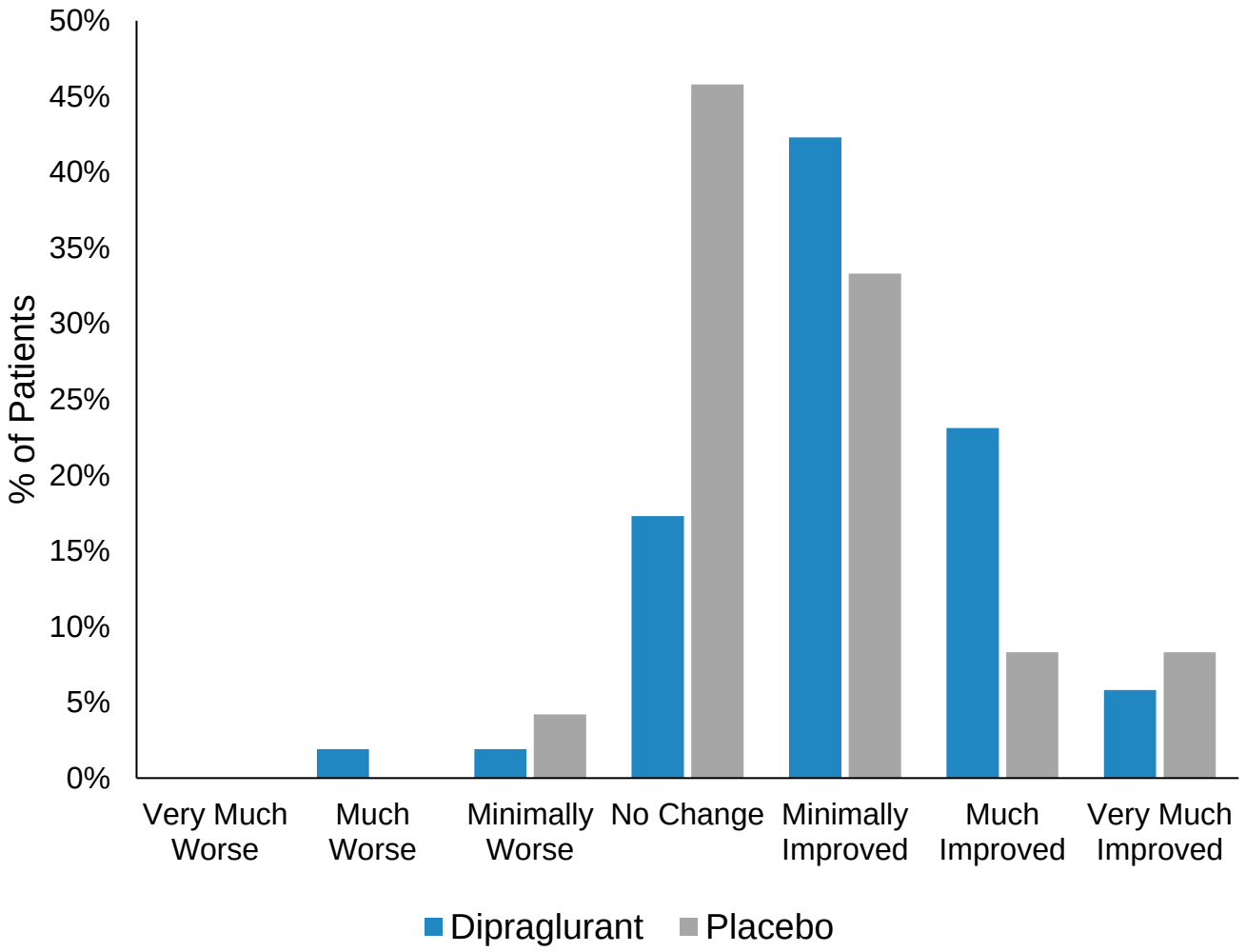



| Responder analysis (≥30% change of mAIMS from baseline) | | | | |
|---|---|---|---|---|
| Midday dose | Dipraglurant | | Placebo | |
| Day 1 (50 mg) | n=13 | 26.0% | n=3 | 12.5% |
| Day 14 (100 mg) | n=29 | 56.9%* | n=6 | 25.0% |
| Day 28 (100 mg) | n=27 | 55.1%* | n=7 | 29.2% |

