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Innovative Treatments for Central Nervous System Disorders

August 2024

Allosteric modulators for human health

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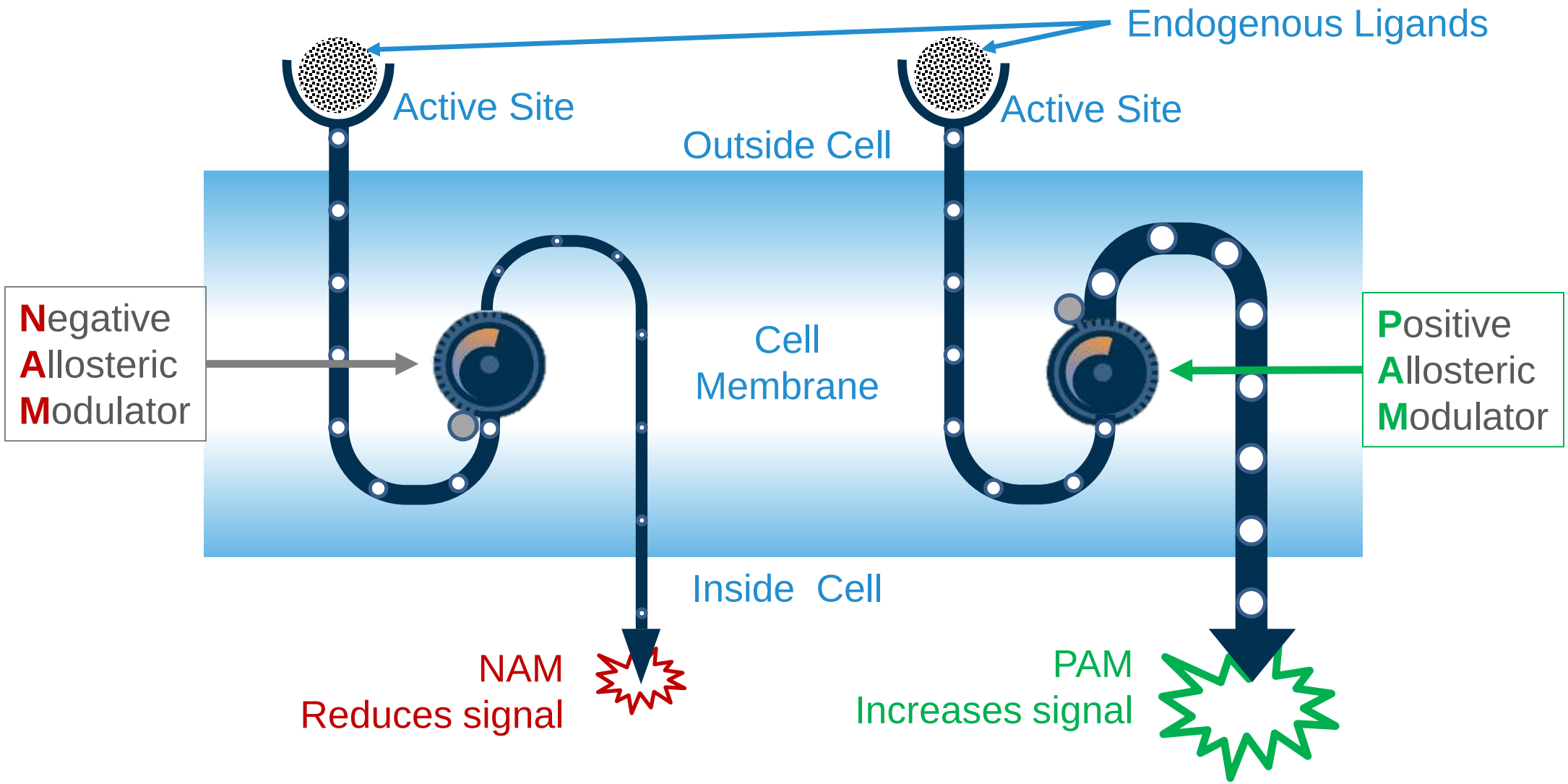
Addex Overview

High value programs reaching significant milestones	➢ GABAB PAM for cough (Addex) & SUD[1] (Indivior) in CCS[2] ➢ Dipraglurant for PD-LID & post-stroke/TBI[3] recovery – Phase 2 ready ➢ Neurosterix portfolio advancing towards IND enabling studies
20% equity interest in spin-out company, Neurosterix	➢ Leading allosteric modulator drug discovery platform – Validated & differentiated pharmacological approach ➢ Preclinical portfolio of high value programs – Lead program: M4 PAM for schizophrenia ➢ $63M series A financing in April 2024 led by Perceptive Advisors
High value industry partnerships driving future value	➢ Indivior - $330M in milestones, royalties up to double digit & funded research program
Strong balance sheet & top tier US investors	➢ Dual listed on SIX Swiss Exchange & US Nasdaq Capital Market ➢ CHF 1.6M ($1.8M) cash at March 31, 2024 – April 2024 Neurosterix spin-out: CHF 5M cash received in April 2024 & reduced future cash burn ➢ Cash runway extended beyond 2026

[1]SUD = Substance use disorder
[2]CCS = Clinical candidate selection phase
[3]TBI = Traumatic Brain Injury

What are Allosteric Modulators?



No activation in the absence of the endogenous ligand

Advantages of Allosteric Modulation Vs Orthosteric Drug Discovery

	Conventional small molecules	Biologics /peptides	Nucleic acid-based therapies	Gene therapies	Allosteric modulators
Selectivity	+	++	+++	+++	✓
Differentiated pharmacology	-	-	+++	+++	✓
Better potential safety/tolerability	++	+	++	-	✓
Non-competitive mechanism	-	-	n/a	n/a	✓
Respect physio-logical rhythm	-	-	-	-	✓
Oral bioavailability	+++	+	-	-	✓
Crossing BBB	+++	-	-	-	✓
No immunogenicity	+++	-	+	+	✓
Low cost of goods	+++	-	-	-	✓

Allosteric modulators

- Address:
  - "Undruggable" targets, such as GPCRs, RTKs, cytokine receptors and enzymes
  - mAb and peptide drug targets with oral small molecules
- Offer exquisite selectivity and superior safety profile
- Are suitable for chronic treatment as potency maintained over prolonged periods
- Require a distinct HTS and characterization approach to discovering small molecule allosteric modulators
- Proven clinical approach (diazepam, cinacalcet, etc)

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Pipeline of In House Discovered Programs

Molecule / MoA	Partner	Stage				Milestone
		Discovery	IND Studies	Phase 1	Phase 2a	
Dipraglurant (mGlu5 NAM)		PD-LID				Ready to start Phase 2b/3 study*
Dipraglurant (mGlu5 NAM)		Post-stroke/TBI recovery				Ready to start Phase 2a study*
ADX71149 (mGlu2 PAM)		Indication under evaluation				
$GABA_B$ PAM	INDIVIOR	Substance use disorders				IND enabling studies expected to start H2 2024
$GABA_B$ PAM		Chronic cough				IND enabling studies ready to start H2 2024

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* Timings subject to financing/partnering
TBI = Traumatic brain injury
NAM = Negative Allosteric Modulator
PAM = Positive Allosteric Modulator

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

First-in-class program ready to start Phase 2b/3

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Compelling Rationale to Develop Dipraglurant for PD-LID

