



# **Innovative Treatments for Central Nervous System Disorders**

**May 2021**

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*Allosteric modulators for human health*

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# Addex Overview

3 clinical programs	<ul style="list-style-type: none"><li>• Dipraglurant PD-L1D study 301 starting Q2 2021*</li><li>• Dipraglurant blepharospasm Phase 2 study starting Q2 2021</li><li>• ADX71149 (J&amp;J) epilepsy Phase 2 study starting Q2 2021</li></ul>
Leading allosteric modulator technology platform	<ul style="list-style-type: none"><li>• Allosteric modulation is a validated &amp; differentiated pharmacological approach to address drug targets</li><li>• Proprietary biological screening assays and chemical library</li></ul>
In house discovered pipeline	<ul style="list-style-type: none"><li>• Multiple novel drug candidates entering clinical candidate selection</li><li>• Driving long term growth &amp; future partnership opportunities</li></ul>
Partnerships	<ul style="list-style-type: none"><li>• J&amp;J - €109M in milestones &amp; double digit royalties</li><li>• Indivior - \$330M in milestones, royalties up to double digit &amp; funded research program</li></ul>
Top tier US investors	<ul style="list-style-type: none"><li>• Dual listed on SIX Swiss Exchange &amp; US Nasdaq Capital Market</li><li>• Cash of CHF18.7M at 31 Dec 2020</li><li>• Completed \$11.5M capital increase 11 Jan 2021</li></ul>

# Addex Pipeline

Molecule / MoA	Indication	Partner	Pre-clinical	Phase 1	Phase 2	Phase 3	Milestone
Dipraglurant (mGlu5 NAM)	PD-L1D						Data Q4 2022
	Blepharospasm						Data Q4 2021
ADX71149 (mGlu2 PAM)	Epilepsy						Data H1 2022
GABA <sub>B</sub> PAM	Addiction						
	CMT1A						
mGlu7 NAM	PTSD						
mGlu2 NAM	Mild neurocognitive disorders						
mGlu4 PAM	Parkinson's disease						
mGlu3 PAM	Neurodegenerative disorders						

Lead Program Entering US Pivotal Study

# Experienced Team

## Leadership Team

<b>Tim Dyer</b> CEO / CFO  Co-Founder of Addex Formerly with PwC UK Chartered Accountant	<b>Dr Roger Mills</b> Chief Medical Officer  Developed Nuplazid in PD Psychosis 30 years in Pharma industry including Pfizer, Gilead and Acadia	<b>Dr Robert Lutjens</b> Head of Discovery Biology  Member of Addex founding team Formerly with Glaxo & Scripps Research Institute	<b>Dr Jean-Philippe Rocher</b> Head of Discovery Chemistry  Member of Addex founding team Formerly with Pierre Fabre, GSK and Mitsubishi
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## Non-executive Directors

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

<b>Darryle Schoepp</b> Chairman of SAB  Former leader of Neuroscience research department at Eli Lilly, and at Merck was Neuroscience research therapeutic area leader	<b>Mark Bear</b> Picower Prof. of Neuroscience at MIT  Formerly on faculty of Brown University School of Medicine and an Investigator of the Howard Hughes Medical Institute	<b>Peter Bernstein</b> Principal, PhaRmaB LLC  Formerly with ICI Astra Zeneca Awarded numerous accolades including Fellow of the American Chemical Society	<b>Benny Bettler</b> Biomedicine Prof. at Basel University  Formerly at Novartis and discovered allosteric modulators at GABA <sub>B</sub> receptor and recipient of the Peter Speiser Award
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# Dipraglurant for Levodopa-Induced Dyskinesia in Parkinson's Disease (PD-LID)

# Compelling Rationale to Develop Dipraglurant for PD-LID

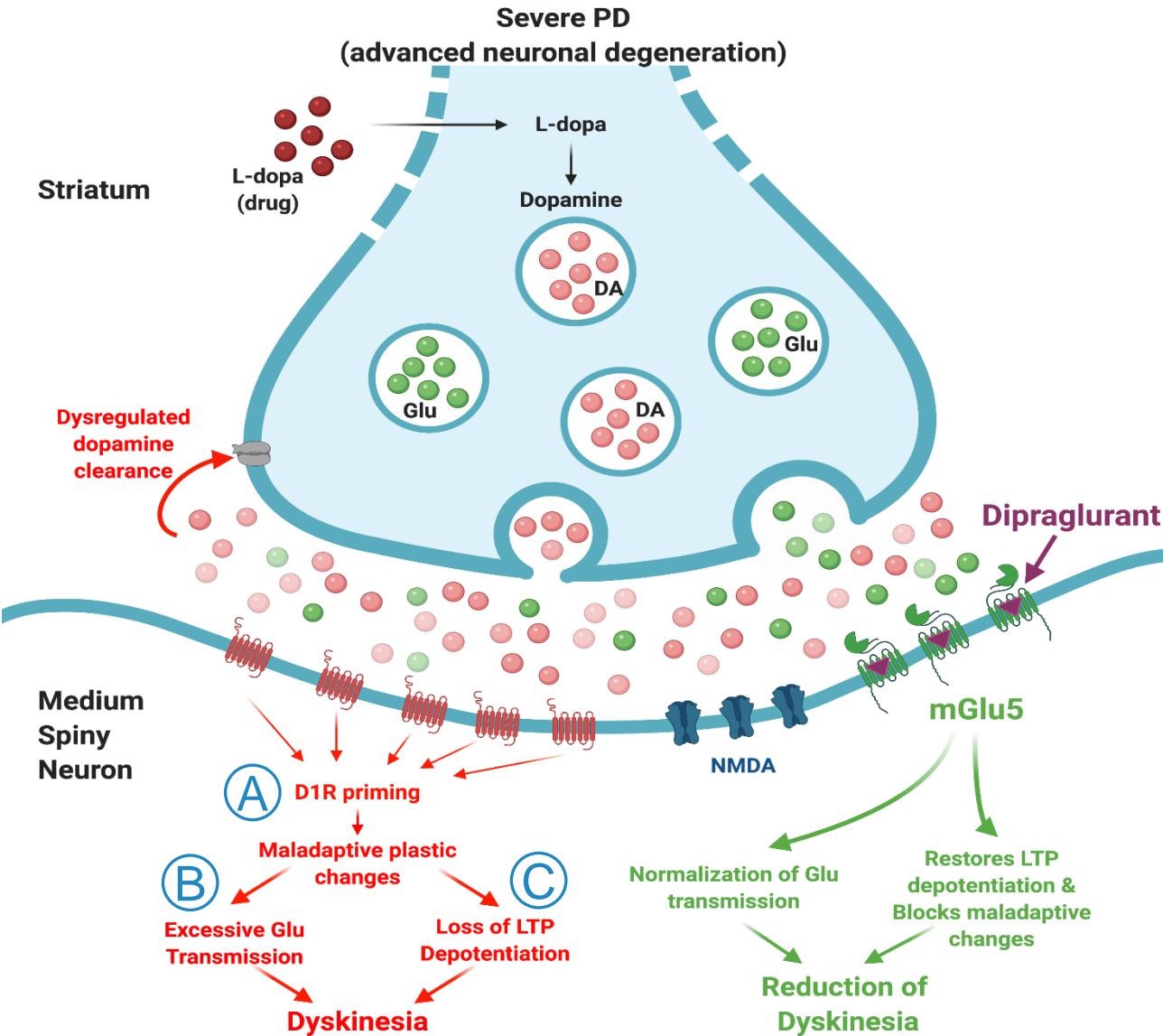
- Large underserved patient population in need of improved treatment options
- Significant commercial opportunity with limited competition
  - 1M Parkinson's disease patients in US of which >170,000 have dyskinesia
  - GOCOVRI® price: \$34K p.a., Nuplazid® price: \$45K p.a.
  - US LID market estimated 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

