



Innovative Treatments for Central Nervous System Disorders

November 2023

Allosteric modulators for human health

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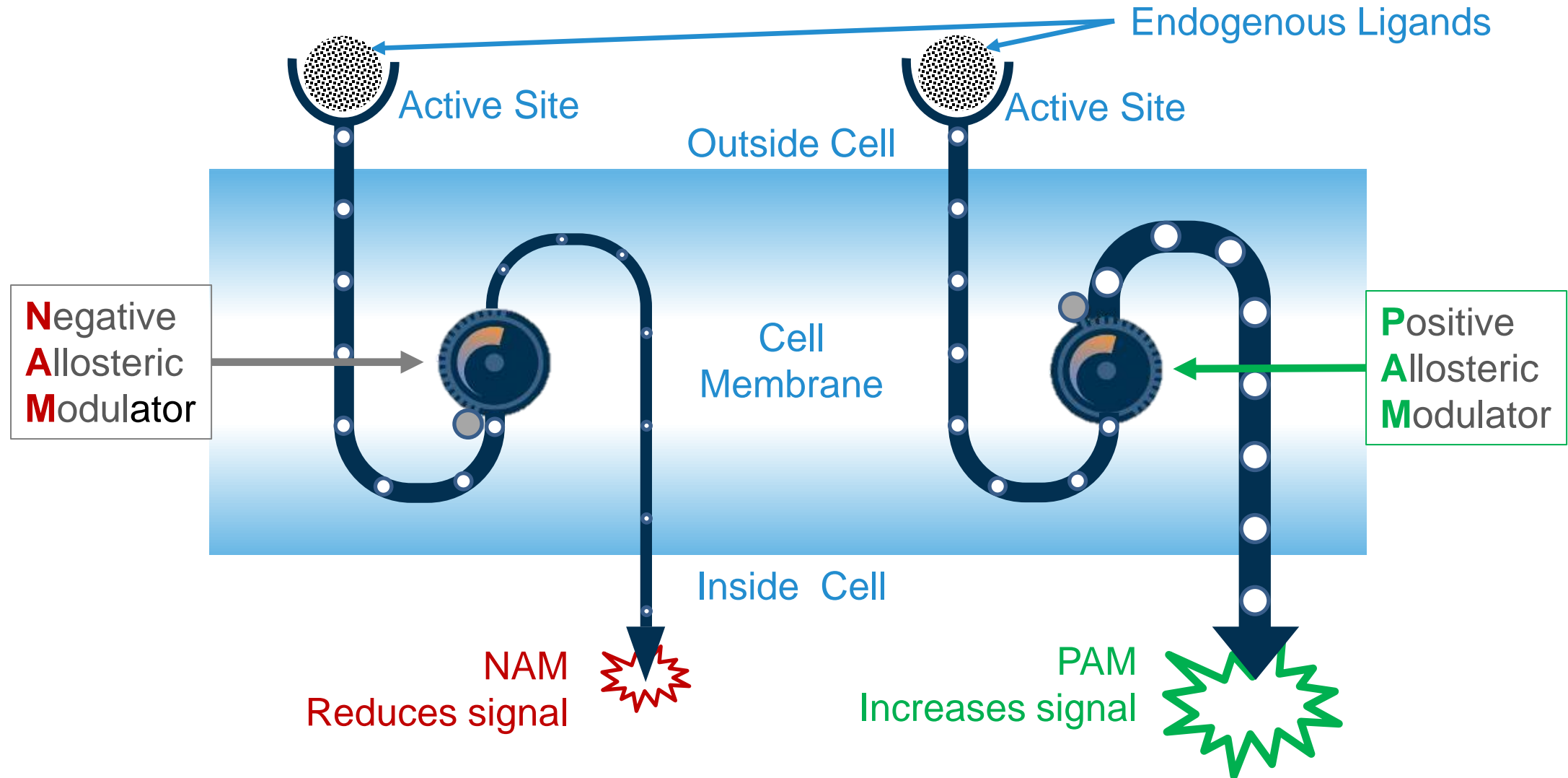
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Addex Overview