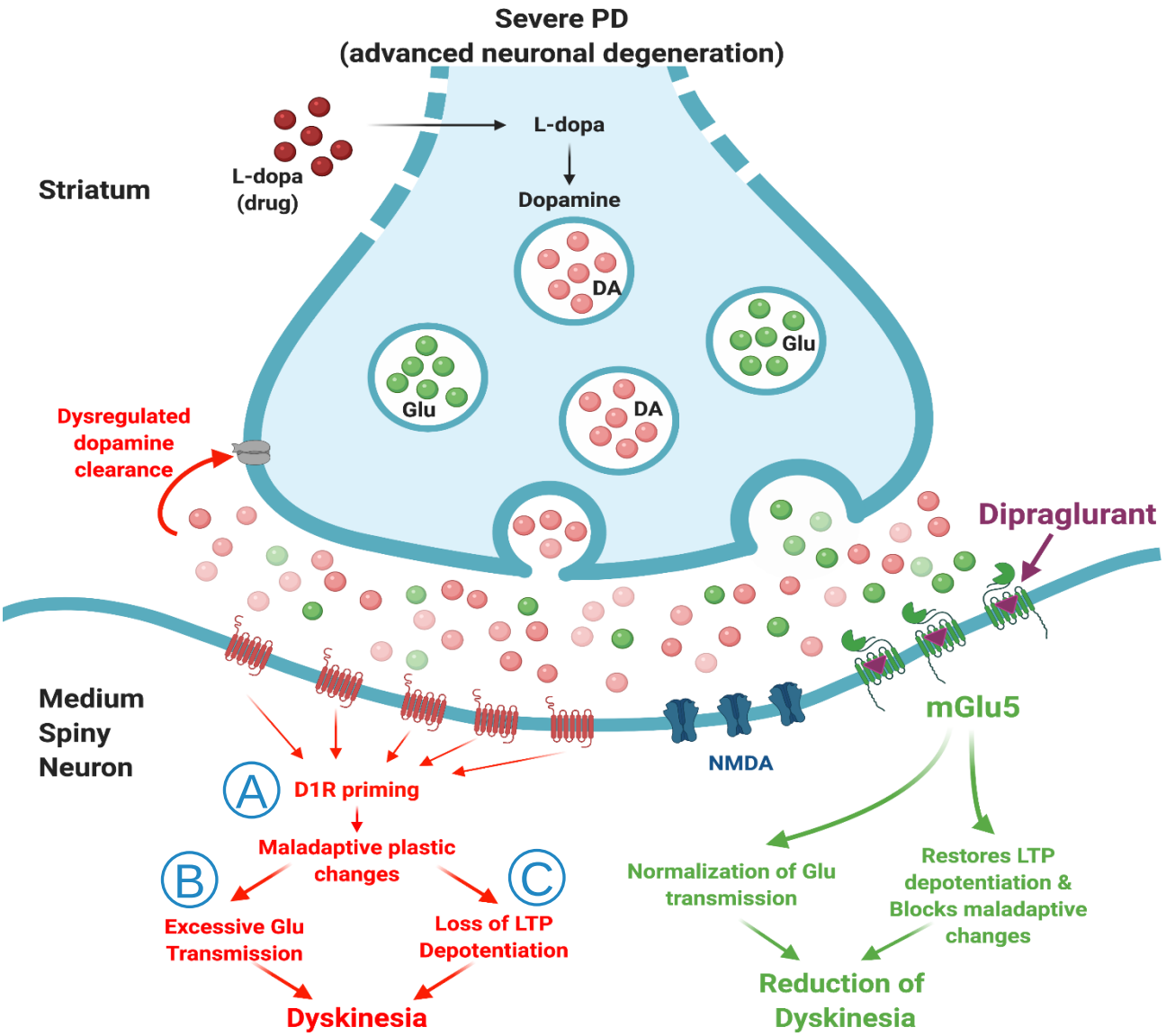
- Large underserved patient population in need of improved treatment options
- Significant commercial opportunity with limited competition
  - 1M Parkinson's disease patients in US of which >170,000 have dyskinesia
  - Orphan drug designation granted for dipraglurant in US
  - GOCOVRI® price: $34K p.a., 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 (AFQ056) 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**

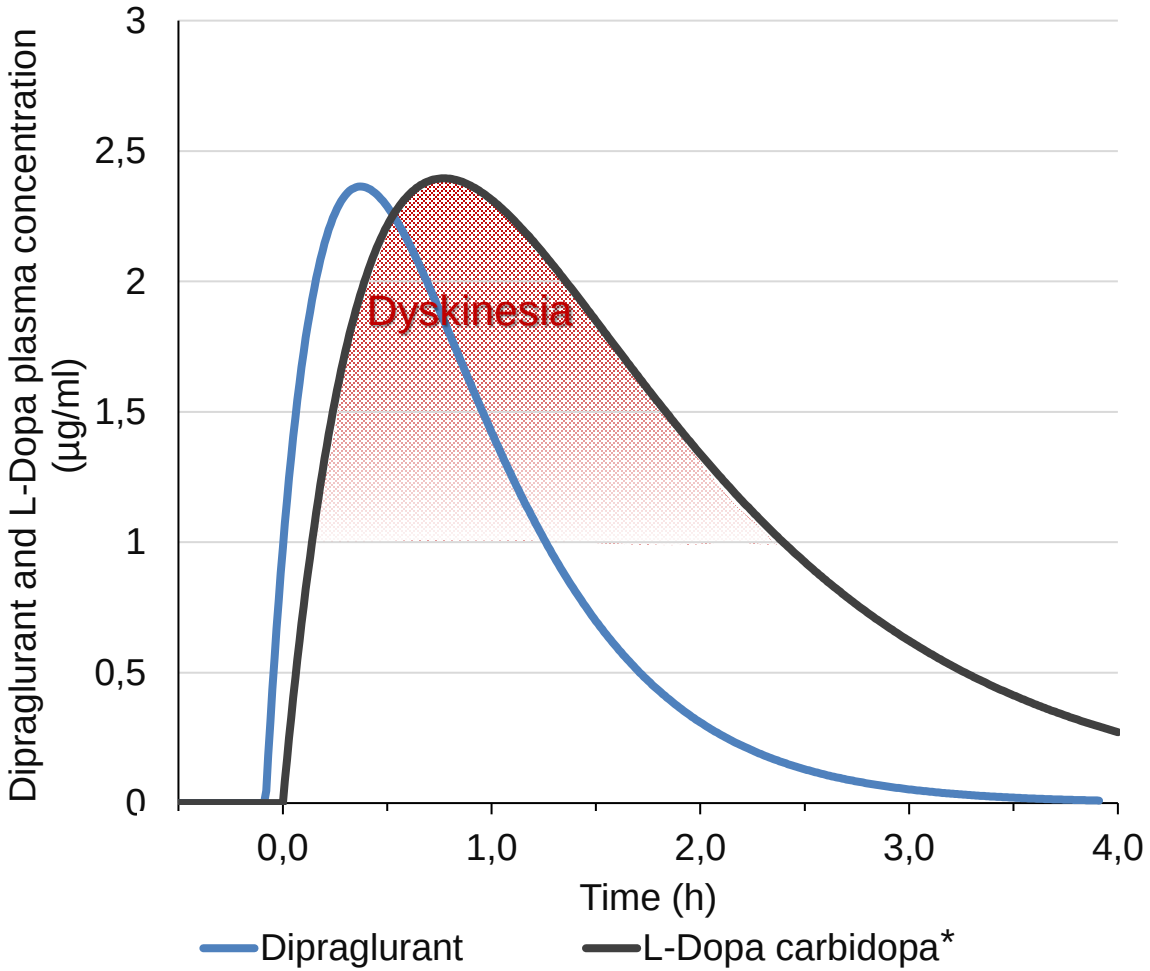
MoA Rationale for Targeting mGlu5 Inhibition in PD-LID



