addex Therapeutics

Innovative Treatments for Central Nervous System Disorders

November 2021

Allosteric modulators for human health

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Addex Overview

3 clinical programs underway	• Phase 3 Parkinson's disease dyskinesia study – data Q4 2022 • Phase 2 blepharospasm study – data Q1 2022 • Phase 2 epilepsy study (J&J) – data Q3 2022
Leading allosteric modulator technology platform	• Validated & differentiated pharmacological approach • Proprietary biological screening assays and chemical library • Track record of delivering novel drug candidates
In house discovered pipeline	• Significant intellectual property portfolio • Multiple novel drug candidates entering clinical candidate selection • Driving long term growth & future partnership opportunities
Partnerships with industry	• J&J - €109M in milestones & double digit royalties • 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 • Cash of CHF15.5M ($16.6M) at 30 September 2021

Addex Pipeline - 3 Clinical Programs Underway

Molecule / MoA	Indication	Partner	Pre-clinical	Phase 1	Phase 2	Phase 3	Milestone
Dipraglurant (mGlu5 NAM)	PD-LID						Data Q4 2022
	Blepharospasm						Data Q1 2022
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 CEO / CFO	Dr Roger Mills Chief Medical Officer	Dr Robert Lutjens Head of Discovery Biology	Dr Jean-Philippe Rocher Head of Discovery Chemistry	Dr Mikhail Kalinichev Head of Translational Science
Co-Founder of Addex Formerly with PwC UK Chartered Accountant	Developed Nuplazid for PD Psychosis >30 years Pharma industry incl. Pfizer, Gilead and Acadia	Member of Addex founding team Formerly with Glaxo & Scripps Research Institute	Member of Addex founding team Formerly with Pierre Fabre, GSK and Mitsubishi	Neuropharmacologist with >20 years experience Formerly with Ipsen, Lundbeck and GlaxoSmithKline

Non-executive Directors

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

Scientific Advisory Board

Darryle Schoepp Chairman of SAB	Mark Bear Picower Prof. of Neuroscience at MIT	Peter Bernstein Principal, PhaRmaB LLC	Benny Bettler 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 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

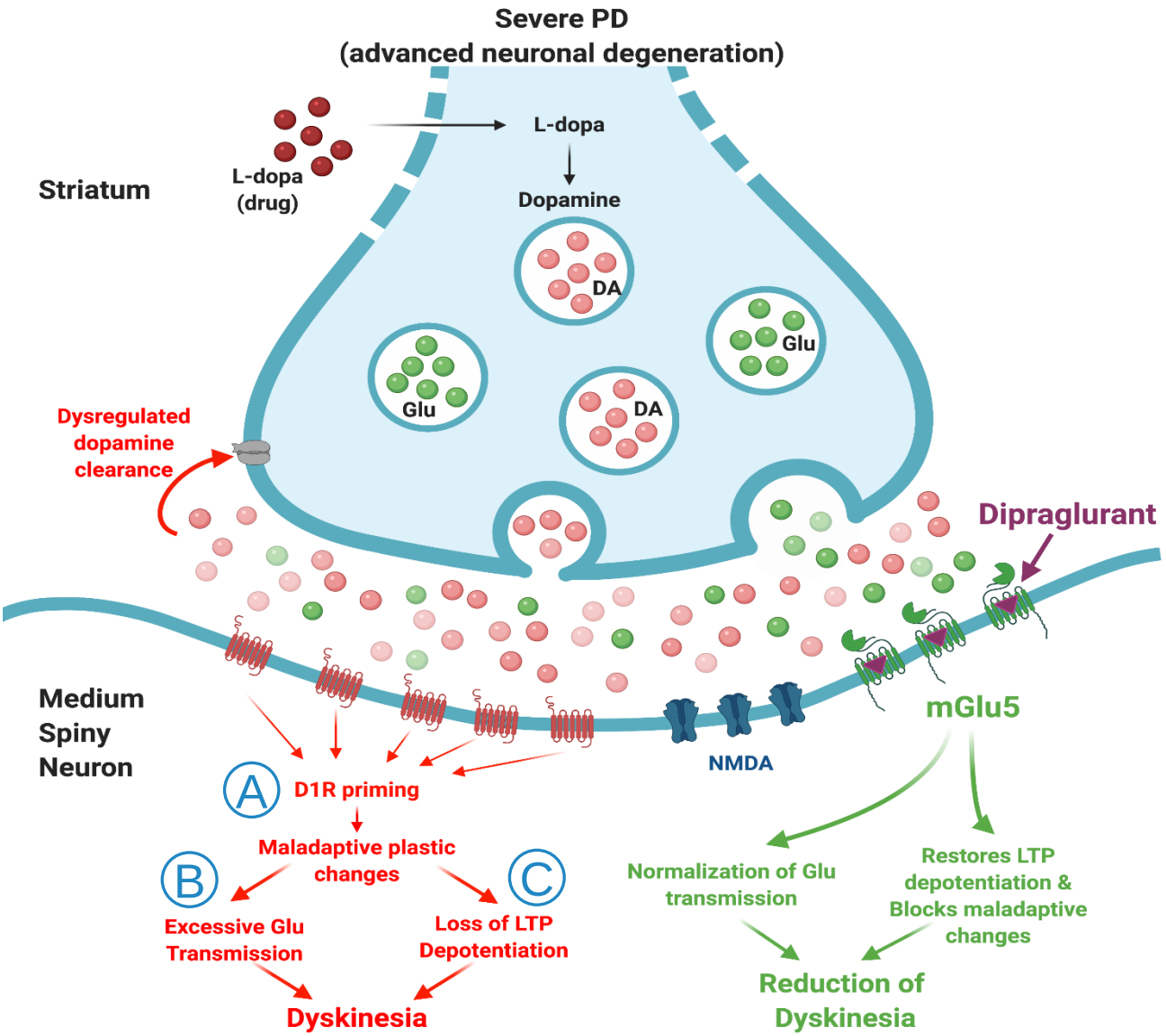
- Large underserved patient population in need of improved treatment options
- Significant commercial opportunity with limited competition
  - 1M Parkinson's disease patients in US of which >170,000 have dyskinesia
  - GOCOVRI® price: $34K p.a., Nuplazid® price: $45K p.a.
  - US LID market estimated 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 • Dopamine replacement lowers the triggering threshold for symptoms • LID can become as disabling as the PD symptoms themselves
Symptoms include dystonia, chorea, and choreoathetosis	• Uncontrollable muscle contractions, twisting and writhing • Painful and severely disabling • Causes fatigue/exhaustion and increased risk for falls and injuries • 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 • Increases to 90% after 9 -15 years • 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**