Multiple high value programs reaching significant milestones	<ul style="list-style-type: none">➤ ADX71149 Phase 2 epilepsy study (J&J) - data expected Q2 2024➤ GABAB PAM for cough (Addex) & SUD** (Indivior) in CCS*➤ M4 PAM for schizophrenia and other psychosis in CCS*➤ Dipraglurant for post-stroke recovery phase 2 ready to start
Leading allosteric modulator technology platform	<ul style="list-style-type: none">➤ Validated & differentiated pharmacological approach➤ Proprietary biological screening assays and chemical library➤ Track record of delivering novel drug candidates
In house discovered pipeline	<ul style="list-style-type: none">➤ Significant intellectual property portfolio➤ Multiple novel drug candidates in clinical candidate selection phase➤ Driving long-term growth & future partnership opportunities
Technology validating partnerships	<ul style="list-style-type: none">➤ J&J - €109M in milestones & double-digit royalties➤ Indivior - \$330M in milestones, royalties up to double digit & funded research program
Top tier US investors	<ul style="list-style-type: none">➤ Dual listed on SIX Swiss Exchange & US Nasdaq Capital Market➤ CHF7.2M (\$8.0M) cash at June 30, 2023

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)

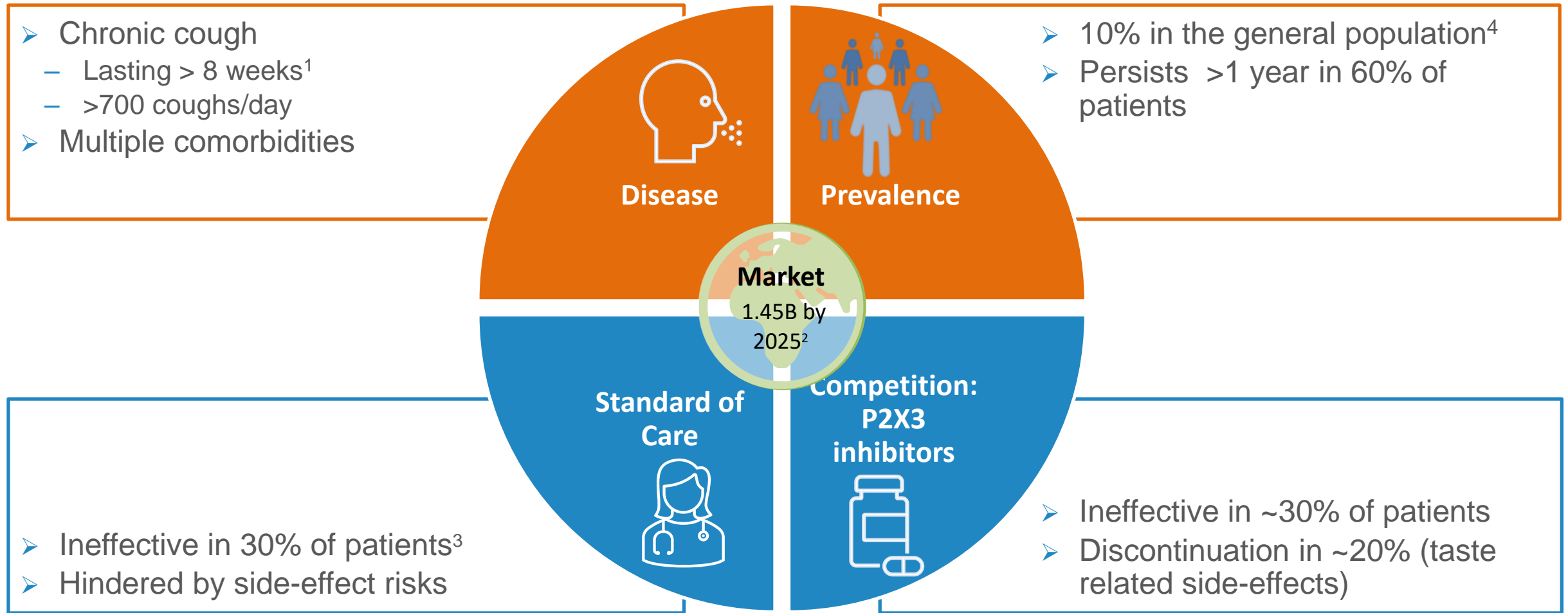
Advancing a Broad Allosteric Modulator Pipeline in Neuroscience