*statistically significant

## Reinforces robustness of dipraglurant anti-dyskinetic effect

# Significant Improvement on CGI-C




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

- Simple scale reflecting clinical assessment by treating physician
- More objective than mAIMS
- Assessed at end of study compared to baseline
- Supports use of UDysRS in pivotal program

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# Dipraglurant Demonstrated Good Safety and Tolerability in PD Patients

- Adverse events common in both treatment groups (dipraglurant 88.5%, placebo 75%)
- Most common AEs:

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

* 3 of 11 AEs of “worsening dyskinesia” occurred in the follow up period (i.e., after drug discontinuation). On treatment incidence = 15.3% dipraglurant, 12.5% placebo

- AEs led to discontinuation in 2 patients (dipraglurant 100 mg)
- Fewer AEs at 50 mg (Weeks 1 and 2)  53% vs 58% placebo compared to 100 mg (Weeks 3 and 4)  73% vs 63% placebo
- No treatment effects on ECG, HR, BP, haematology and biochemistry

Safety profile supports continued development in PD-LID (KOLs and DSMB)

# Dipraglurant PD-LID Registration Program Started

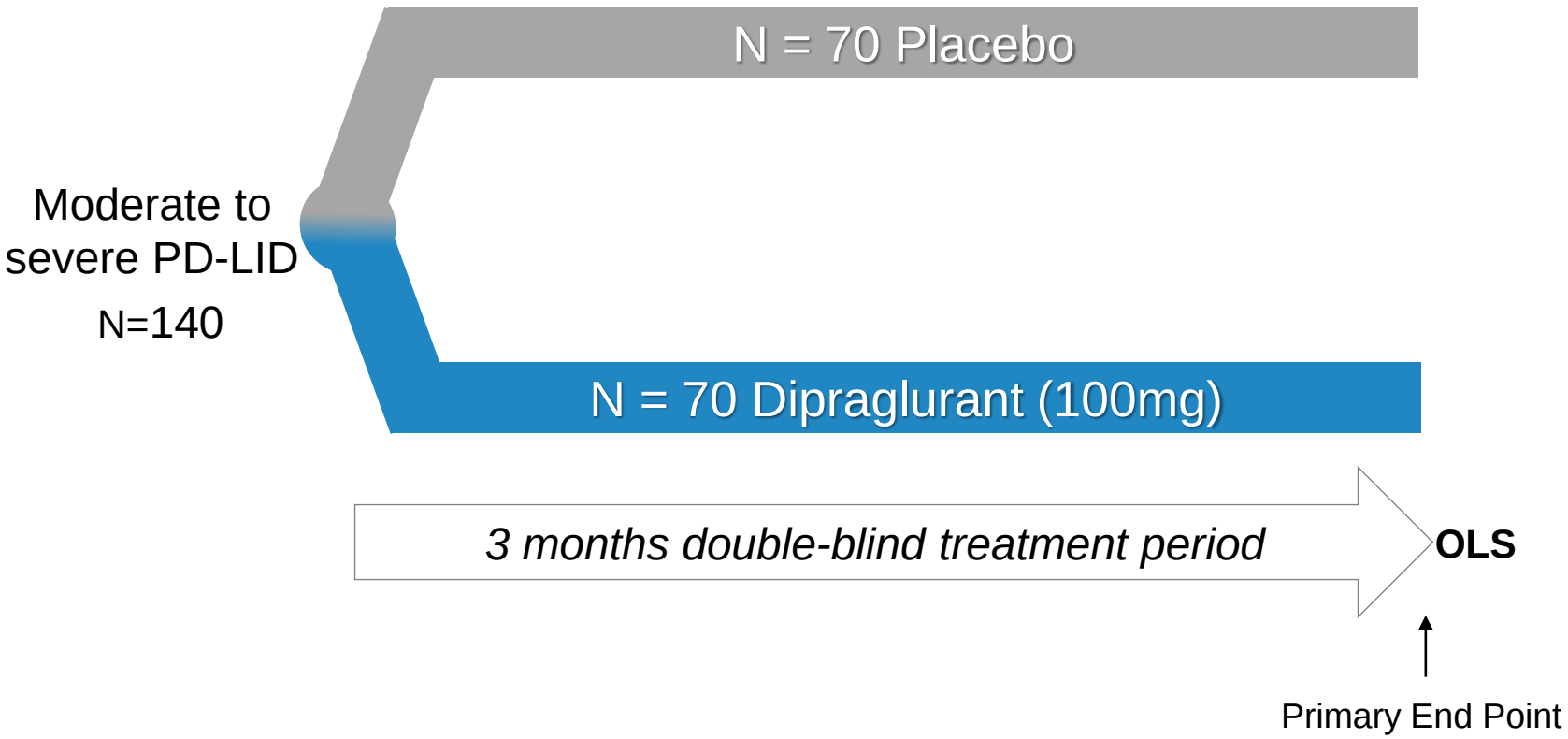
- Pivotal registration program ongoing

- Study 301 started in June 2021
  - Data read-out expected Q4 2022
  - Primary endpoint: UDysRS
  - Placebo mitigation is a priority

- 12-month Open Label Study (302) starting in parallel to study 301
  - 6- and 12-month safety data

- Second pivotal registration study (303) to follow study 301 completion