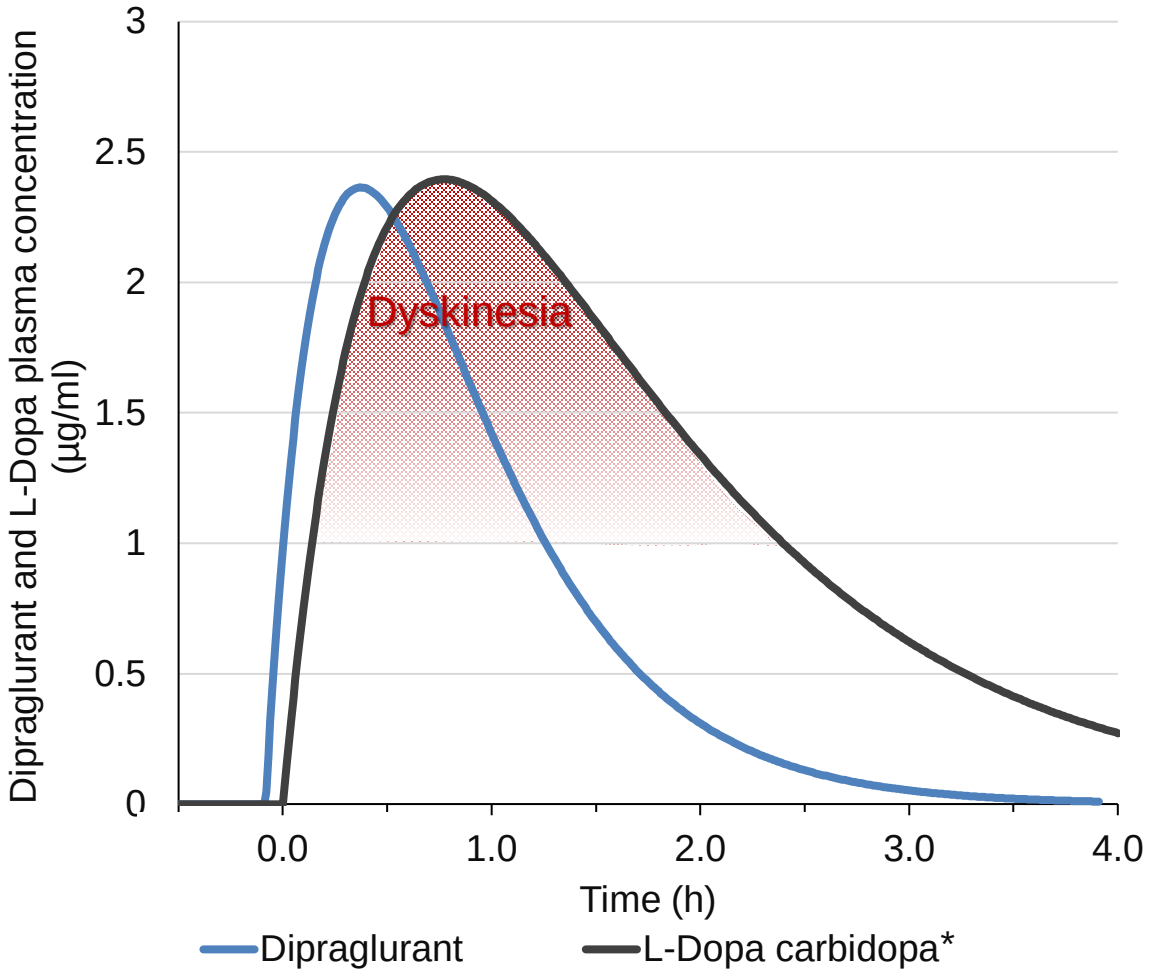
MoA Rationale for Targeting mGlu5 Inhibition in PD-LID