Molecule / MoA	Partner	Stage				Milestone
		Discovery	IND Studies	Phase 1	Phase 2	
In house Lead Programs						
GABA _B PAM		Chronic cough				IND enabling studies expected to start H1 2024
M4 PAM		Schizophrenia / other psychosis				IND enabling studies expected to start H2 2024
Partnered Programs						
ADX71149 (mGlu2 PAM)		Epilepsy				Data expected Q2 2024
GABA _B PAM		Substance use disorders				IND enabling studies expected to start H2 2024
Other Programs Available for Partnering						
Dipraglurant (mGlu5 NAM)		Post-stroke recovery				Ready to start Phase 2a study
mGlu7 NAM		Stress-related disorders – PTSD				Ready to enter IND enabling studies
mGlu2 NAM		Mild neurocognitive disorders				Clinical candidate selection expected to start H2 2024

GABAB PAM for Chronic Cough

Going beyond baclofen to treat cough with improved safety and tolerability

Cough - Unmet Medical Need and Commercial Opportunity



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

Standard of Care in Cough - Strengths and Weaknesses

Use / side-effects	Dextro-metorphan	Opioids	Gabapentin & pregabalin	Amitriptyline	P2X3*	GABAB	
						Agonist Baclofen	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

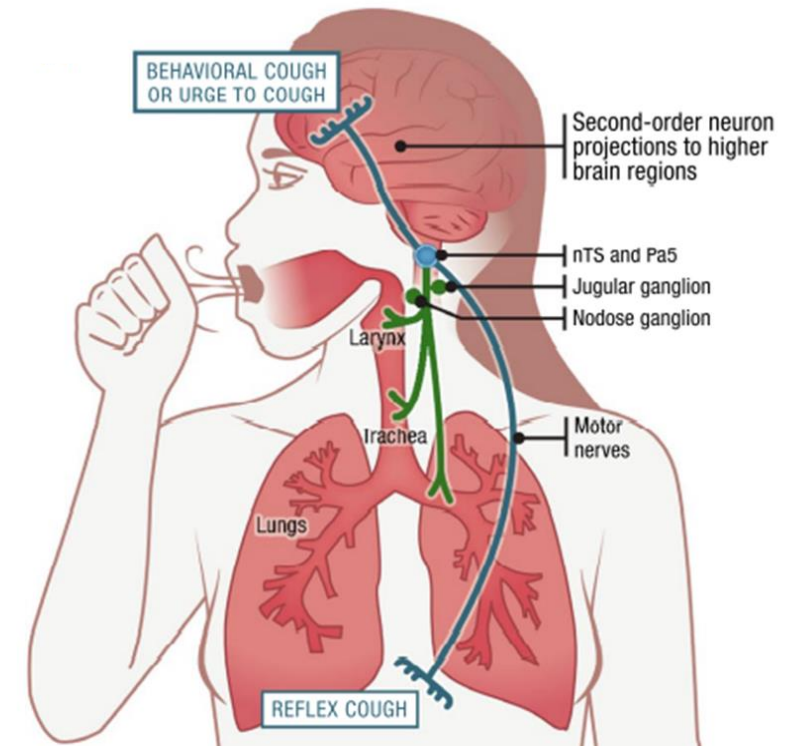
➤ P2X3 inhibitor Gefapixant

- * Ineffective in 30% of patients
- ** Taste-related side effects observed in up to 97% of patients, leading to discontinuation in up to 20% of patients¹