# Disability and Impact of PD-LID

Invariably associated with long-term L-dopa use	<ul style="list-style-type: none"><li>• Dyskinesias caused by neurodegeneration</li><li>• Dopamine replacement lowers the triggering threshold for symptoms</li><li>• LID can become as disabling as the PD symptoms themselves</li></ul>
Symptoms include dystonia, chorea, and choreoathetosis	<ul style="list-style-type: none"><li>• Uncontrollable muscle contractions, twisting and writhing</li><li>• Painful and severely disabling</li><li>• Causes fatigue/exhaustion and increased risk for falls and injuries</li><li>• Social withdrawal, reduced quality of life and increased burden on caregiver</li></ul>
Prevalence related to disease duration	<ul style="list-style-type: none"><li>• &gt;40% of patients experience LID within 4-6 years of L-dopa treatment</li><li>• Increases to 90% after 9 -15 years</li><li>• Patients treated with next-generation L-dopa will still experience LID</li></ul>
PD drug efficacy wanes over time - exacerbated by emergence of LID	<b>Treatment becomes a balancing act requiring constant adjustments to ensure symptom control &amp; minimize intolerable side effects</b>

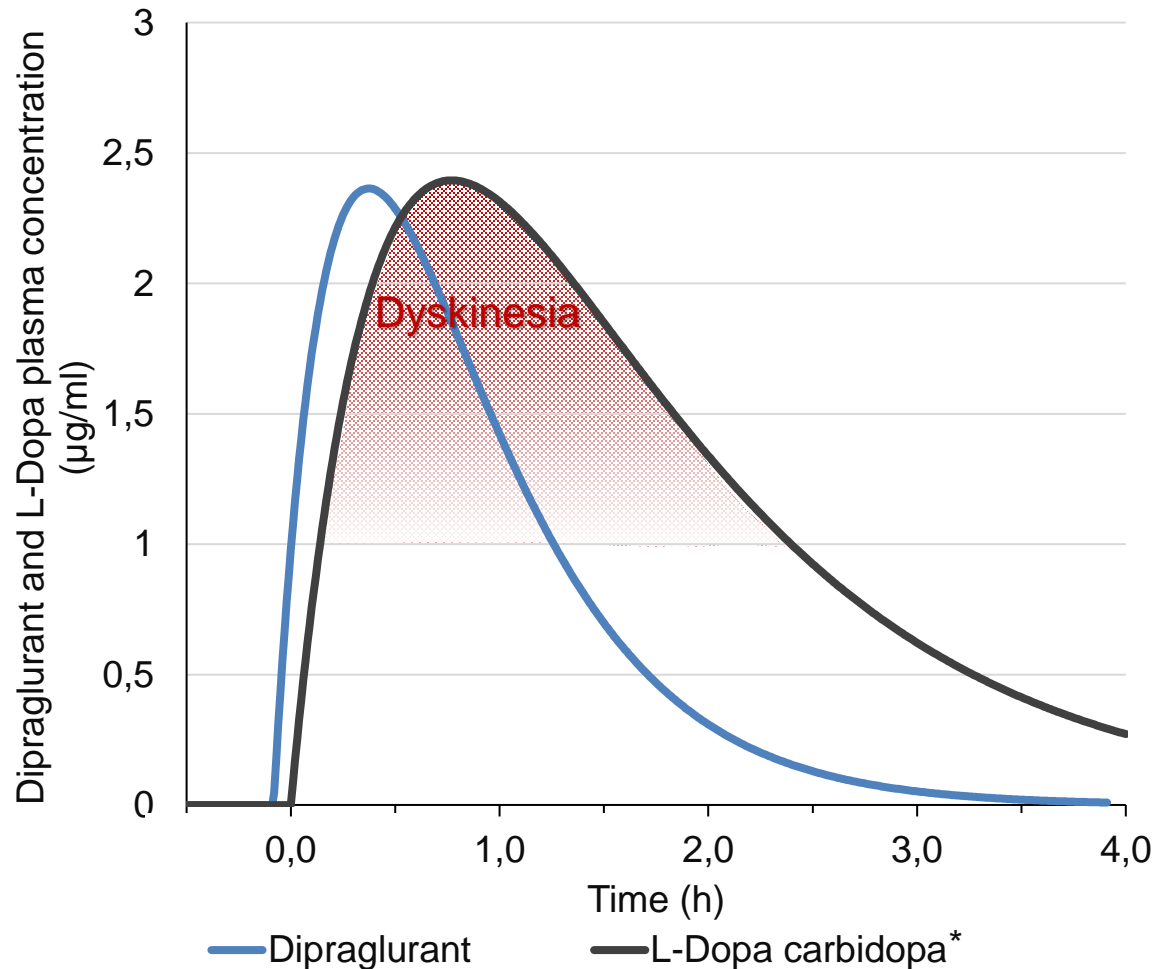


# MoA Rationale for Targeting mGlu5 Inhibition in PD-LID



- 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

# Dipraglurant PK is a Key Advantage for Treating LID

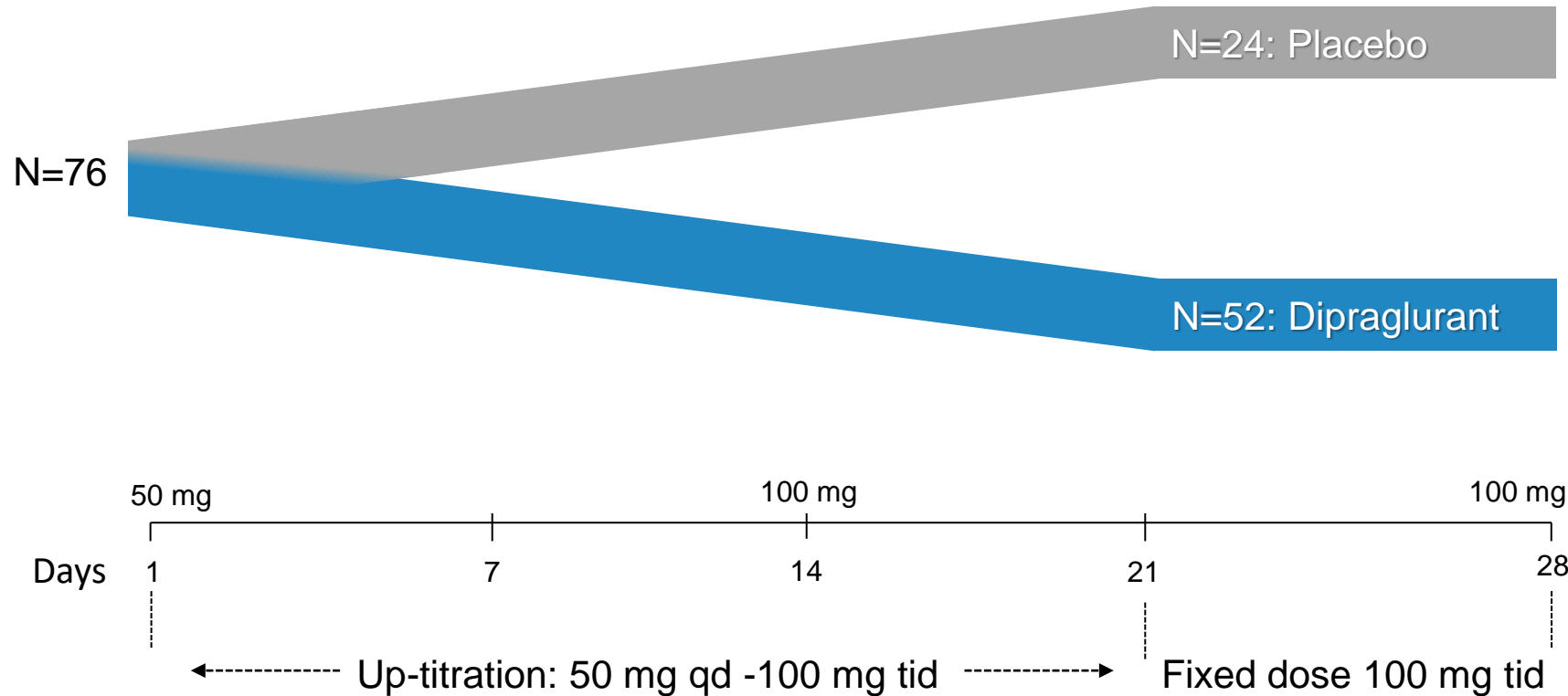


- Dyskinesia symptoms are correlated to peak levels of L-dopa
- PK of dipraglurant allows control of glutamatergic tone ahead of L-dopa Cmax

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

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

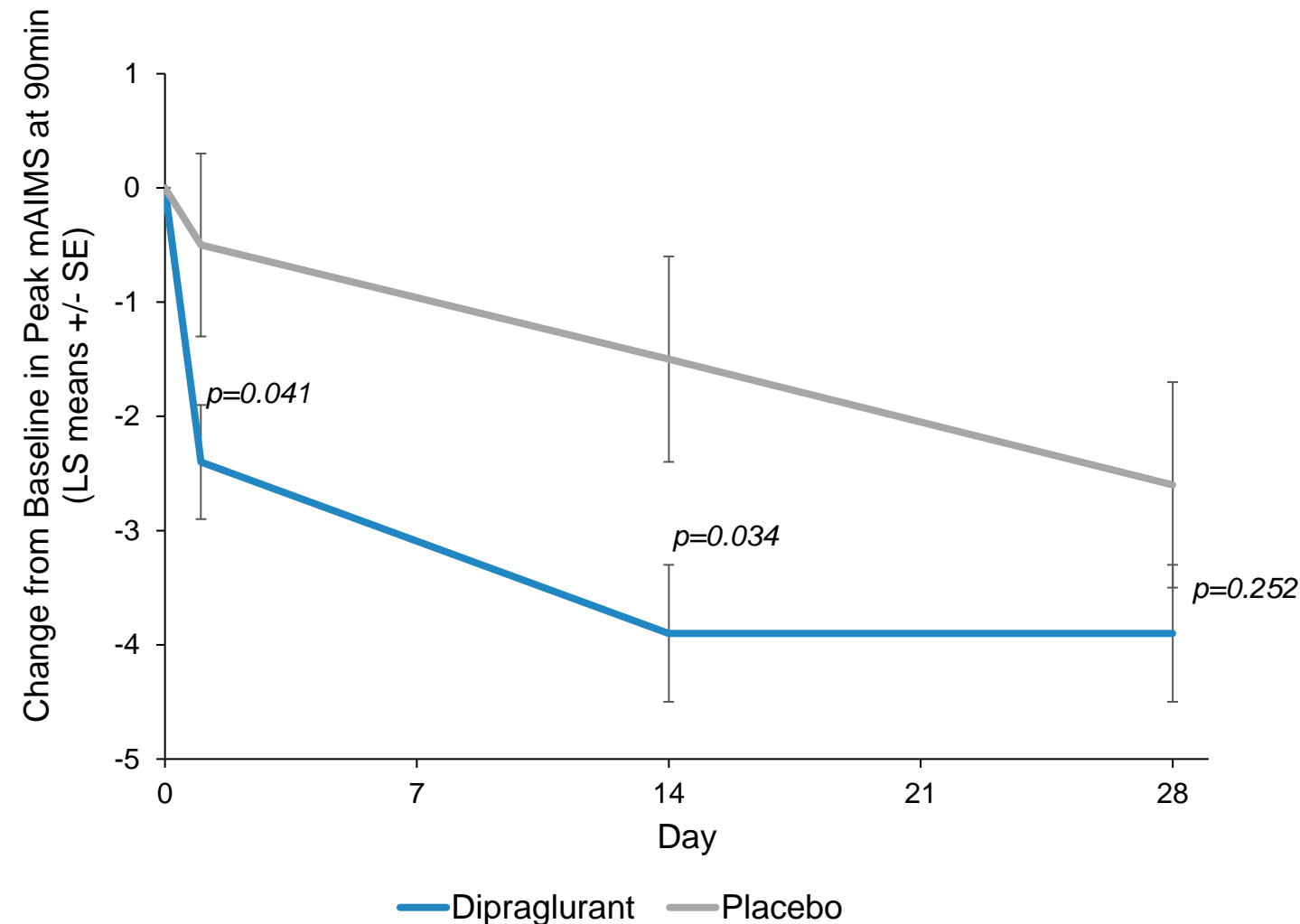
# Dipraglurant Phase 2a Study in LID (in US and Europe)