- 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



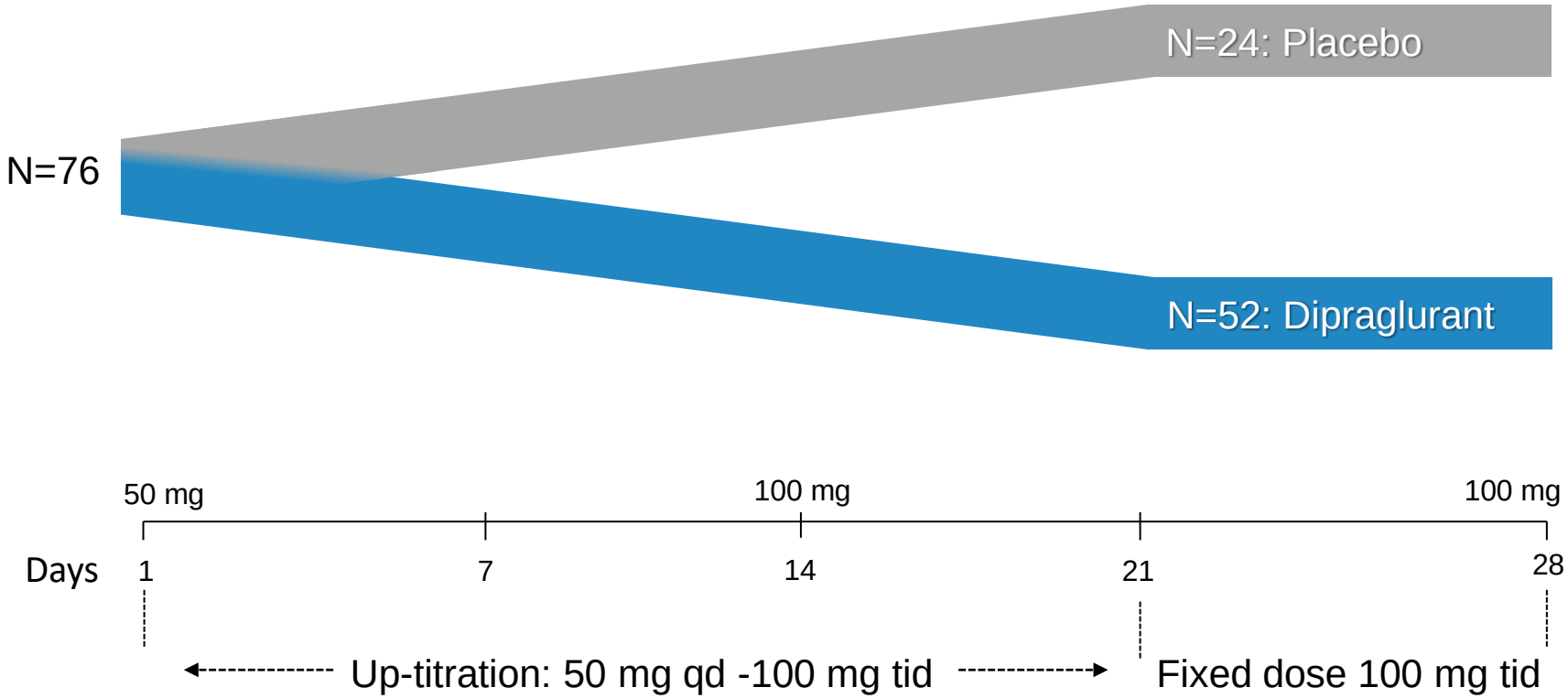
- Dyskinesia symptoms are correlated to peak levels of L-dopa
- PK of dipraglurant allows control of glutamatergic tone ahead of L-dopa Cmax

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

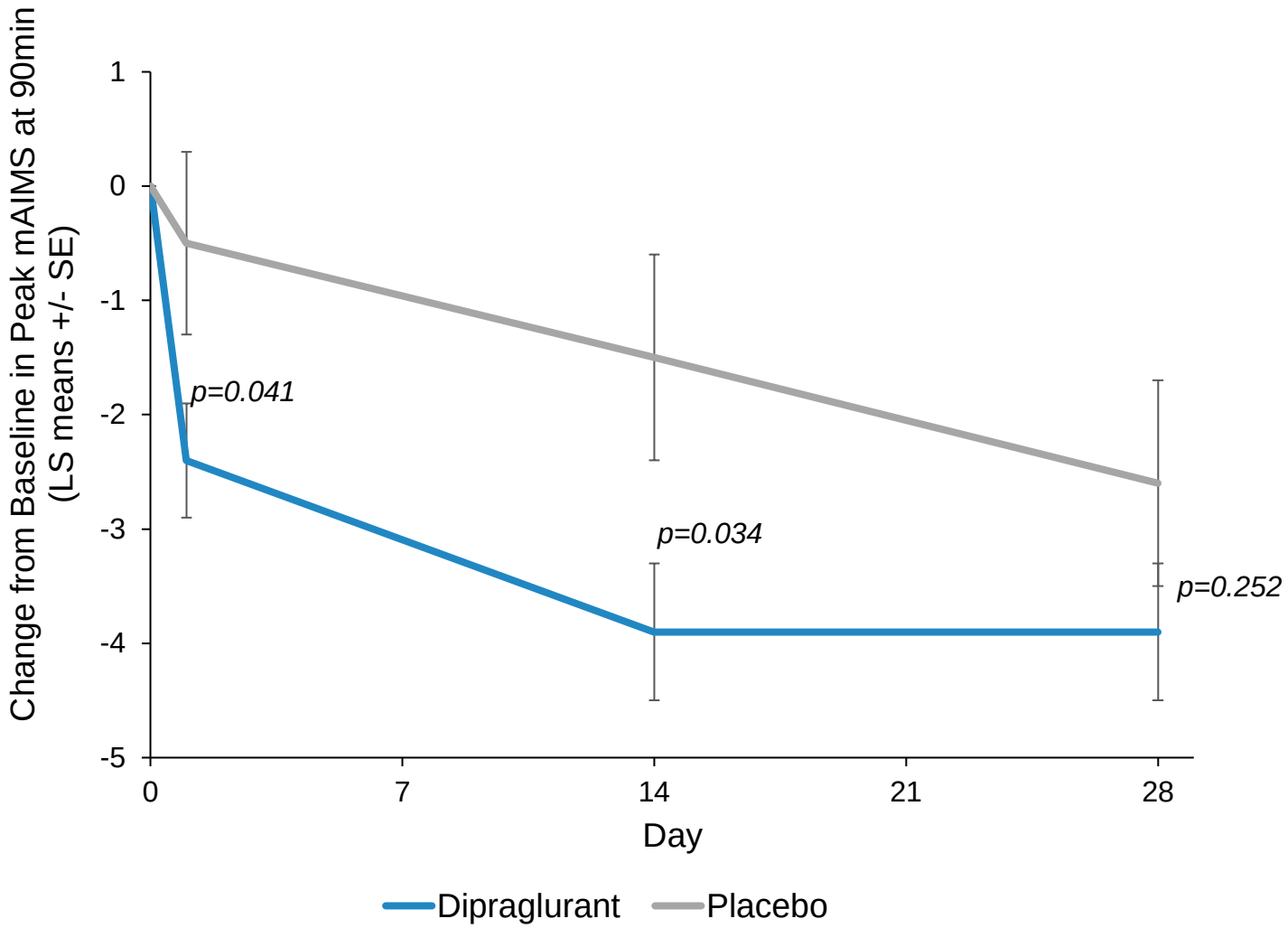
Dipraglurant Phase 2a Study in LID (in US and Europe)