- 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:
  - (A) *D1 receptor priming*
  - (B) *Excess glutamate transmission*
  - (C) *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



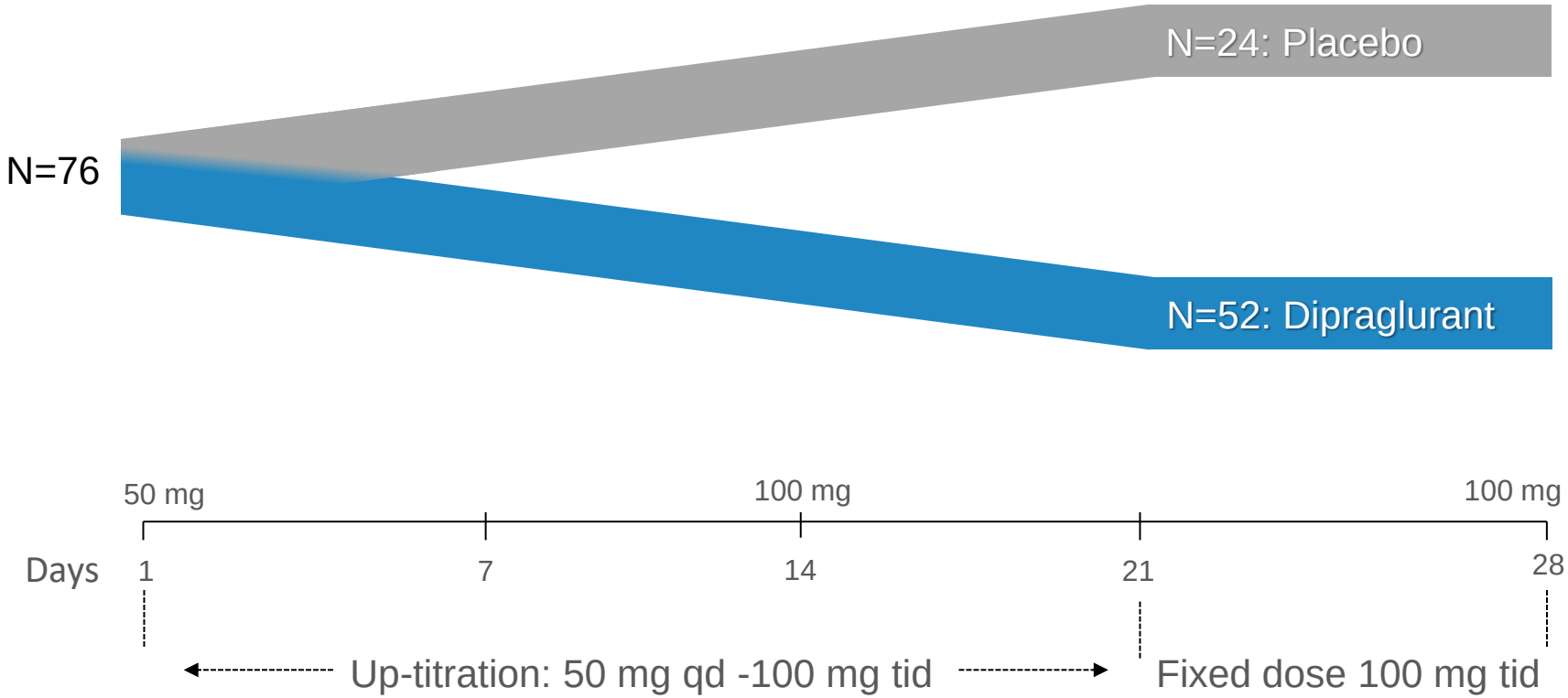
- Dyskinesia symptoms are correlated to peak levels of L-dopa
- PK of dipraglurant allows control of glutamatergic tone ahead of L-dopa Cmax

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

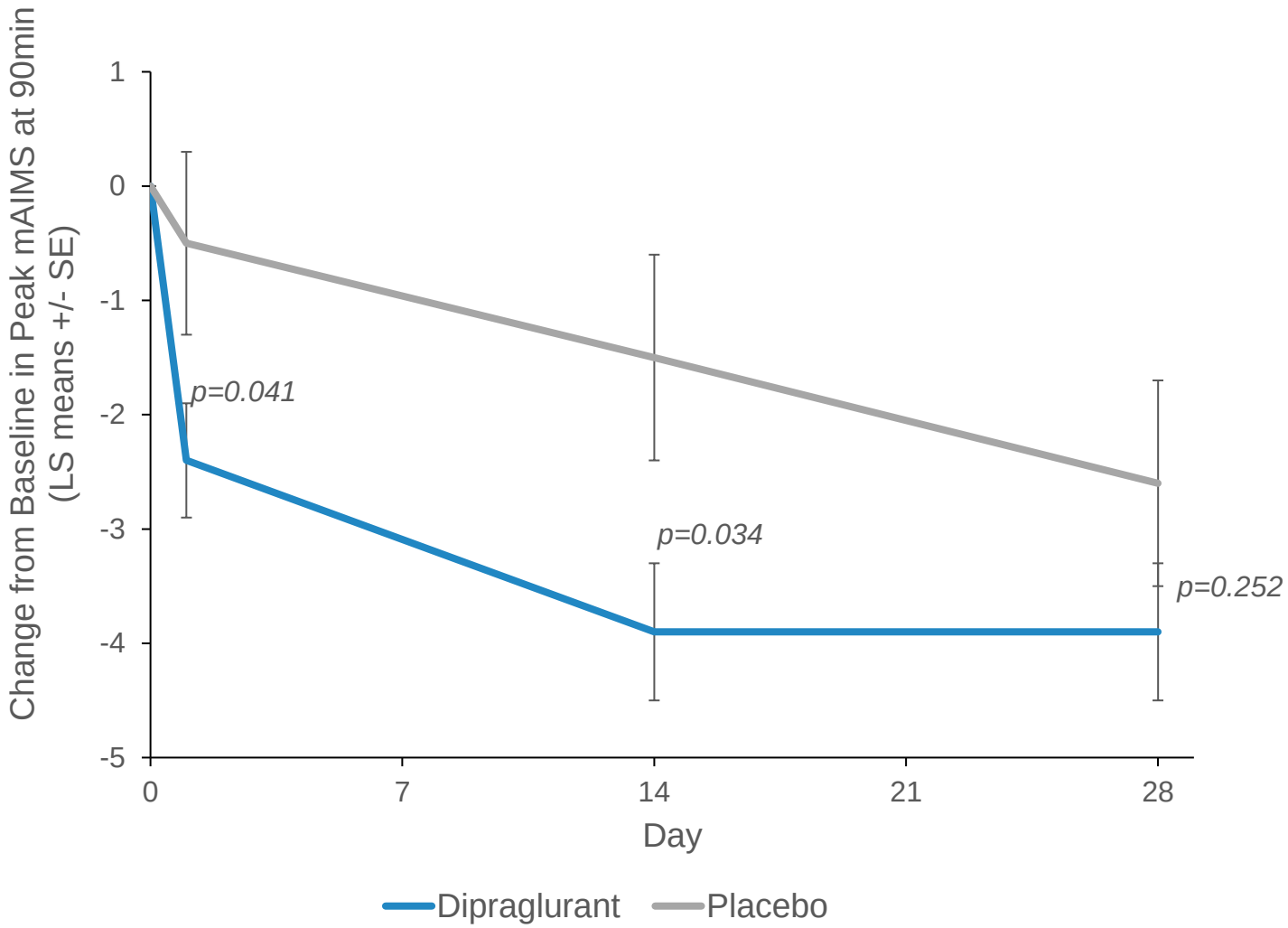
Dipraglurant Phase 2a Study in LID (in US and Europe)