- **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%

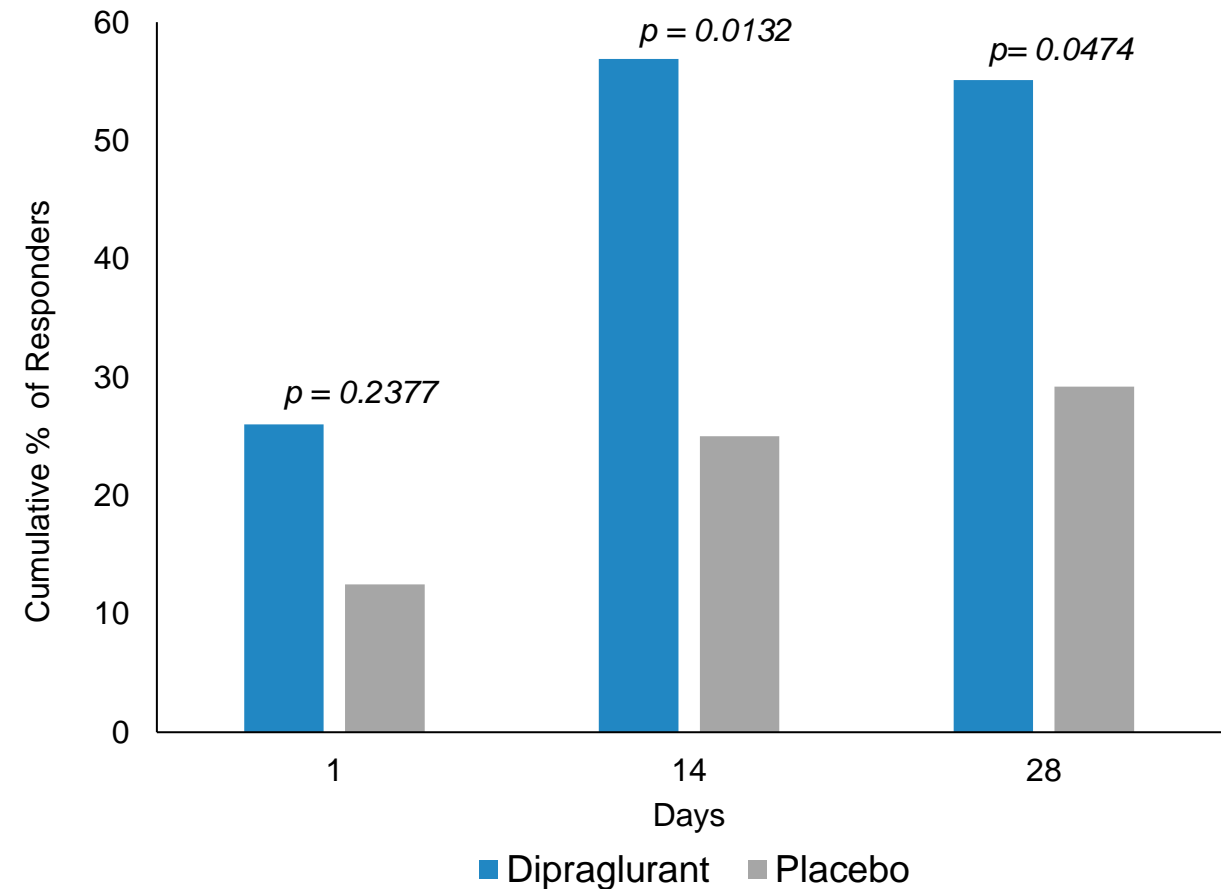


- Statistically significant effects: Day 1 (50mg) and Day 14 (100mg)
- Improvement maintained through Day 28
- Increasing placebo response caused significance to be lost at Day 28
- No placebo mitigation in study