- **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%

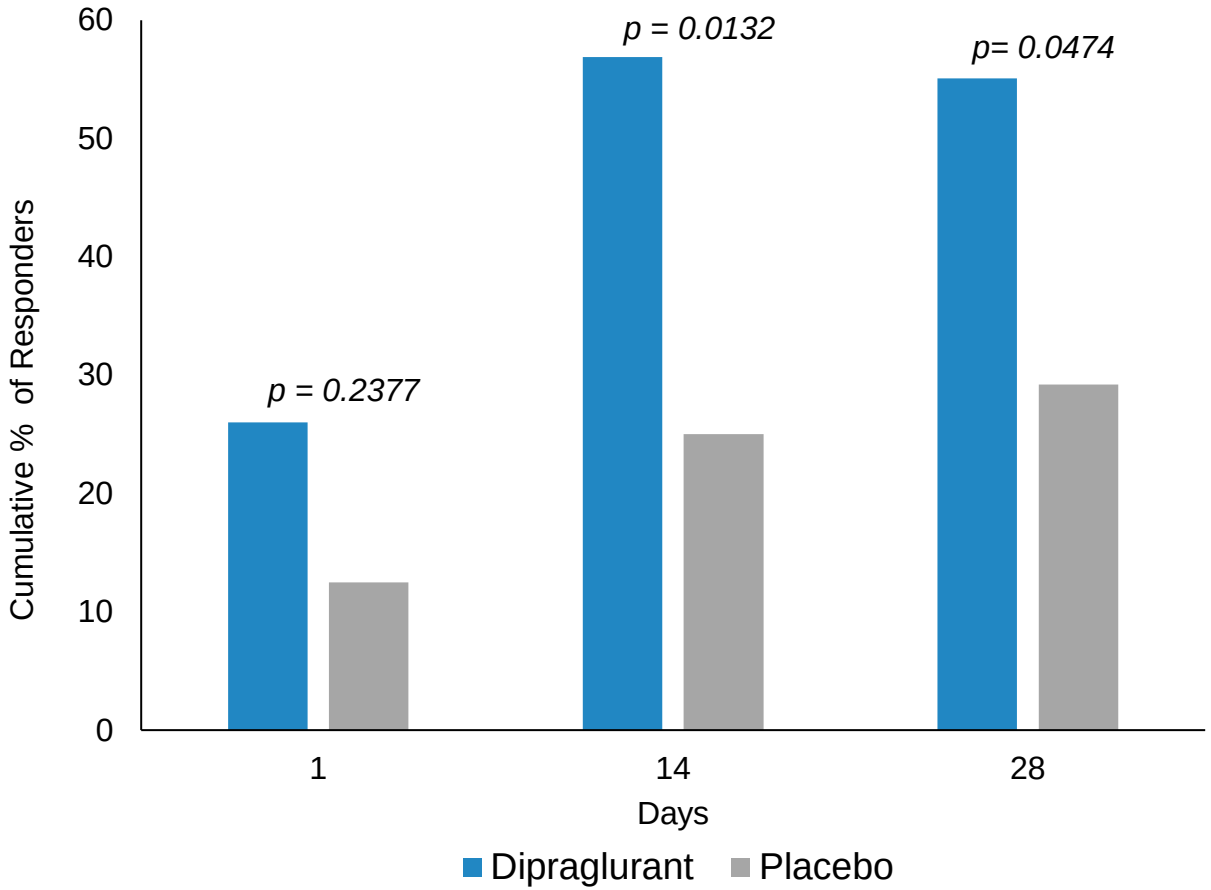


- Statistically significant effects: Day 1 (50mg) and Day 14 (100mg)
- Improvement maintained through Day 28
- Increasing placebo response caused significance to be lost at Day 28
- No placebo mitigation in study