- **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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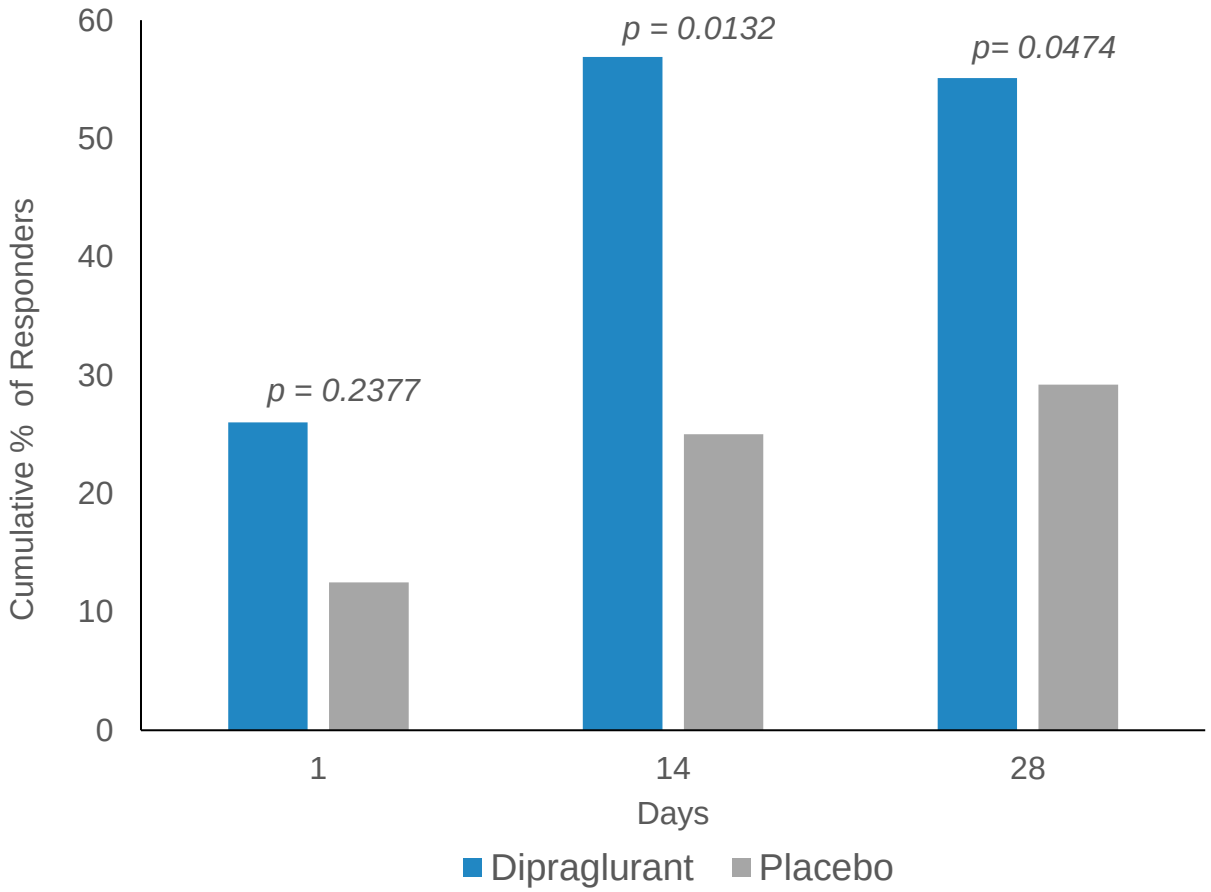
Responder Analysis Demonstrates Dipraglurant Significant Benefit

Percent of patients with ≥ 30% improvement on mAIMS

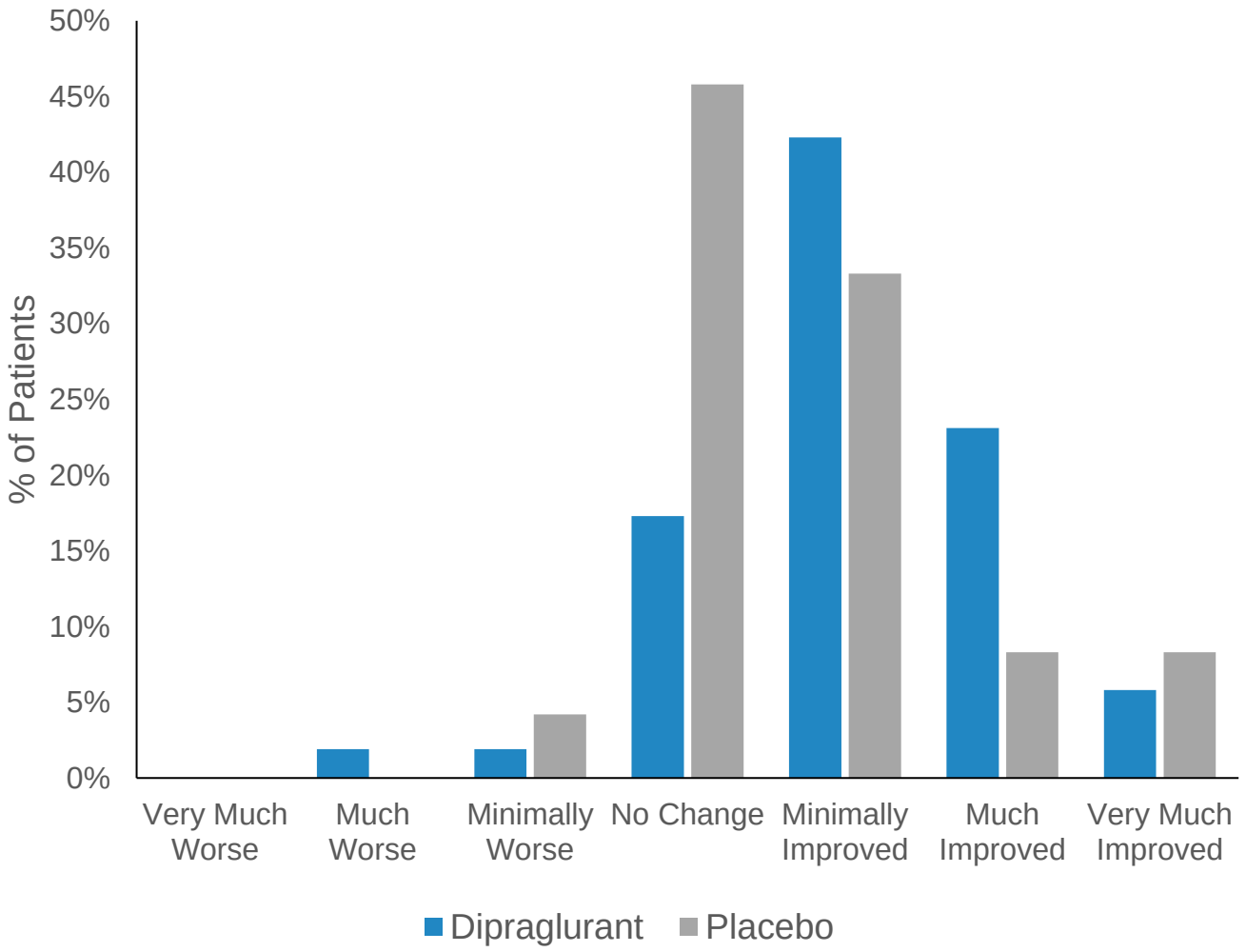


Responder analysis (≥30% change of mAIMS from baseline)				
Midday dose	Dipraglurant		Placebo	
Day 1 (50 mg)	n=13	26.0%	n=3	12.5%
Day 14 (100 mg)	n=29	56.9%*	n=6	25.0%
Day 28 (100 mg)	n=27	55.1%*	n=7	29.2%