# Dipraglurant First Pivotal PD-LID Study (301)




- Primary objective: Efficacy in reducing LID
  - UDysRS change from baseline at 3 months
- Secondary objectives
  - CGI-S
  - MDS-UPDRS Part III change from baseline
  - Patient diaries, on & off time
  - Safety and tolerability

OLS = Open label study

# UDysRS: An Improved and Validated Dyskinesia Rating Scale

| | UDysRS | mAIMS |
|---|---|---|
| Characteristics | • Recommended by Movement Disorder Society (MDS)<br>• FDA regulatory precedent (GOCOVRI® approval)<br>• Contains anchored objective clinician evaluated measures of dyskinesia<br>• Includes both patient and physician assessments of impairment<br>• Less prone to placebo effect | • Suboptimal for detecting treatment-related changes<br>• Limited to patient assessments<br>• Prone to placebo effect |
| Clinimetrics | • Validated | • Only the original version has been validated |
| Development | • Developed in 2009 specifically for dyskinesia in PD | • Developed in 1970 for tardive dyskinesia in psychiatry |

UDysRS= Unified Dyskinesia Rating Scale

# Dipraglurant PD-LID Studies – Management of Placebo Response

- Use of UDysRS
  - More sensitive to changes in LID
  - Less prone to placebo response
- Raters will be qualified by the MDS
  - Expert rater review to further ensure quality
- Requirement for moderate to severe symptom scores at screening and baseline
- BPST-Dys (non-pharmacologic intervention) to be used during screening
- Longer 12-week treatment period expected to mitigate placebo response