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%

# Responder Analysis Demonstrates Dipraglurant Significant Benefit

Percent of patients with ≥ 30% improvement on mAIMS

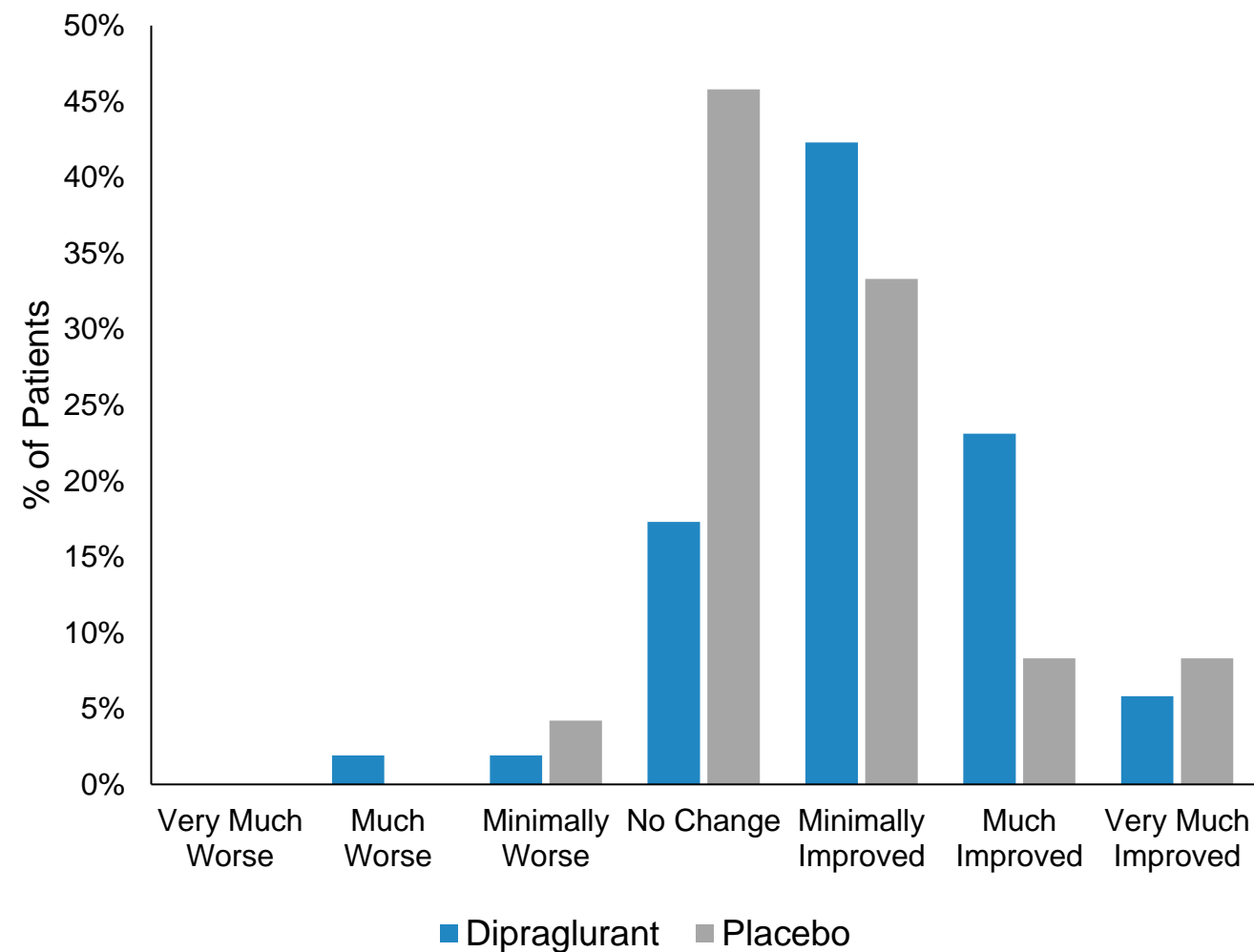


Responder analysis (≥30% change of mAIMS from baseline)				
Midday dose	Dipraglurant		Placebo	
Day 1 (50 mg)	n=13	26.0%	n=3	12.5%
Day 14 (100 mg)	n=29	56.9%*	n=6	25.0%
Day 28 (100 mg)	n=27	55.1%*	n=7	29.2%

\*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

# 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% <b>(15.3%*)</b>	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

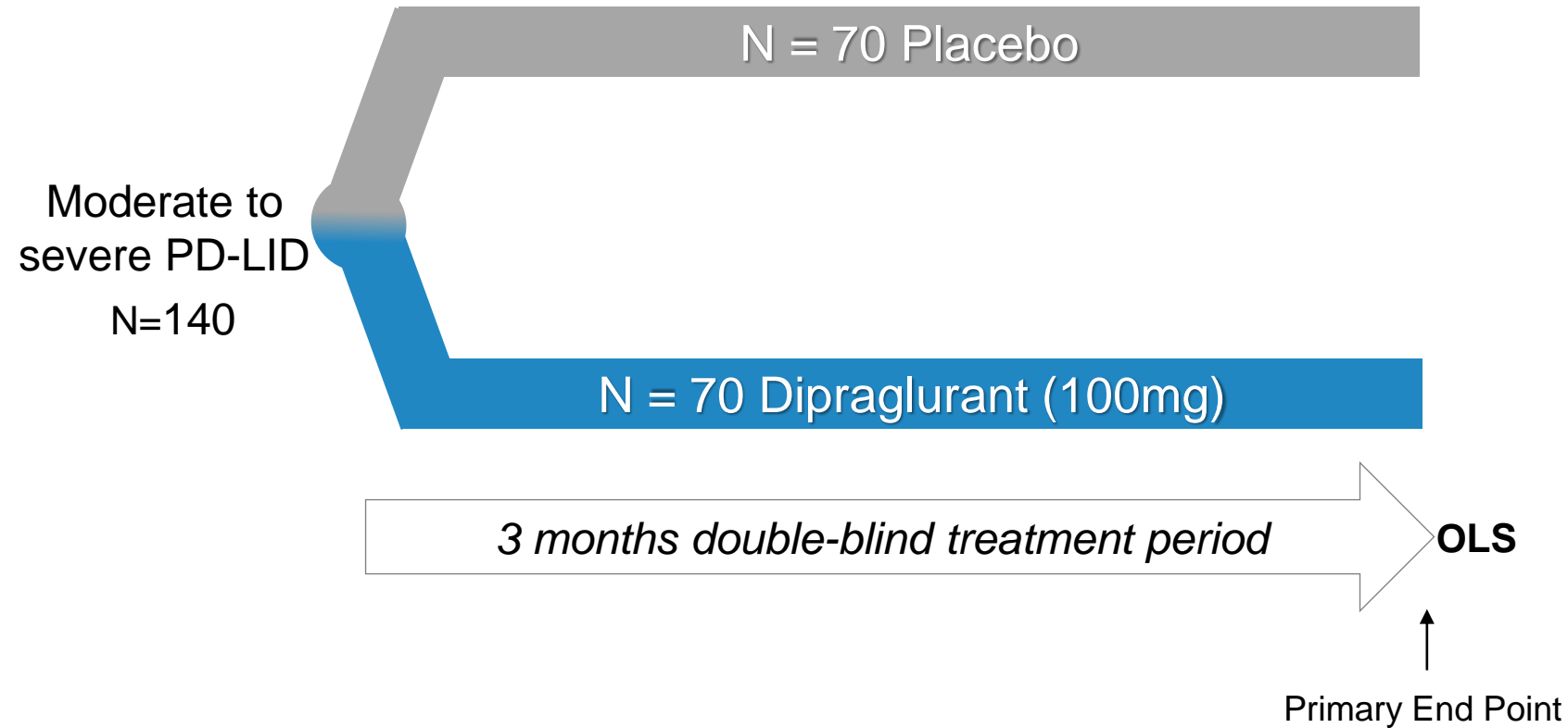
Safety profile supports continued development in PD-LID (KOLs and DSMB)

# Dipraglurant PD-L1D Registration Program Started

- Pivotal registration program ongoing
- Study 301 expected to start Q2 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