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

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



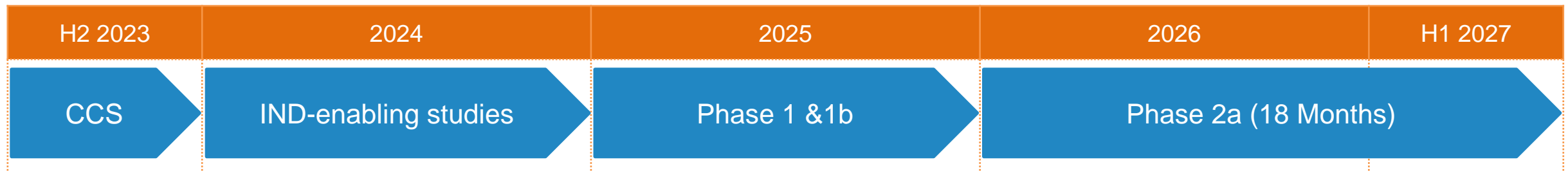
The anatomical mediators of cough (1)

GABAB PAM offers potential for improved treatment for cough patients

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

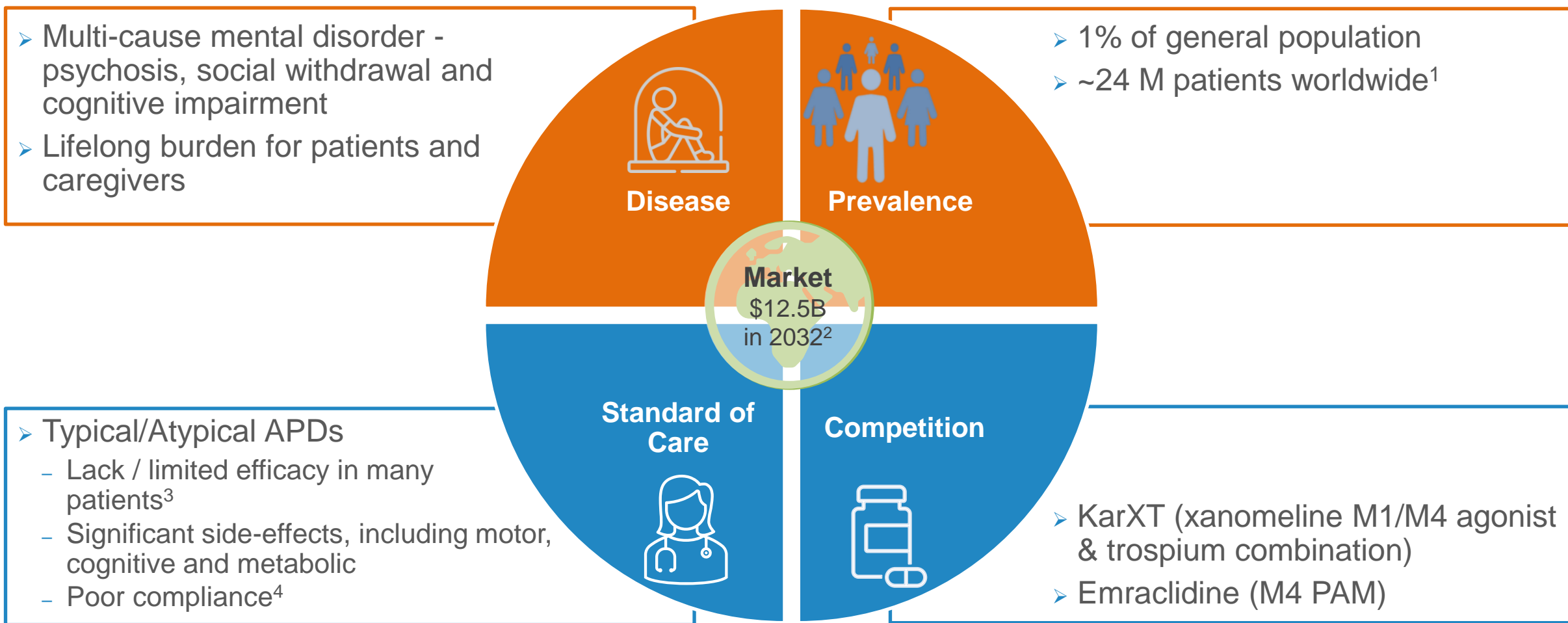


On track for first-in-human studies in 2025

M4 PAM for Schizophrenia

*Selectively targeting the M4 receptor to treat psychosis related symptoms
with improved safety and tolerability compared to standard of care*