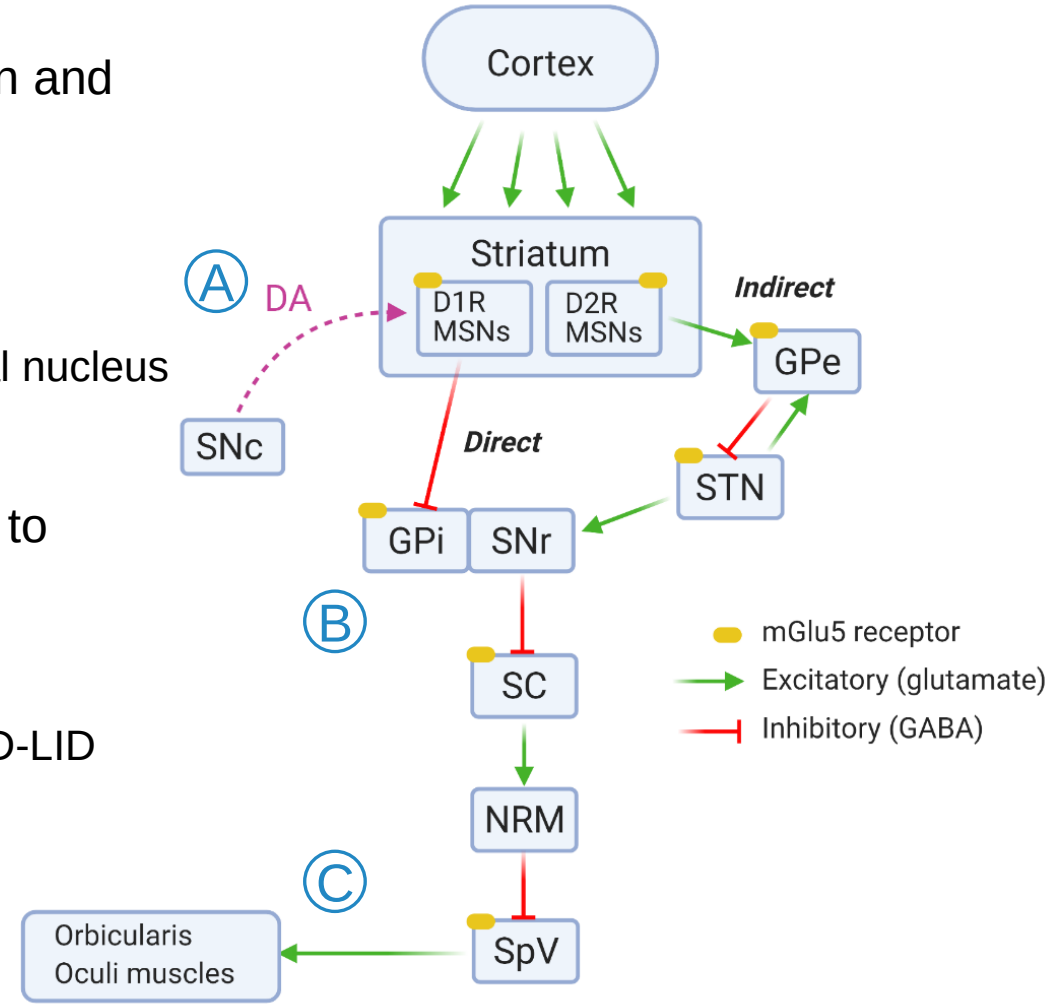
# Dipraglurant for Dystonia – Blepharospasm

# Blepharospasm (BSP)

- Type of dystonia affecting eyelid muscles
  - Results in sustained eyelid closure causing substantial visual disturbance or functional blindness
  - >50% of BSP patients symptoms spread to other cranio-facial muscles
- At least 50,000 BSP patients in US, ~2000 new patients diagnosed annually
- Botulinum toxin (BoNT) injections are the only approved treatment
- Surgical approaches including myectomy are invasive and frequently not of benefit
- Phase 2 feasibility study in BSP with dipraglurant IR expected to start in Q3 2021 and read out data by the end of 2021
- Dipraglurant extended release (ER) formulation being developed
- Phase 2a proof of concept with dipraglurant ER planned for 2022
- Potential to expand to other dystonias