# UDysRS: An Improved and Validated Dyskinesia Rating Scale

	UDysRS	mAIMS
Characteristics	<ul style="list-style-type: none"><li>• Recommended by Movement Disorder Society (MDS)</li><li>• FDA regulatory precedent (GOCOVRI® approval)</li><li>• Contains anchored objective clinician evaluated measures of dyskinesia</li><li>• Includes both patient and physician assessments of impairment</li><li>• Less prone to placebo effect</li></ul>	<ul style="list-style-type: none"><li>• Suboptimal for detecting treatment-related changes</li><li>• Limited to patient assessments</li><li>• Prone to placebo effect</li></ul>
Clinimetrics	<ul style="list-style-type: none"><li>• Validated</li></ul>	<ul style="list-style-type: none"><li>• Only the original version has been validated</li></ul>
Development	<ul style="list-style-type: none"><li>• Developed in 2009 specifically for dyskinesia in PD</li></ul>	<ul style="list-style-type: none"><li>• Developed in 1970 for tardive dyskinesia in psychiatry</li></ul>

# 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

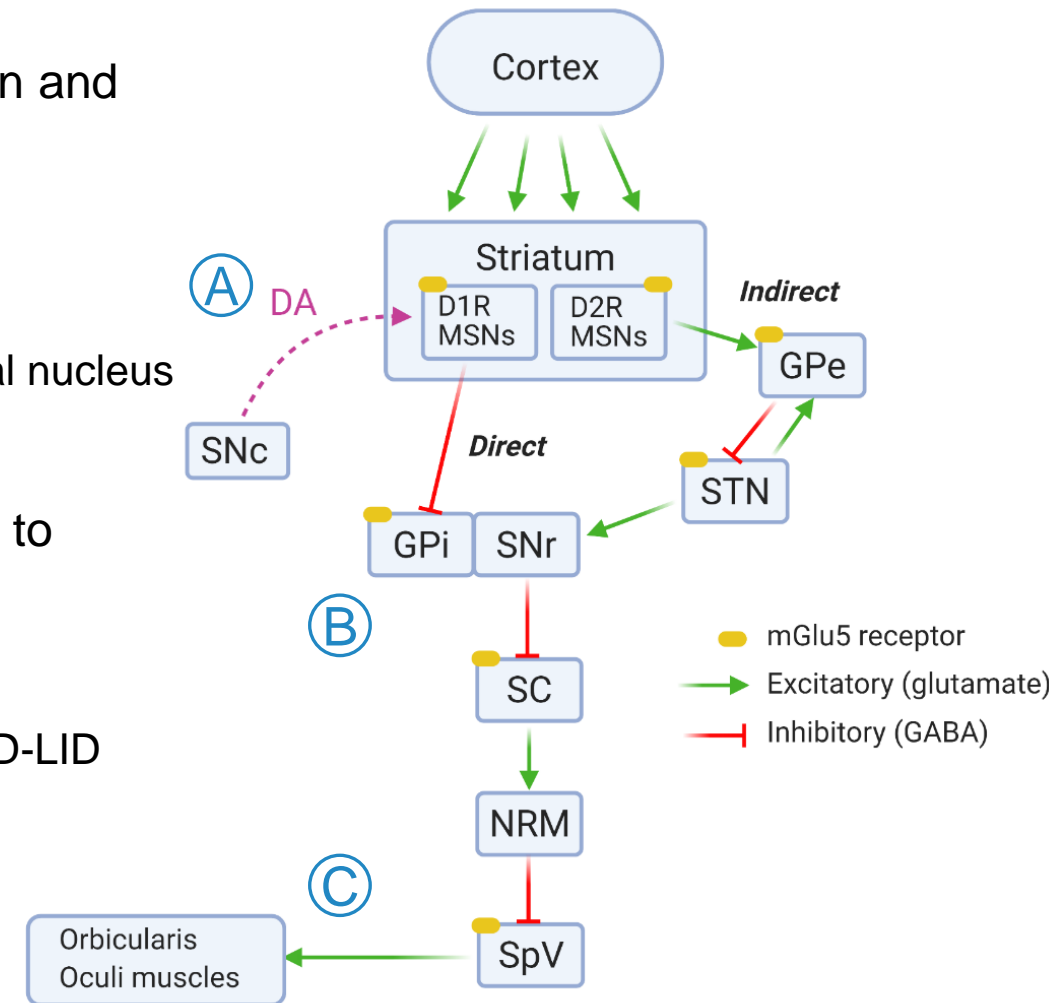
# Dipraglurant for Dystonia – Blepharospasm

# 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 Q2 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

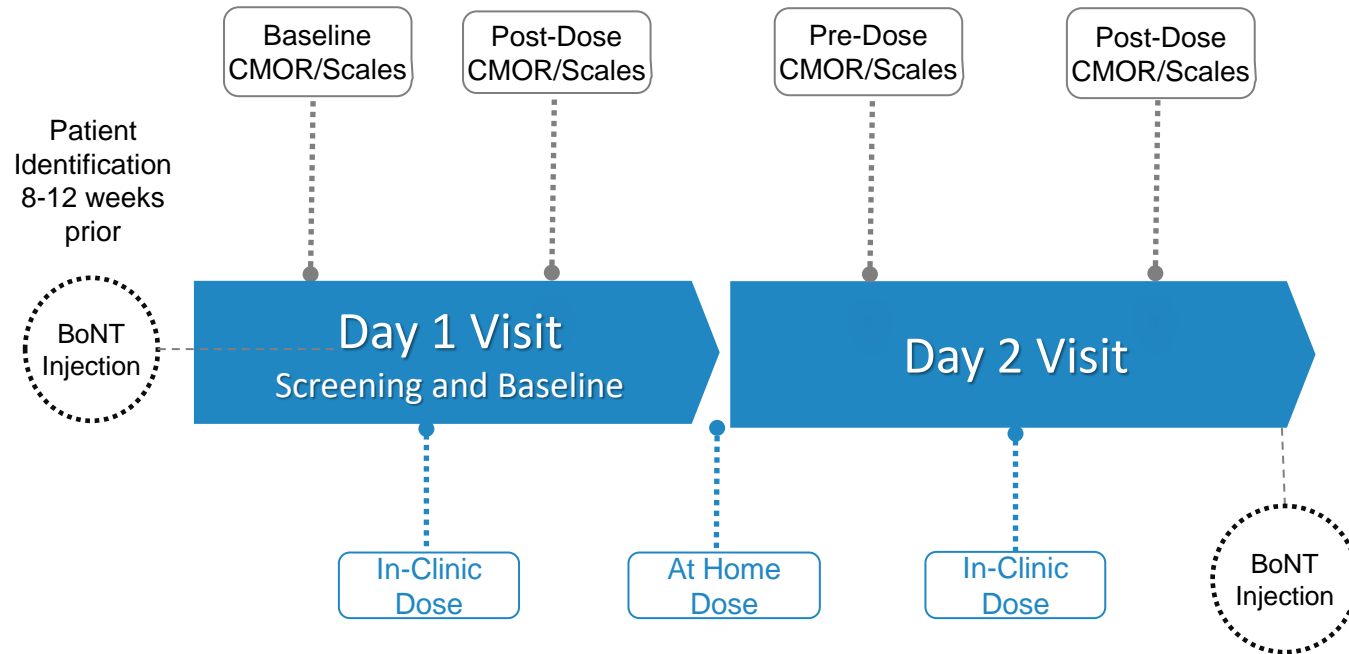
# Rationale for Targeting mGlu5 Inhibition in Dystonia & BSP