*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

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 - Development Status

- Fast onset of action and short half-life
  - Ideally suited normalizes abnormal glutamate stimulation during peak levodopa dose
- Extensively profiled Phase 1 studies
  - 5 studies with >100 patients, including receptor occupancy (PET ligand study)
- Phase 2 studies conducted
  - Safe and well tolerated in PD-LID patients with 7 patients exposed >6 months
  - Significant improvement in peak mAIMS from baseline (at days 1 &14)
  - Significant improvement seen in responder analysis
  - Significant Improvement on CGI-C
  - Pivotal registration study started in June 2021 and stopped in June 2022 due to poor enrolment related to COVID-19
- CMC Status
  - >30kg API in stock & 7.5kg drug product available in 50mg and 100mg tablets with placebo
- IP
  - Patent through 2034 (without extensions)
  - Use patent of mGlu5 NAMs in treatment of brain damage until 2035 – option to exclusive license

First-in-class program for PD-LID ready to start Phase 2b/3

Dipraglurant (mGlu5 NAM) for Post-Stroke Recovery

Targeting neuroplasticity early in rehabilitation to promote recovery

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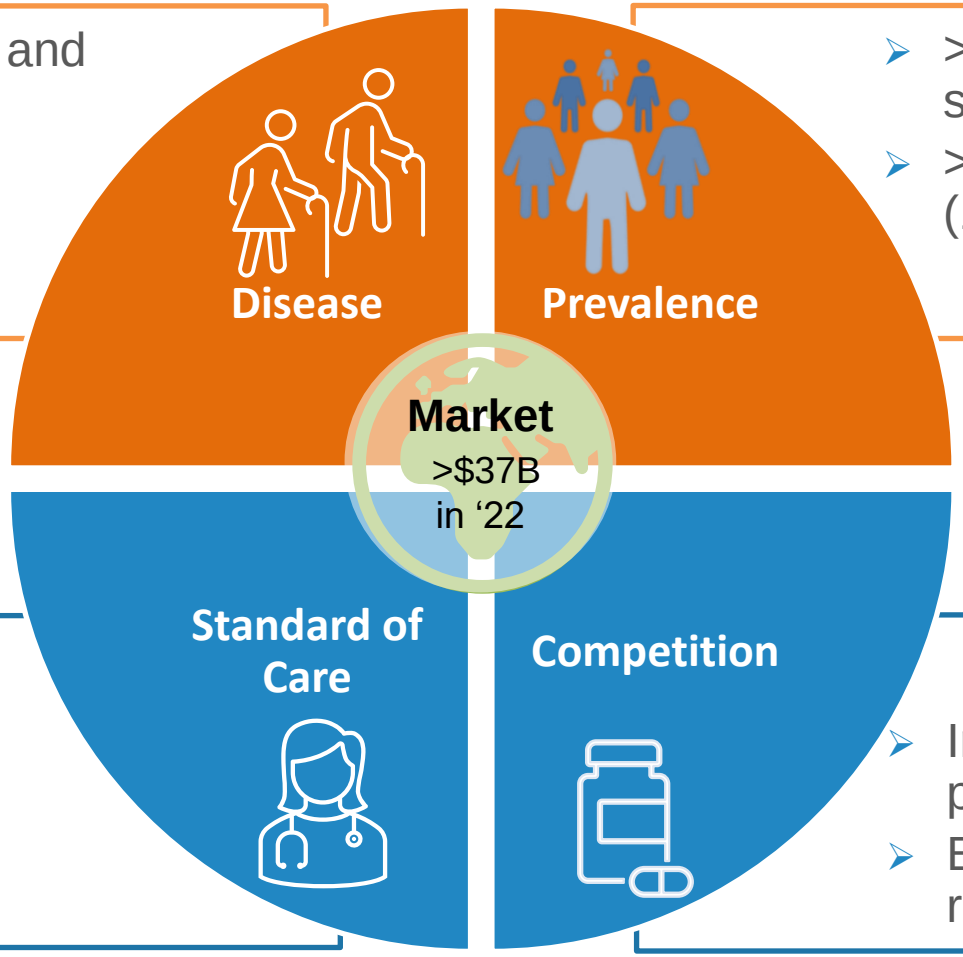
Post Stroke Recovery - Unmet Medical Need & Commercial Opportunity

- Post stroke many suffer motor and somatosensory impairment
- Potential chronic disability & low quality of life



- >101 million ischemic stroke survivors worldwide[1]
- >12 million new strokes/yr (1 every 3 seconds)[1]

- Rehabilitation therapies: e.g. physiotherapy, speech, communication and cognitive
- Majority never fully recover

- Intense early rehabilitation promotes recovery
- But, no approved drugs to support rehabilitation therapies

Urgent medical need to promote sensorimotor recovery in post-stroke patients

[1]World Stroke Association 2022

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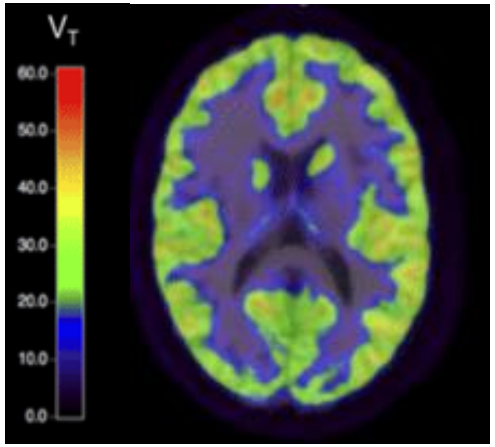
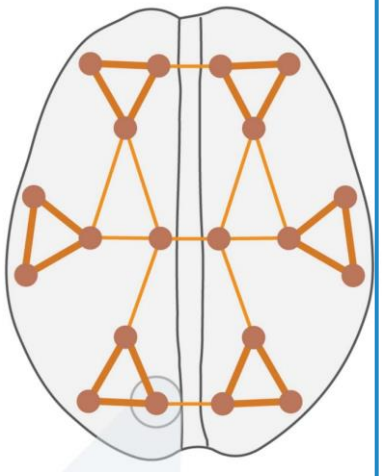
mGlu5: An Innovative Target for Post-Stroke Recovery