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%

Responder Analysis Demonstrates Dipraglurant Significant Benefit

Percent of patients with ≥ 30% improvement on mAIMS

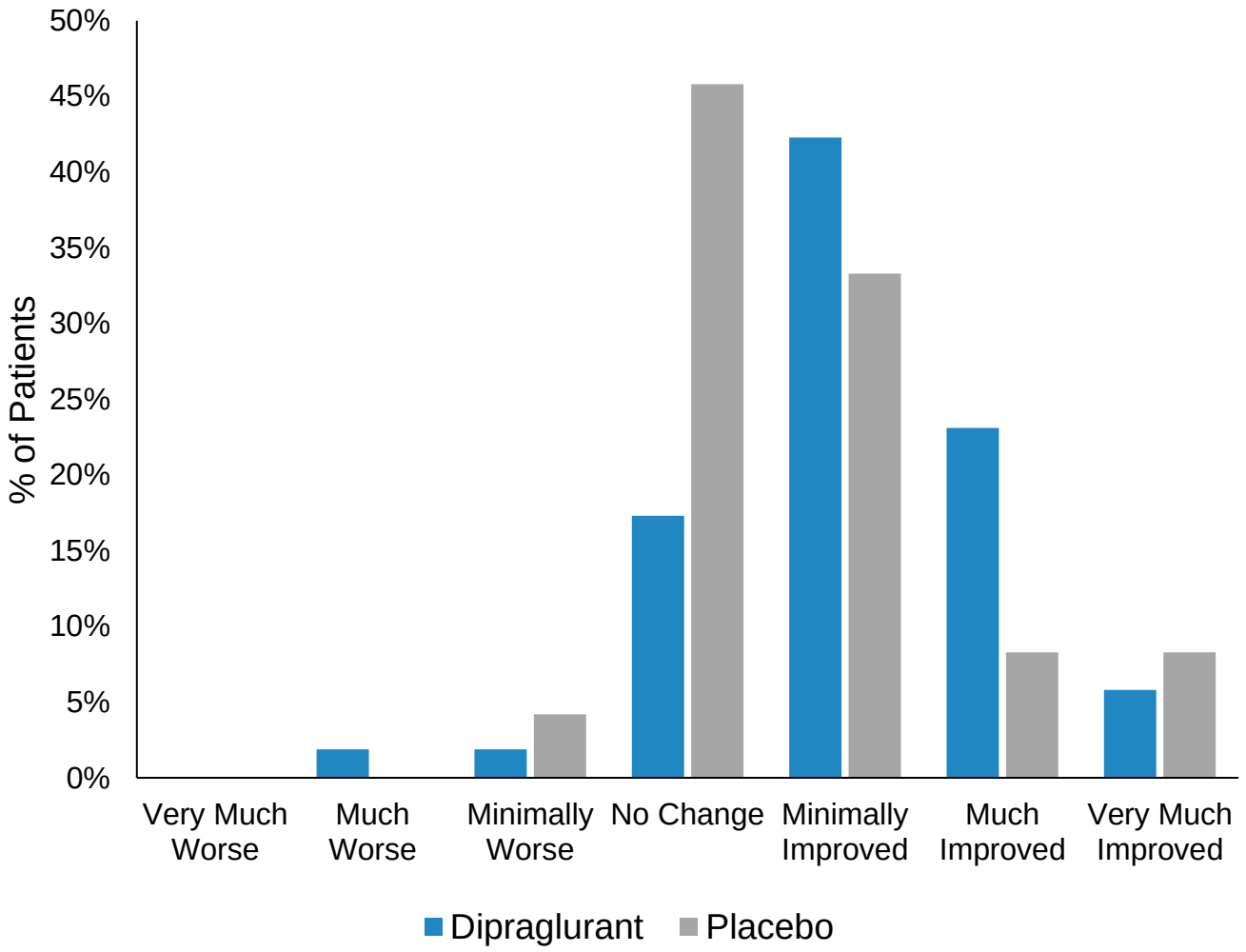


Responder analysis (≥30% change of mAIMS from baseline)				
Midday dose	Dipraglurant		Placebo	
Day 1 (50 mg)	n=13	26.0%	n=3	12.5%
Day 14 (100 mg)	n=29	56.9%*	n=6	25.0%
Day 28 (100 mg)	n=27	55.1%*	n=7	29.2%

*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

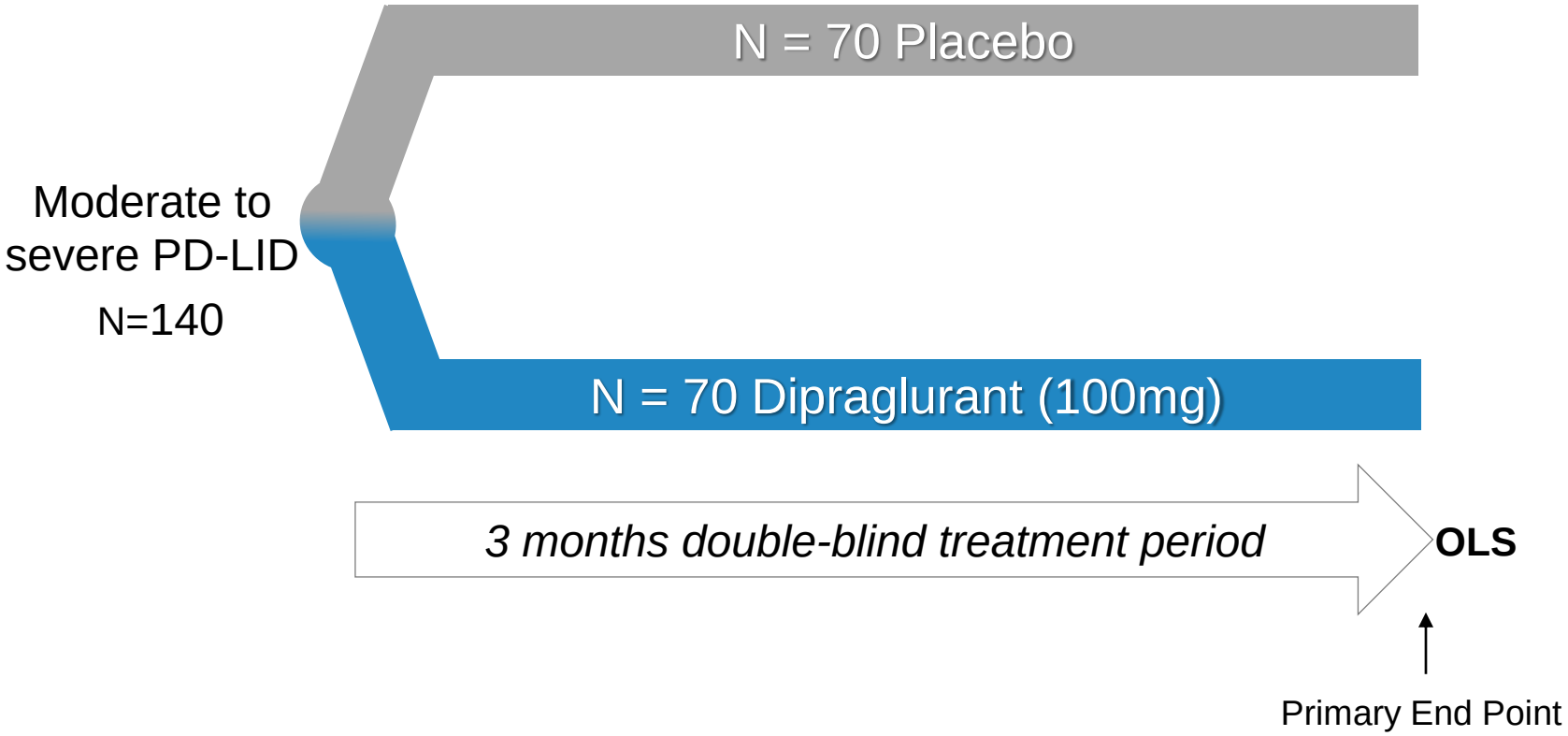
- Pivotal registration program ongoing

- 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) on going
  - 6- and 12-month safety data