# Rationale for Targeting mGlu5 Inhibition in Dystonia & BSP

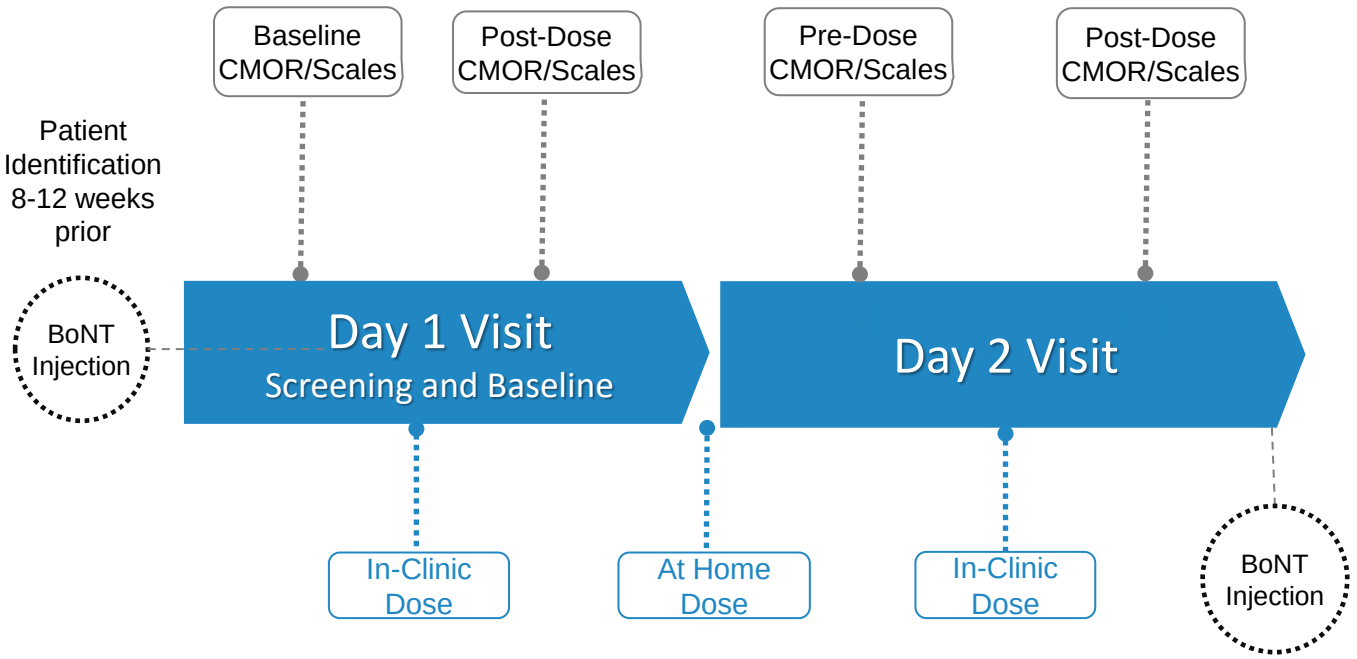
- Dystonias are *neuro-functional* rather than *neuro-degenerative*
- Common features include alterations in neuronal connectivity/function and synaptic communication
- BSP pathophysiology is linked to:
  - Ⓐ Reduction of dopamine input into striatum
  - Ⓑ Increased inhibition of direct pathway from superior colliculus to trigeminal nucleus
  - Ⓒ Overexcitation of the signal leading to blink reflex
- Pathogenesis involves aberrant or maladaptive brain plasticity linked to excessive sensory stimulation and/or repetitive motor tasks
- Dipraglurant shows robust preclinical validation:
  - Dose-dependent reduction of dystonia in MPTP-lesioned NHP model of PD-LID
  - Effective in tottering mouse model of generalized dystonia
  - Reverses synaptic plasticity alterations observed in two distinct genetic models of dystonia (DYT1 mice & DYT25 rats)
- Dipraglurant has shown anti-dystonic effect in PD patients




Adapted from Peterson & Sjenowski , 2017

SNc = Substantia Nigra pars compacta
SC = Superior Colliculus
GPi /GPe = Globus Pallidus internal/external
SNr = Subst Nigra pars reticulata
NRM = nucleus raphe magnus
STN = subthalamic nucleus
SpV = spinal trigeminal nucleus

# Blepharospasm Phase 2 Feasibility Study Design




- Patients with benign essential BSP, who experience moderate/severe symptoms prior to their regular dose of BoNT
- Single center, randomized, double-blind, placebo controlled
- Approx. 15 patients
- Dipraglurant IR - 50mg, 100 mg and placebo
- Efficacy endpoints include:
  - Computational Motor Objective Rater (CMOR)
  - Clinician rating scales
  - Patient reported outcomes

# ADX71149 (JNJ-40411813) for Epilepsy
# Partnered with Janssen Pharmaceuticals, Inc.

# ADX71149 Opportunity in Epilepsy

| | |
|---|---|
| Large market & unmet medical need | • Market projected to reach $20 billion by 2026*<br>– Keppra market leader with approx. 2.2M patients & >€800M p.a.**<br>• High proportion of refractory patients (¼ of new patients***) - combination treatments have limited therapeutic benefit<br>• Large underserved patient population in need of improved treatment options |
| ADX71149: true synergistic MoA | • Selective oral mGlu2 PAM with clear MoA in epilepsy<br>• Showed 35-fold increase in Keppra efficacy in preclinical model<br>• Potential first rational polypharmacy in epilepsy |
| Development path | • Extensive preclinical and clinical data<br>– 8 Phase 1 and 2 Phase 2 studies<br>• Janssen Pharmaceuticals, Inc. started POC study in June 2021<br>– Top line data expected in Q3 2022 |
| Strategic Partner Janssen Pharmaceuticals, Inc. | • Eligible to receive €109 million in pre-launch milestones and double digit royalties |