Healthy brain

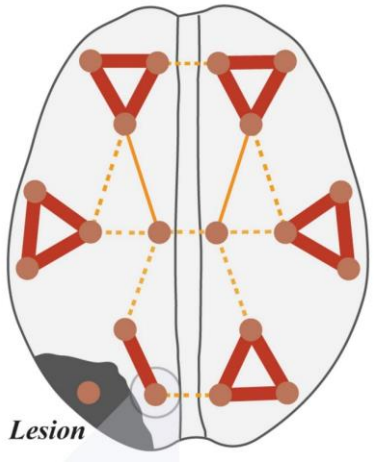


mGlu5 brain distribution



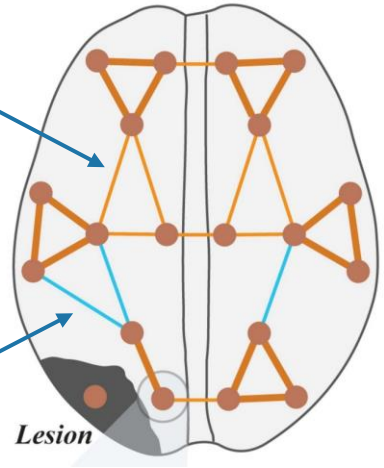
Good inter & intra-nodal connectivity

mGlu5 NAM supports post-stroke recovery



Recovery

+ mGlu5 NAM



mGlu5

- Densely expressed in the brain
- Involved in neural plasticity
- Modulates excitation/inhibition equilibrium

Lesion effects:

- Confined neural tissue necrosis
- Network disruption & module segregation
- Imbalance in excitation/inhibition

mGlu5 NAM promotes synaptic plasticity

- Cortical reorganization & new functional pathways (a)
- Connectivity changes toward pre-lesion state (b)
- Restoration of excitation/inhibition equilibrium

Adapted from DOI: 10.3389/fnsys.2021.806544

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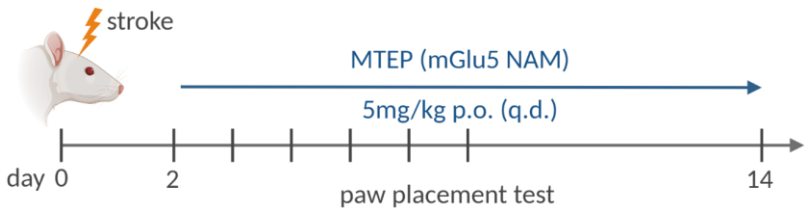
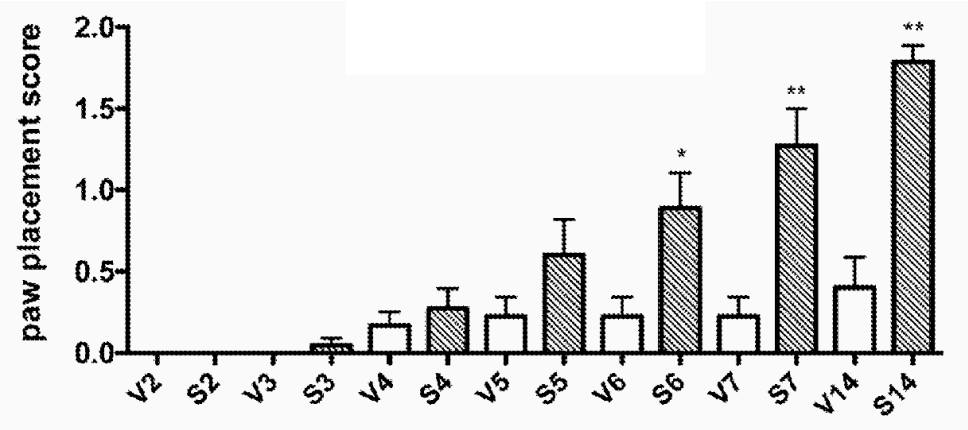
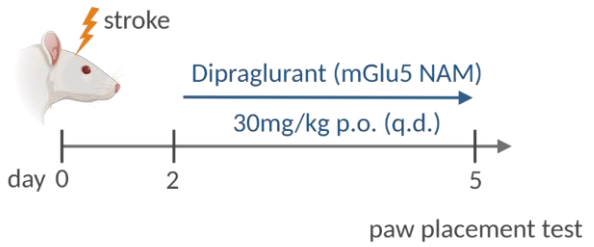
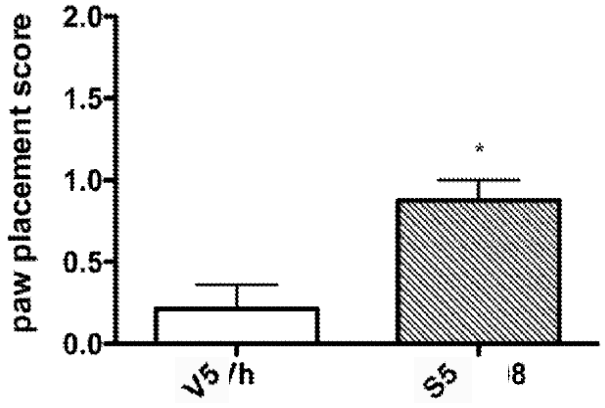
Preclinical Data: mGlu5 Inhibition Promotes Post-Stroke Recovery





MTEP treatment resulted in a significant recovery of functional control



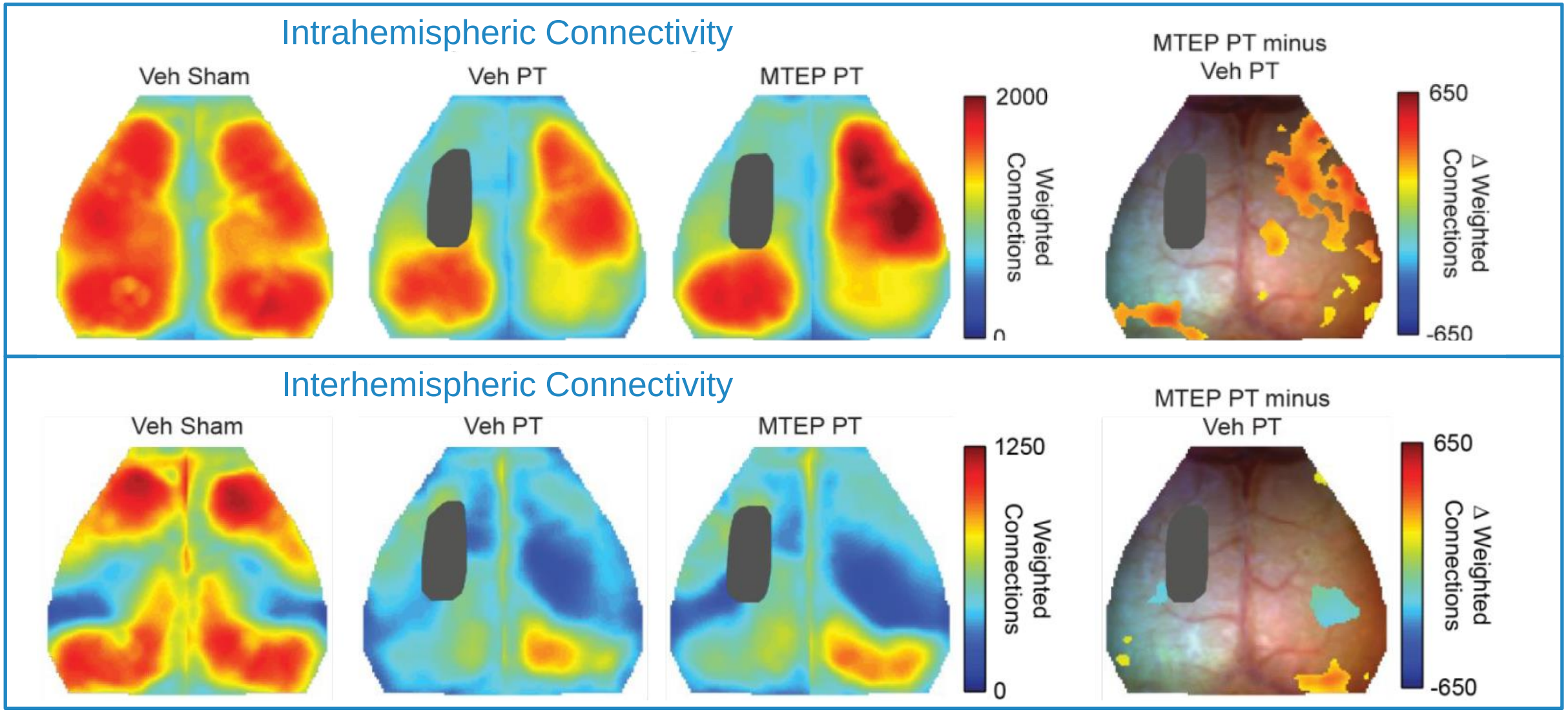


Dipraglurant significantly restored functional control in a one-week experiment

Dipraglurant enhanced functional brain recovery in a rat model of experimental stroke