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

Dipraglurant 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

Data expected in Q4 2022

OLS = Open label study

UDysRS: An Improved and Validated Dyskinesia Rating Scale

	UDysRS	mAIMS
Characteristics	• Recommended by Movement Disorder Society (MDS) • FDA regulatory precedent (GOCOVRI® approval) • Contains anchored objective clinician evaluated measures of dyskinesia • Includes both patient and physician assessments of impairment • Less prone to placebo effect	• Suboptimal for detecting treatment-related changes • Limited to patient assessments • 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

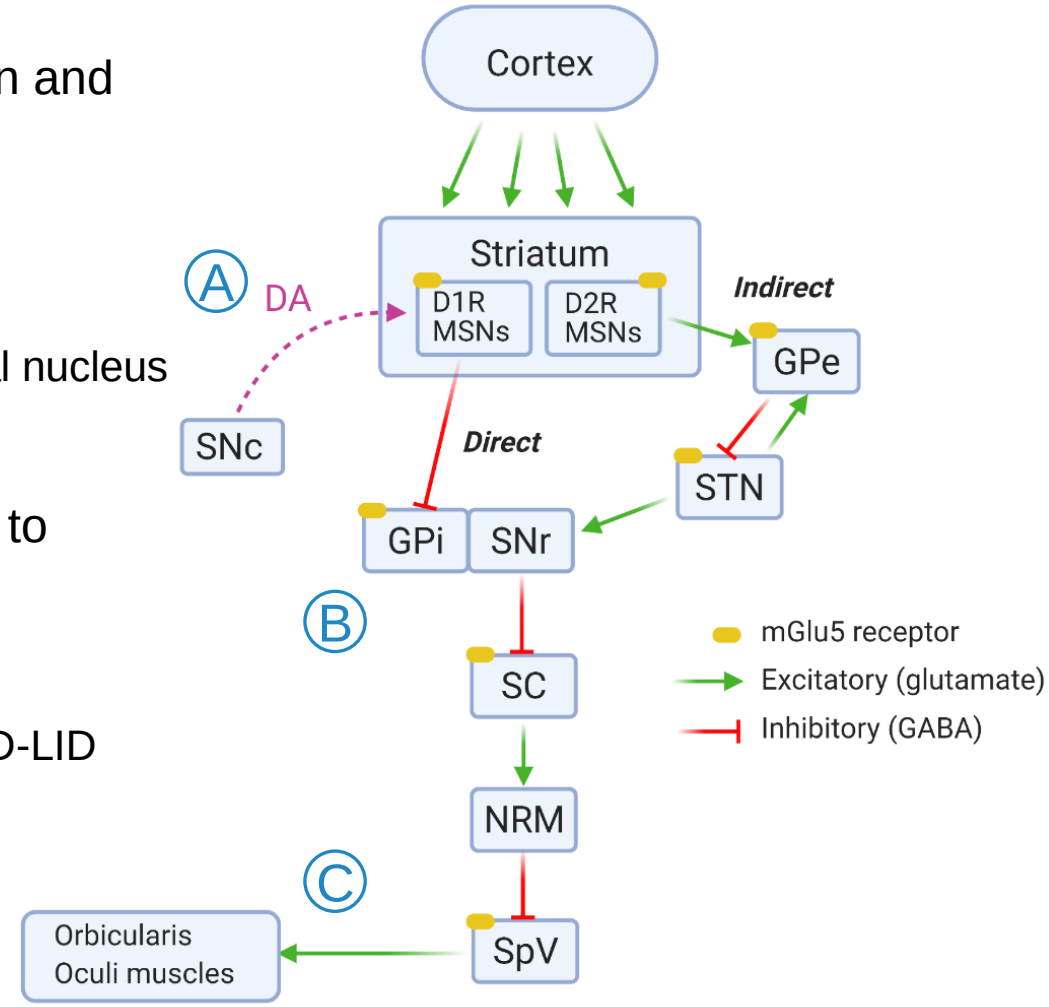
Dipraglurant for Dystonia – Blepharospasm

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 started in September 2021 with data expected in Q1 2022
- 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

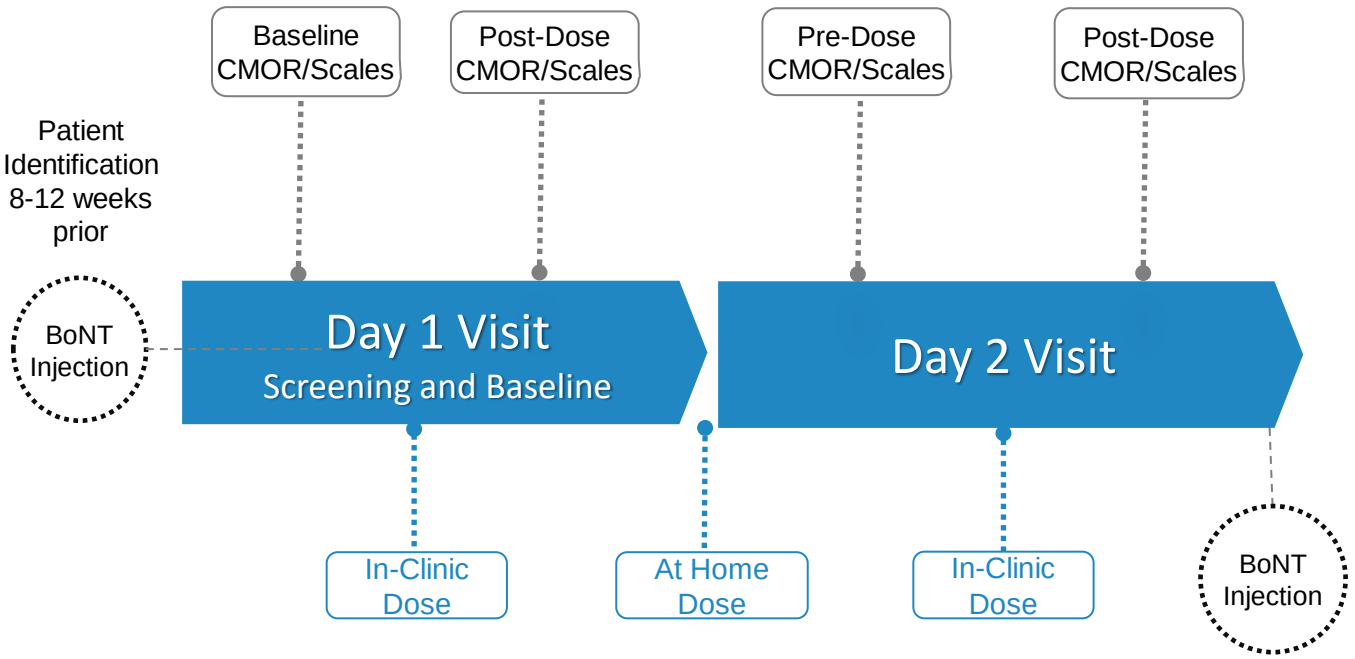
- Dystonias are *neuro-functional* rather than *neuro-degenerative*
- Common features include alterations in neuronal connectivity/function and synaptic communication
- BSP pathophysiology is linked to:
  - Ⓐ Reduction of dopamine input into striatum
  - Ⓑ Increased inhibition of direct pathway from 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