- 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

# 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\*
  - Keppra market leader with approx. 2.2M patients & >€800M p.a.\*\*
- High proportion of refractory patients (¼ of new patients\*\*\*) - combination treatments have limited therapeutic benefit
- Large underserved patient population in need of improved treatment options

## ADX71149: true synergistic MoA

- Selective oral mGlu2 PAM with clear MoA in epilepsy
- Showed 35-fold increase in Keppra efficacy in preclinical model
- Potential first rational polypharmacy in epilepsy

## Development path

- Extensive preclinical and clinical data
  - 8 Phase 1 and 2 Phase 2 studies
- Janssen Pharmaceuticals, Inc. expect to start POC study in Q2 2021
  - Top line data expected in H1 2022

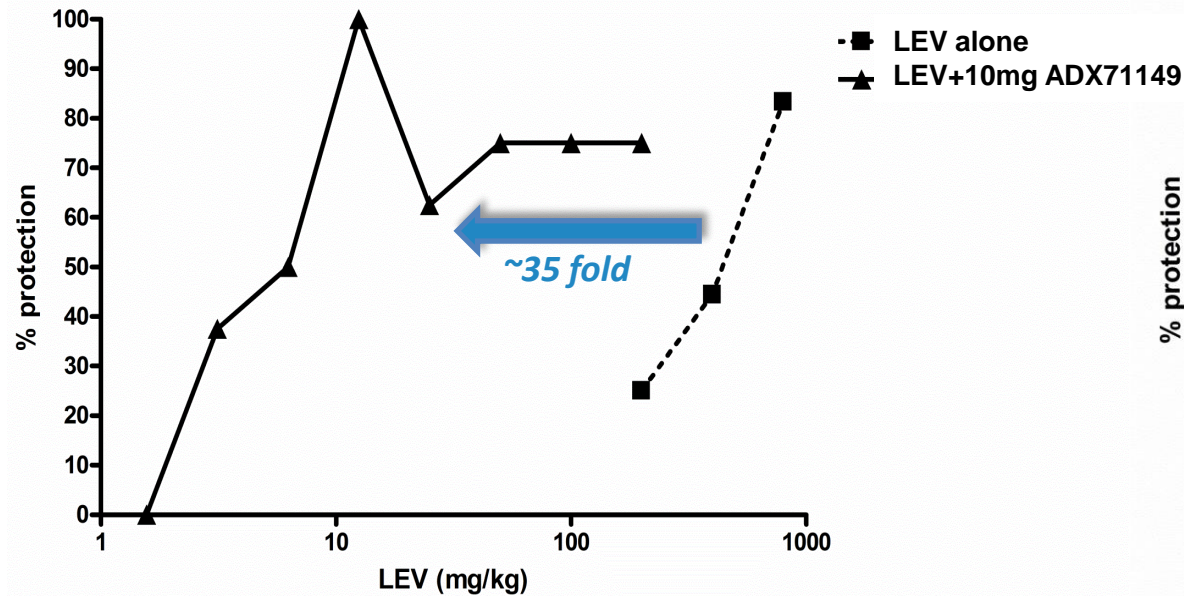
## Strategic Partner Janssen Pharmaceuticals, Inc.

- Eligible to receive €109 million in pre-launch milestones and double digit royalties

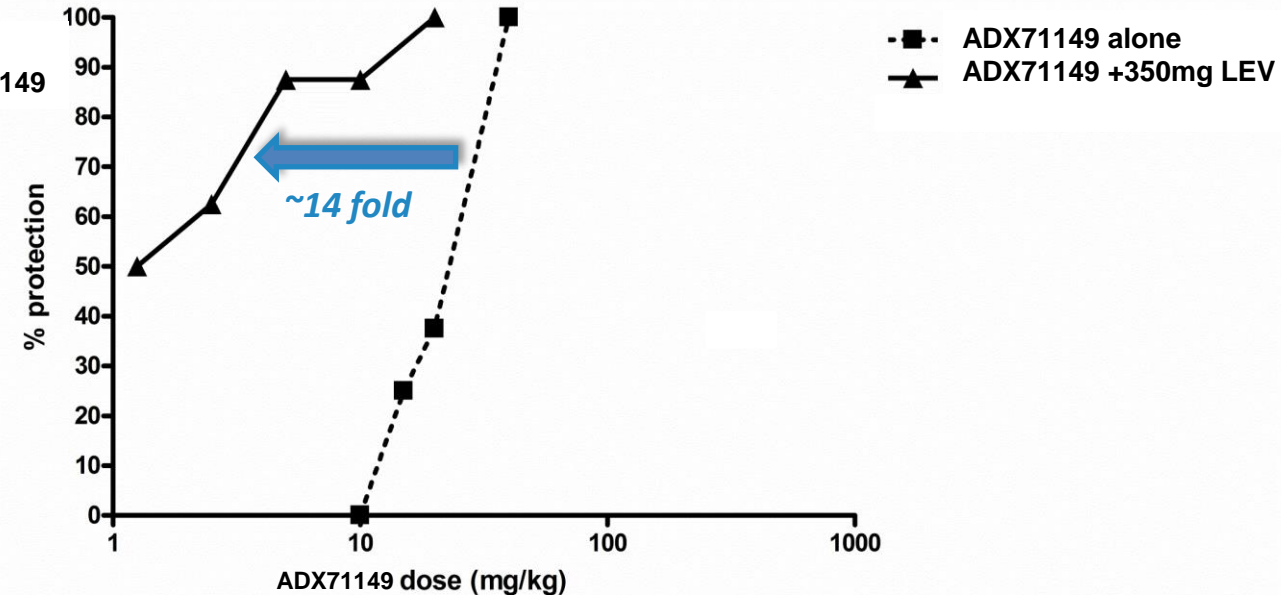
# ADX71149 Preclinical Efficacy in Epilepsy - 6Hz Model