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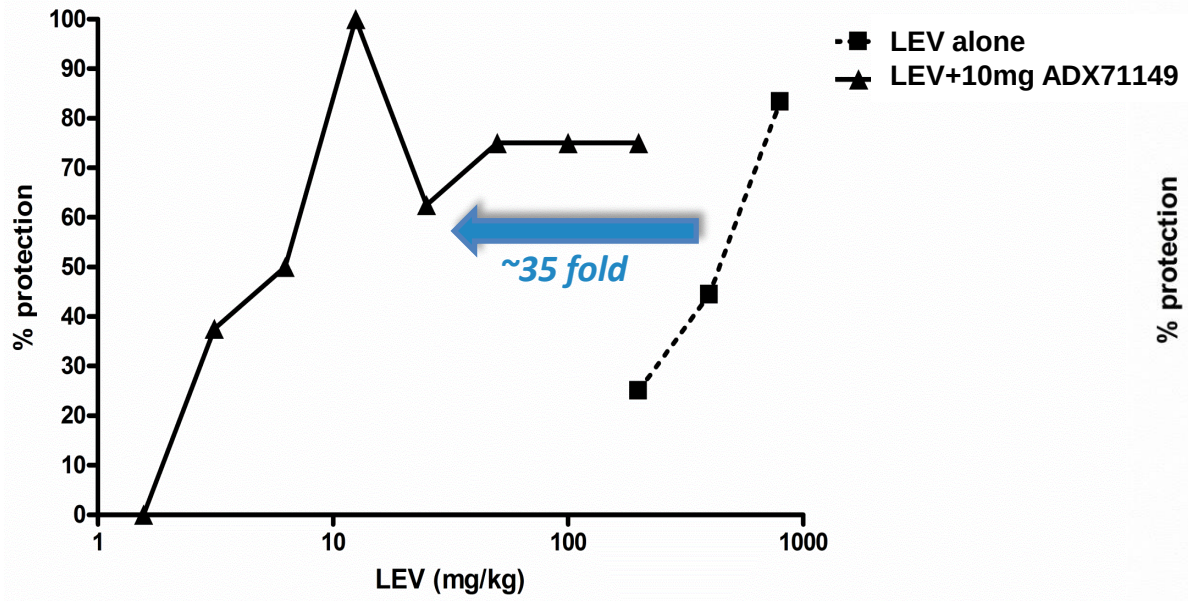
* Fortune Business Insights April 8, 2020
**UCB H1 2020
*** Xue-Ping et al, Medicine July 2019

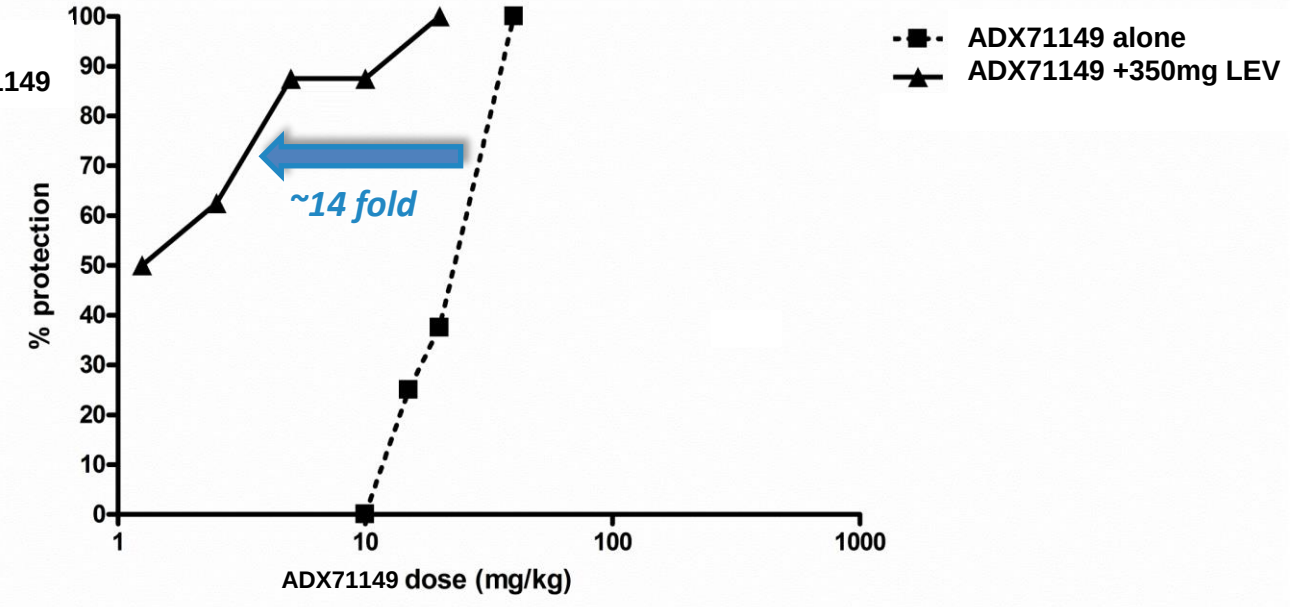
# ADX71149 Preclinical Efficacy in Epilepsy - 6Hz Model