Schizophrenia - Unmet Medical Need and Commercial Opportunity

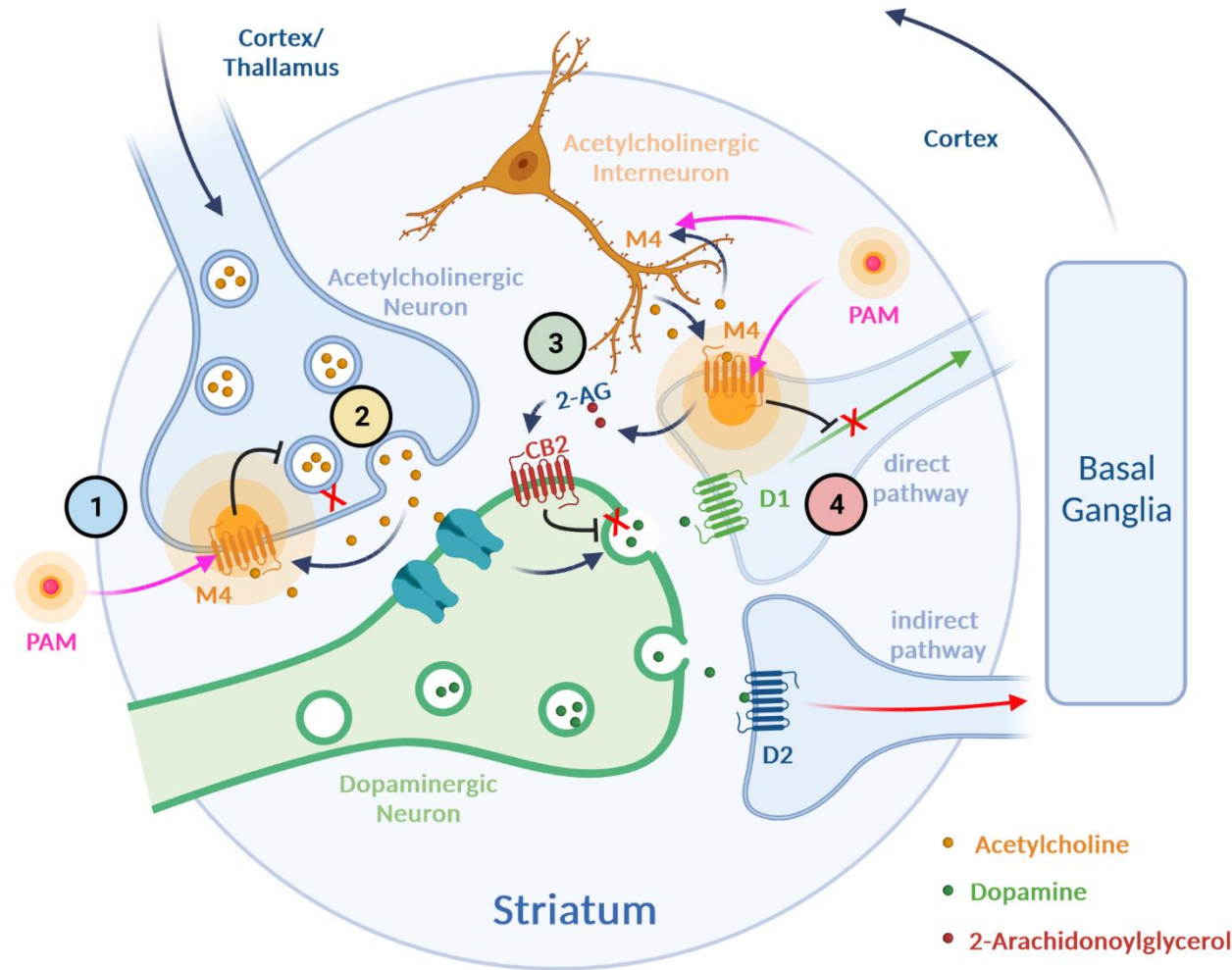


High unmet need for better treatment options

M4 PAM Mode of Action in Schizophrenia

1 M4 auto-receptor activation with a PAM or agonist prevents Ach release

2 Decreased Ach binding to nicotinic receptors reduces dopamine release



3 Activation of M4 receptor indirectly leads to activation of pre-synaptic CB2 receptor and further reducing dopamine signaling