- Preclinical validation in pharmaco-resistant mouse epilepsy model:

ED<sub>50</sub> shift of Keppra by adding low dose of ADX71149

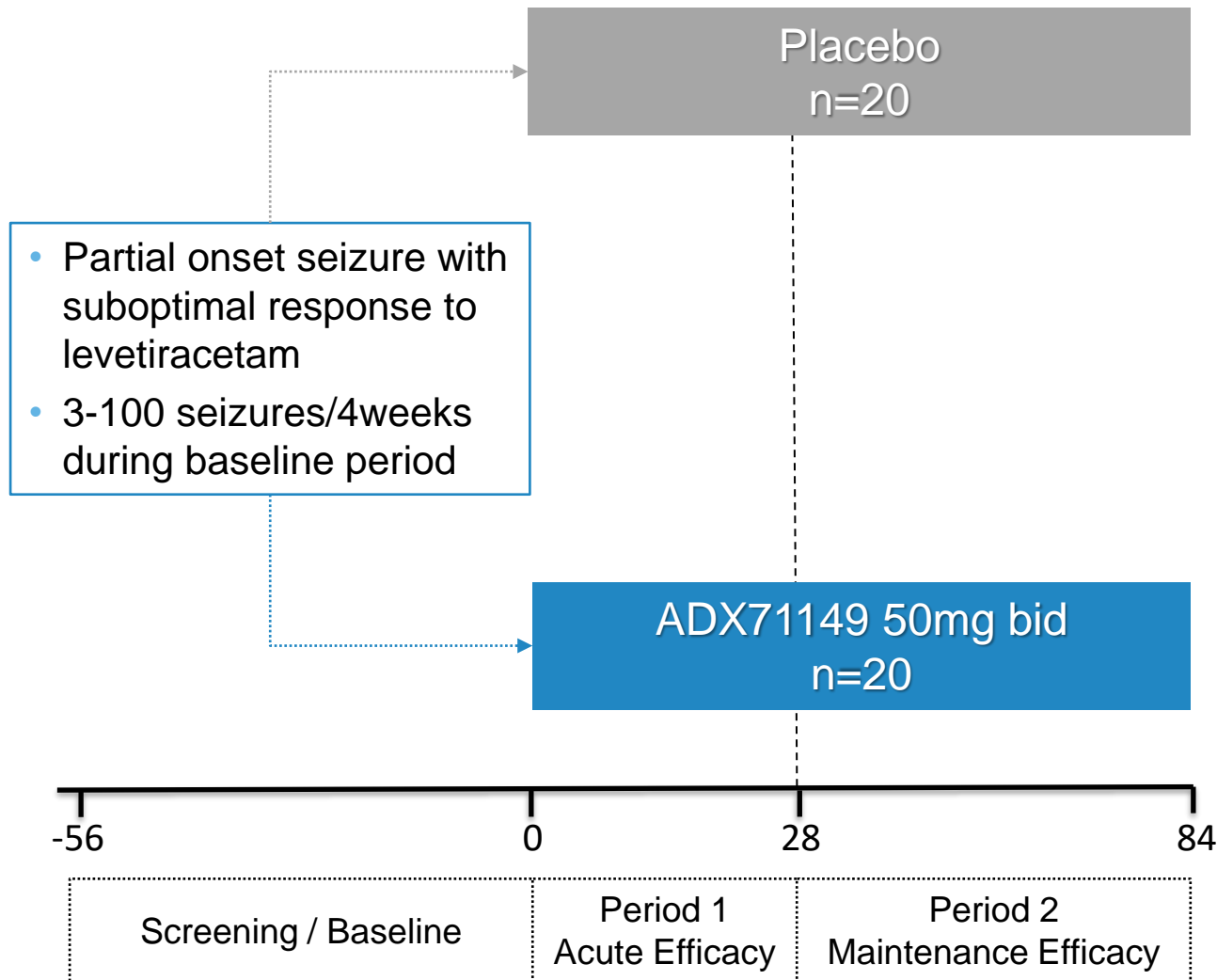


ED<sub>50</sub> shift of ADX71149 by adding ED<sub>50</sub> dose of LEV



- 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

# Financials

# Financials and Stock

- Cash runway through 2022
  - Cash at 31 Dec 2020: CHF18.7 million
  - Completed \$11.5M capital increase 11 Jan 2021
- 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 - 4.86%
  - Credit Suisse Asset Management - 3.01%
  - 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 - start study	Q2 2021
Phase 2b/3 - topline results	Q4 2022
Dipraglurant for Blepharospasm	
Phase 2a - start study	Q2 2021
Phase 2a - topline results	Q4 2021
ADX71149 for Epilepsy	
Phase 2a - start study	Q2 2021
Phase 2a - topline results	H1 2022
GABA <sub>B</sub> PAM for Addiction and CMT1a	
Complete clinical candidate selection	Q4 2021
Start IND enabling studies	Q1 2022

# Summary

3 clinical programs starting in Q2 2021	<ul style="list-style-type: none"><li>• Dipraglurant PD-L1D registration study</li><li>• Dipraglurant blepharospasm Phase 2</li><li>• ADX71149 (J&amp;J) epilepsy Phase 2</li></ul>
Technology and capabilities to deliver	<ul style="list-style-type: none"><li>• Experienced team of drug developers</li><li>• Pioneering allosteric modulation drug development<ul style="list-style-type: none"><li>– Proprietary screening assays and unique chemical library</li></ul></li><li>• All programs developed in-house, protected with &gt;200 patents</li></ul>
Solid foundation	<ul style="list-style-type: none"><li>• Partnerships with industry leaders</li><li>• Top tier US investors - NEA, NLV and CAM Capital Program</li><li>• Dual listed SIX Swiss exchange &amp; US Nasdaq</li></ul>
Promising outlook	<ul style="list-style-type: none"><li>• Rich news flow in 2021 and beyond<ul style="list-style-type: none"><li>– Clinical programs</li><li>– Multiple drug candidates in CCS</li></ul></li></ul>



# ALLOSTERIC MODULATORS FOR HUMAN HEALTH

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[www.addextherapeutics.com](http://www.addextherapeutics.com)