- Preclinical validation in pharmaco-resistant mouse epilepsy model:

$ED_{50}$ shift of Keppra by adding low dose of ADX71149

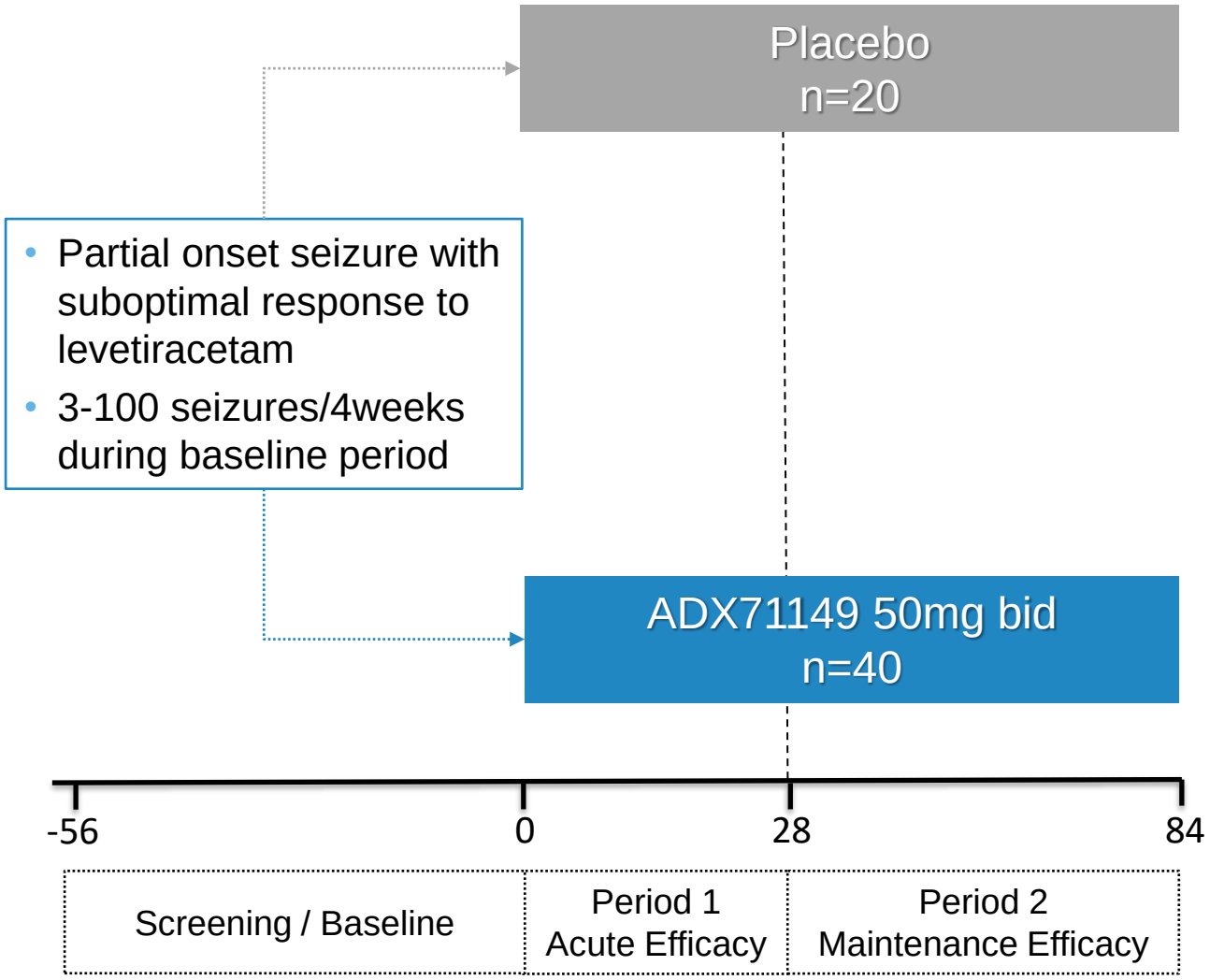



$ED_{50}$ shift of ADX71149 by adding $ED_{50}$ dose of LEV




- Keppra efficacy increased 35-fold when administered with a low dose of ADX71149
- Low dose of Keppra leads to 14-fold increase in efficacy of ADX71149
- True synergistic effect

# ADX 71149 Phase 2a Epilepsy Study Design




- Double blind placebo controlled
- Establish 28-day seizure count (over 56-day baseline period)
- Primary endpoint: time to monthly baseline seizure count
- Period 1: 4-week acute efficacy phase
- Period 2: 8-week maintenance efficacy phase
  - Subjects who do not reach or exceed their monthly baseline seizure count in Period 1 continue double-blind treatment during Period 2
- First patient enrolled in June 2021

# Financials

# Financials and Stock

- Cash runway through 2022
  - Cash at 30 June 2021: CHF18.1 million
- No debt
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- ADS representing 6 shares traded on Nasdaq: ADXN (ISIN: US00654J107; CUSIP: 00654J107)

- 34.1M outstanding shares
- 49.3M issued shares incl. treasury shares (62.3M fully diluted)
  - New Enterprise Associated - 14.21%
  - New Leaf Venture Partners - 4.86%
  - CAM Capital – 3.24%
  - Credit Suisse Asset Management – 2.54%
  - Management & board holds -12.05% (fully diluted basis)
- Analyst coverage:
  - HC Wainwright – Raghuram Selvaraju
  - Van Leeuwenhoek - Marcel Wijma
  - valuationLab - Bob Pooler