From patent application PCT WO2017/171594A1

MRI Imaging Data: Post-Stroke Resting State Functional Connectivity



mGlu5 inhibitors promote intra- and inter-hemispheric connectivity following stroke

https://doi.org/10.1093/brain/awad293

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Dipraglurant for Post-stroke/TBI Recovery - Development Status

- Fast onset of action and short half-life
  - Ideally suited for concurrent dosing with rehabilitation
- Extensively profiled Phase 1 studies
  - 5 studies with >100 patients
  - Including receptor occupancy (PET ligand study)
- Phase 2 studies conducted
  - Safe and well tolerated in patients suffering from neurological disease – Parkinson's disease
  - Mild to moderate CNS type AEs at doses < 200mg
  - 7 PD-LID patient exposed >6 months
- CMC Status
  - >30kg API in stock
  - 7.5kg drug product available in 50mg and 100mg tablets with placebo
- IP
  - Patent through 2034 (without extensions)
  - Use patent of mGlu5 NAMs in treatment of brain damage until 2035 – option to exclusive license

First-in-class program for post-stroke recovery ready to start Phase 2

GABAB PAM for Substance Use Disorders (Indivior Partnership)

Going beyond baclofen to treat substance use disorders with improved safety and tolerability

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GABAB PAM for Substance Use Disorder

Large market & unmet medical need	➢ High prevalence;1.8% of US population[1] ➢ Current treatments have undesirable side-effects and prone to relapse ➢ Burden to society in US is >$600B annually[2]
Clinically validated MoA	➢ Baclofen (GABAB agonist) used off label for alcohol use disorder ➢ ADX71441 attenuates alcohol self-administration and relapse to alcohol seeking in rats[3] and alcohol consumption in mice[4] ➢ ADX71441 reduces cocaine self-administration in non-human primates[5]
Status of program and near-term milestone	➢ Addex is executing Indivior funded GABAB PAM research program ➢ Multiple compounds in late clinical candidate selection phase ➢ Differentiated leads and backups with robust novel IP potential ➢ IND enabling studies expected to start in H2 2024
Strategic partnership with Indivior	➢ Eligible to receive $330 million in milestones and tiered royalties from high single digits to low double digits ➢ Conducting a funded research program to discover novel GABAB PAMs – Right to select compounds for development in reserved indications

[1]Merikangas et al. 2010
[2]NIDA
[3]Augier et al 2017
[4]Hwa et al 2014
[5]Addex int. report

GABAB PAM for Chronic Cough

Going beyond baclofen to treat cough with improved safety and tolerability

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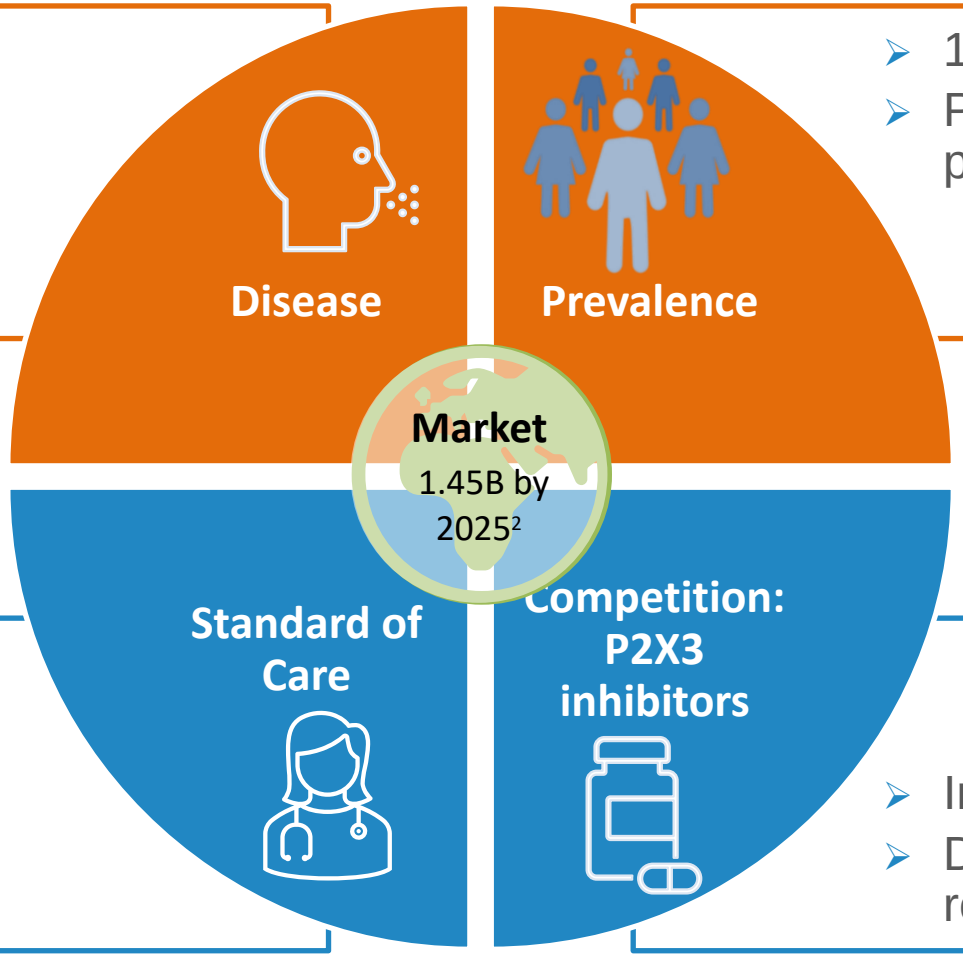
Cough - Unmet Medical Need and Commercial Opportunity

- Chronic cough
  - Lasting > 8 weeks[1]
  - >700 coughs/day
- Multiple comorbidities



- 10% in the general population[4]
- Persists >1 year in 60% of patients

- Ineffective in 30% of patients[3]
- Hindered by side-effect risks

- Ineffective in ~30% of patients
- Discontinuation in ~20% (taste related side-effects)

High unmet medical need for an efficacious and safe treatment of cough

[1]Morice et al. *Eur Respir Rev* 2021
[2]Cough Remedies Market Share, Size and Industry Growth Analysis 2021 - 2026 (industryarc.com)
[3]Ryan *Expert Opin Pharmacother* 2018
[4] Song WJ, Chang YS, Faruqi S, et al. 2015.