4 Activation of M4 receptor also inhibits cAMP thus reducing dopaminergic tone

M4 PAM reduces striatal dopamine tone without direct antagonism of D1/D2 receptors

Selective M4 PAM - Differentiated Approach to Treat Schizophrenia

M4 PAM selectivity and high brain penetration offers potential improvements

Effects / Side Effects	Standard of Care	Muscarinic	
		Non-selective	Selective M4 PAM
Discontinuation	High	High	Low
Cognition	Impairment	Improved	Improved
Metabolic & GI	Yes	Yes	No
Cardiovascular	Yes	Yes	?

Addex M4 PAM is highly potent, exquisitely selective with high brain penetration

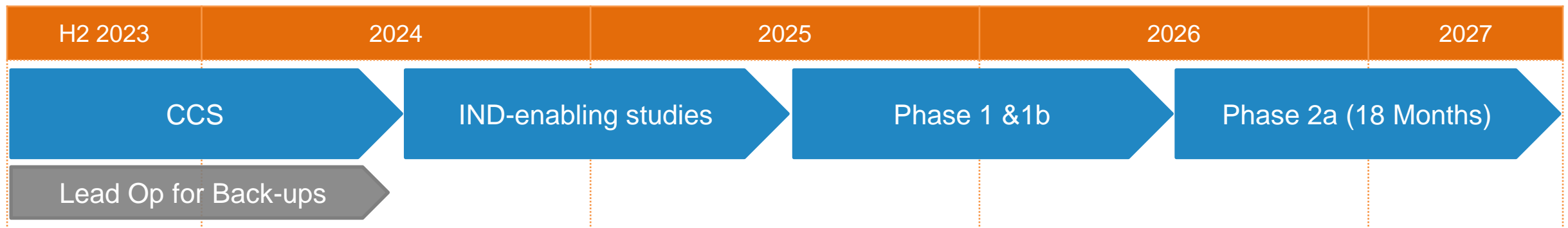
- Limiting peripheral exposure
- Potentially offering best-in-class efficacy and tolerability

- Xanomeline (M1/M4 agonist) shows efficacy in schizophrenia and Alzheimer's patients
 - But with cholinergic and muscarinic GI side effects
- KarXT addresses these side effects by adding trospium, a peripheral muscarinic blocker
 - But still non-selective approach
- Xanomeline anti-psychotic effect driven by M4 receptor
 - M4 knock-out mice data
- Emraclidine (M4 PAM) is more selective
 - Ph1b in schizophrenia patients positive
 - But retains a small activity on M2 receptor

Target Product Profile, Project Status and Development Plan

- A best-in-class selective M4 PAM to treat schizophrenia and other psychosis
 - Once-a-day oral dosing suitable for chronic treatment
 - Improved tolerability in comparison to non-selective muscarinic agonists
- Status of program: clinical candidate selection
 - Potent, highly selective compounds with good developability properties
 - In vivo PoC with PK/PD confirmed in preclinical models of schizophrenia