- 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

First patient enrolled in Sept 2021 - data expected in Q1 2022

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 > 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. started POC study in June 2021 – 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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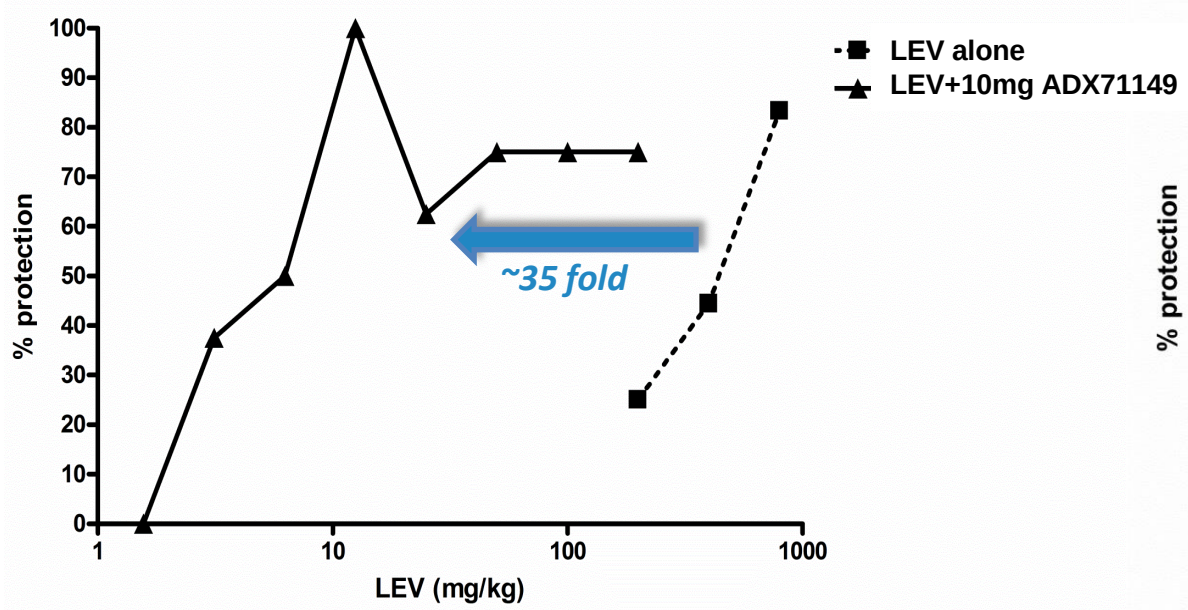
* Fortune Business Insights April 8, 2020
** UCB FY 2020
*** Xue-Ping et al, Medicine July 2019

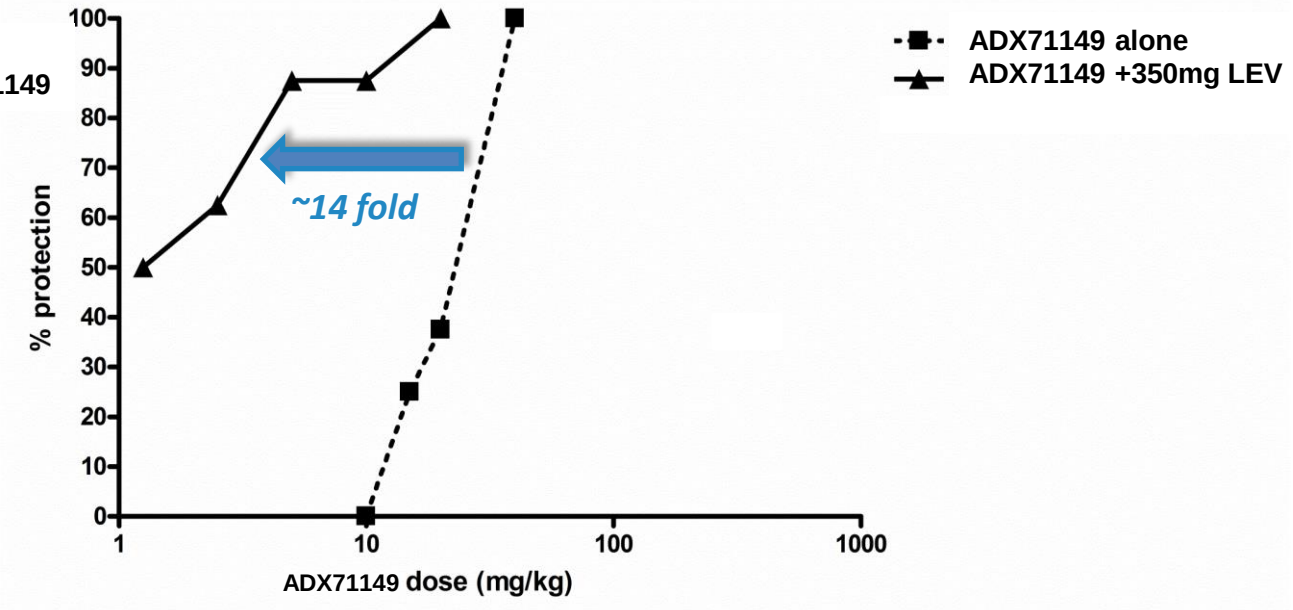
ADX71149 Preclinical Efficacy in Epilepsy - 6Hz Model