  - ZKB - Dr. Michael Nawrath
  - Baader Helvea AG - Bruno Bulic

# Milestones

| Milestone | Timing |
|---|---|
| Dipraglurant for PDLID | |
| Phase 2b/3 – study started | June 2021 |
| Phase 2b/3 - topline results | Q4 2022 |
| Dipraglurant for Blepharospasm | |
| Phase 2a - start study | Q3 2021 |
| Phase 2a - topline results | Q4 2021 |
| ADX71149 for Epilepsy | |
| Phase 2a – study started | June 2021 |
| Phase 2a - topline results | Q3 2022 |
| $GABA_B$ PAM for Addiction and CMT1a | |
| Complete clinical candidate selection | Q4 2021 |
| Start IND enabling studies | Q2 2022 |

# Summary

| | |
|---|---|
| 3 clinical programs – data reading out from Q4 2021 | • Dipraglurant PD-LID registration study – started June 2021<br>• Dipraglurant blepharospasm Phase 2 – start Q3 2021<br>• ADX71149 (J&J) epilepsy Phase 2 – started June 2021 |
| Technology and capabilities to deliver | • Experienced team of drug developers<br>• Pioneering allosteric modulation drug development<br>– Proprietary screening assays and unique chemical library<br>• All programs developed in-house, protected with >200 patents |
| Solid foundation | • Partnerships with industry leaders<br>• Top tier US investors - NEA, NLV and CAM Capital Program<br>• Dual listed SIX Swiss exchange & US Nasdaq |
| Promising outlook | • Rich news flow in 2021 and beyond<br>– Clinical data reading out Q4 2021, Q3 2022 and Q4 2022<br>– Multiple drug candidates in CCS |

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# ALLOSTERIC MODULATORS FOR HUMAN HEALTH