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Standard of Care in Cough - Strengths and Weaknesses

Use / side-effects	Dextro-metorphan	Opioids	Gabapentin & pregabalin	Amitriptyline	P2X3*	GABAB Agonist Baclofen	GABAB Addex PAM
Treatment type	Chronic	Acute	Acute	Acute	Chronic	Acute	Chronic
Risk of Abuse	Yes	Yes	Yes	Yes	No	No	No
Respiratory	No	Yes	Yes	Yes	No	Yes	No
Other CNS	Yes	Yes	Yes	Yes	No	Yes	No
Gastrointestinal	Yes	Yes	No	No	No	No	No
Taste-related	No	No	No	No	Yes**	No	No

- P2X3 inhibitor Gefapixant
  - * Ineffective in 30% of patients
  - ** Taste-related side effects observed in up to 97% of patients, leading to discontinuation in up to 20% of patients[1]

A highly selective and targeted GABAB PAM has the potential to offer best-in-disease efficacy and tolerability profile suitable for chronic treatment

[1]Niimi et al. *Allergology International* 2022

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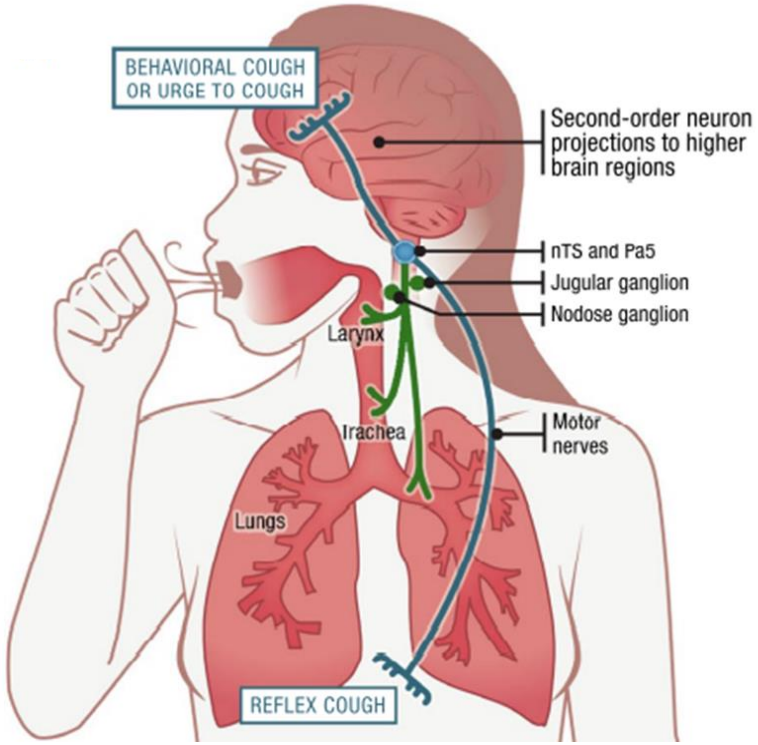
GABAB Receptor - Validated Target in Cough

- GABAB receptor
  - Expressed throughout the cough neural circuit
  - Activation reduces neuronal excitability
  - Potential for broad application in cough patients
- Baclofen, an orthosteric agonist
  - Used off-label in patients with chronic cough
  - Clinical studies with cough patients showed efficacy
  - Efficacious in healthy volunteer and multiple preclinical models
- Selective GABAB PAM
  - Differentiated pharmacology
  - Improved efficacy and tolerability demonstrated in preclinical models
  - Absence of receptor desensitization with chronic treatment



The anatomical mediators of cough (1)

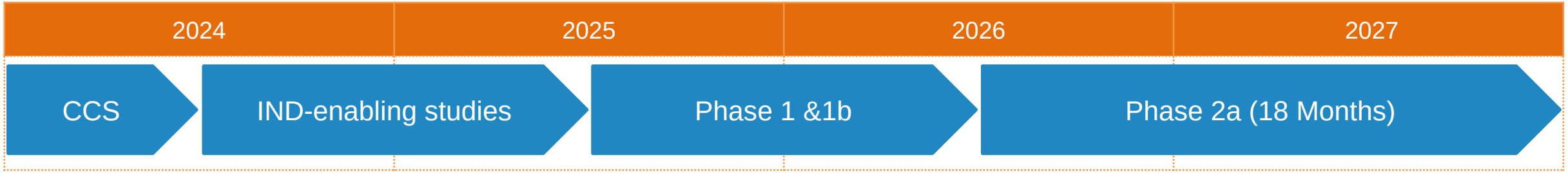
GABAB PAM offers potential for improved treatment for cough patients

[1]Mazzone and McGargey *Clin Pharm Ther* 2021

Target Product Profile, Project Status and Development Plan

- A first-in-class GABAB PAM to treat Cough
  - Once-a-day oral dosing suitable for chronic treatment
  - Reduction in cough bouts and severity and improvement in quality of life
  - Superior tolerability with no taste related side-effects
- Status of program: clinical candidate selection
  - Potent, highly selective compounds with good developability properties identified
  - In vivo PoC with PK/PD confirmed in multiple preclinical models of cough with comparable efficacy to P2X3 inhibitors

Development Plan



On track for first-in-human studies in 2025

Timings beyond CCS are subject to funding/partnering

20% Equity Interest in Neurosterix

Well funded preclinical portfolio of high value assets

Neurosterix

- Addex spin-out company
  - Series A funding of $63 million in April 2024 led by Perceptive Advisors
  - Addex contributed allosteric modulator drug discovery platform and portfolio of preclinical programs
  - Addex received CHF5 million and a 20% equity interest
- High value pipeline advancing toward the clinic:
  - M4 PAM for schizophrenia
    - Clinically validated target
    - IND enabling studies expected to start in H2 2024
  - mGlu7 NAM for stress related disorders
    - First-in-class program
    - IND enabling studies expected to start in H2 2024
  - mGlu2 NAM for mild neurocognitive disorders
    - Progressing through lead optimization

Multiple high value programs funded to significant milestones

Addex Financials and Stock

Financials and Stock

- Cash at March 31, 2024:
  CHF 1.6M (USD 1.8M)
  - CHF 5M from sale of Neurosterix received in April 2024
- No debt
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- ADS representing 120 shares traded on Nasdaq: ADXN (ISIN: US00654J206; CUSIP: 00654J206)

- 128.26 M outstanding shares
  - Armistice Capital LLC – 26.13%*
  - New Enterprise Associates – 3.03%*
- 184.35M shares incl. treasury shares (254.03M fully diluted)
  - Management & board holds – 13.47%*
- Analyst coverage:
  - HC Wainwright - Raghuram Selvaraju
  - valuationLab - Bob Pooler
  - Baader Helvea AG - Leonildo Delgado
  - ZKB – Edouard Riva

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* Percentage of ownership calculated based on shares and warrants divided by fully diluted shares

Summary

Multiple high value partnerships	➢ GABAB PAM for substance use disorder (Indivior) in clinical candidate selection ➢ 20% equity interest in Neurosterix (backed by Perceptive Advisors)
In house programs driving future value	➢ Dipraglurant - PD-LID Phase 2b ready to start ➢ Dipraglurant - post-stroke recovery Phase 2a ready to start ➢ GABAB PAM for chronic cough in clinical candidate selection ➢ ADX71149 indication under evaluation
Solid foundation	➢ Partnerships with industry leaders - Indivior ➢ Top tier US investors - Armistice Capital, NEA and NLV ➢ Dual listed SIX Swiss exchange & US Nasdaq ➢ Strong balance sheet and cash runway through 2026
Promising outlook	➢ GABAB PAM - start IND enabling studies in H2 2024 ➢ Dipraglurant Phase 2 ready to start Phase 2 in PD-LID &/or post-stroke recovery ➢ Neurosterix lead program - M4 PAM – IND enabling studies expected to start H2 2024

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