- Preclinical validation in pharmaco-resistant mouse epilepsy model:

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

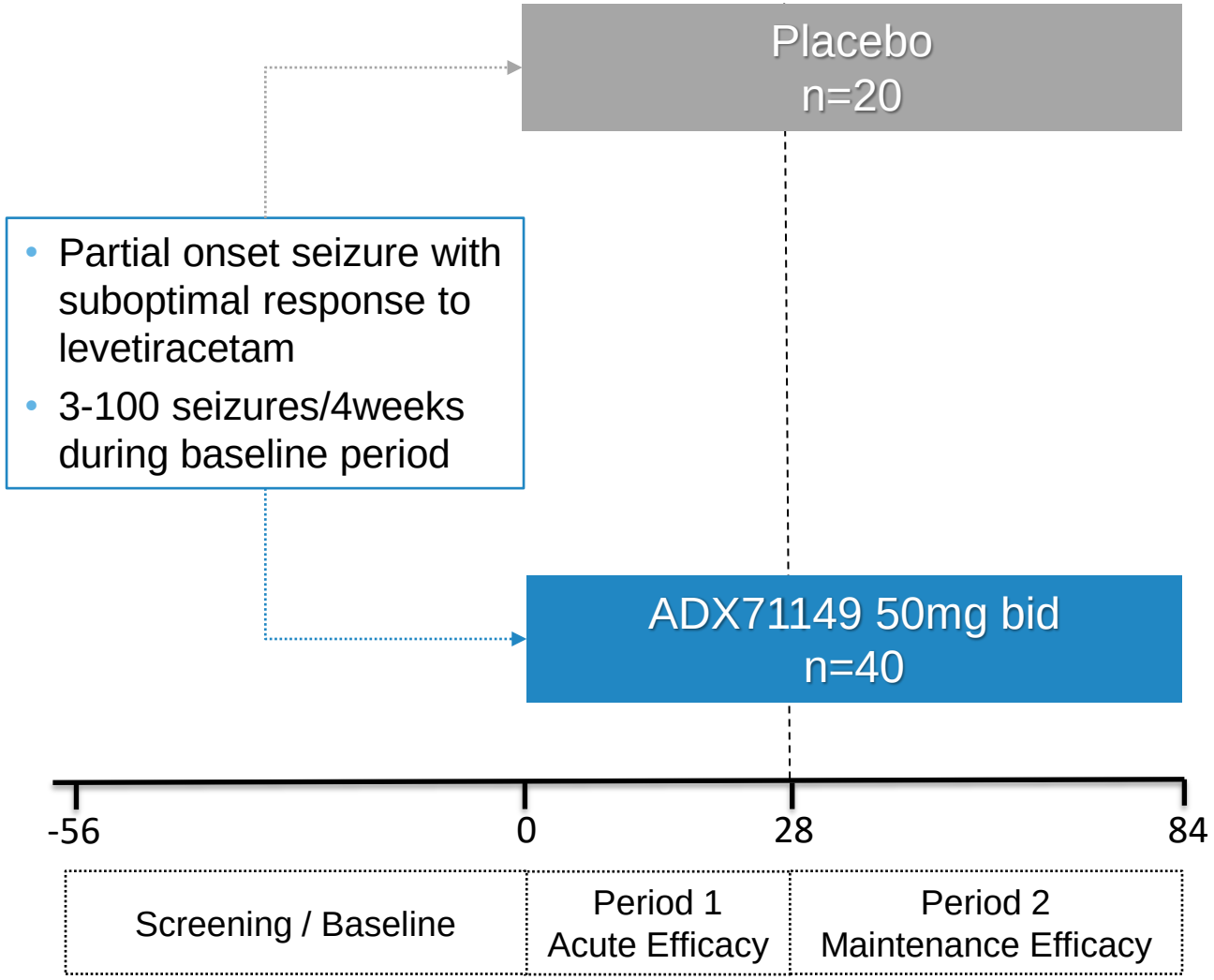


ED_{50} shift of ADX71149 by adding ED_{50} dose of LEV



- 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



- 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

Data expected in Q3 2022

Financials

Financials and Stock

- Cash runway through 2022
  - Cash at 30 September 2021: CHF15.5 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 – 2.46%
  - 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 – study started	Sept 2021
Phase 2a - topline results	Q1 2022
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 Q1 2022	• Phase 3 Parkinson's disease dyskinesia study – data Q4 2022 • Phase 2 blepharospasm study – data Q1 2022 • Phase 2 epilepsy study (J&J) – data Q3 2022
Technology and capabilities to deliver	• Experienced team of drug developers • Pioneering allosteric modulation drug development – Proprietary screening assays and unique chemical library • All programs developed in-house, protected with >200 patents
Solid foundation	• Partnerships with industry leaders • Top tier US investors - NEA, NLV and CAM Capital Program • Dual listed SIX Swiss exchange & US Nasdaq
Promising outlook	• Rich news flow in 2022 and beyond – Clinical data reading out Q1 2022, Q3 2022 and Q4 2022 – Multiple drug candidates in CCS

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