Development Plan



Addex M4 PAM on track to start first-in-human studies in H2 2025

ADX71149 (JNJ-40411813) for Epilepsy

Partnered with Janssen Pharmaceuticals, Inc

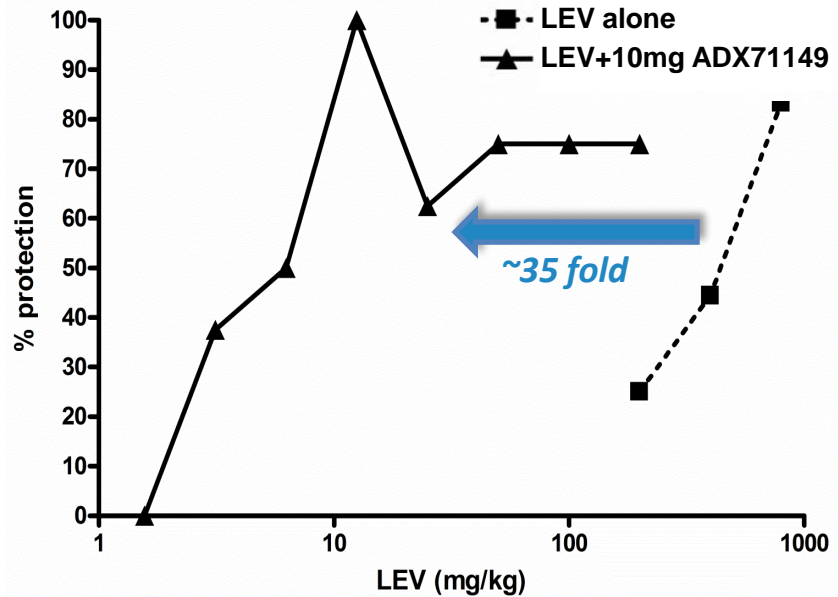
ADX71149 - Opportunity in Epilepsy

Large market & unmet medical need	<ul style="list-style-type: none">➤ Market projected to reach \$20 billion by 2026¹<ul style="list-style-type: none">– Keppra & Briviact net sales in 2022 of €1.2 billion treating 2M patients²➤ High proportion of refractory patients (¼ of new patients³) - combination treatments have limited therapeutic benefit➤ Large underserved patient population needing improved treatment options
Strong MoA & synergistic effect	<ul style="list-style-type: none">➤ Selective oral mGlu2 PAM demonstrated clear MoA in epilepsy➤ Showed 35-fold increase in Keppra (SV2A antagonist) efficacy➤ Potential to reduce SV2A antagonist dosing – improve efficacy & reduce side effects
Status of development	<ul style="list-style-type: none">➤ Phase 2 study ongoing<ul style="list-style-type: none">– Cohort 1 (60 patients) completed– Cohort 2 (50 patients) recruitment completed - November 2023– Open label extension study ongoing
Strategic Partner Janssen Pharmaceuticals, Inc.	<ul style="list-style-type: none">➤ Eligible to receive €109 million in pre-launch milestones and double-digit royalties

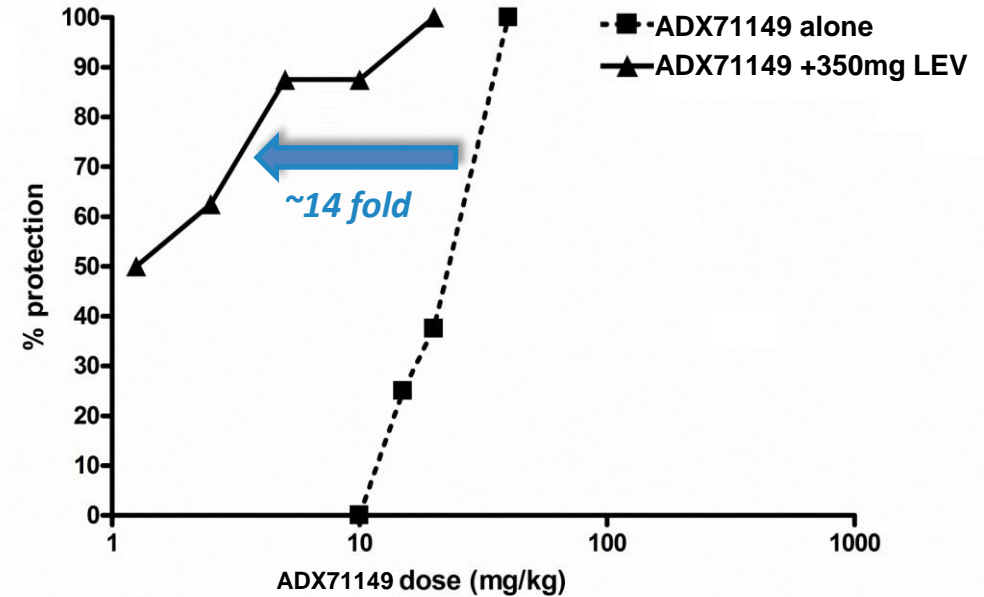
ADX71149 Preclinical Efficacy in Epilepsy - 6Hz Model

Validation in pharmaco-resistant mouse epilepsy model with high translational value:

ED₅₀ shift of Keppra by adding low dose of ADX71149

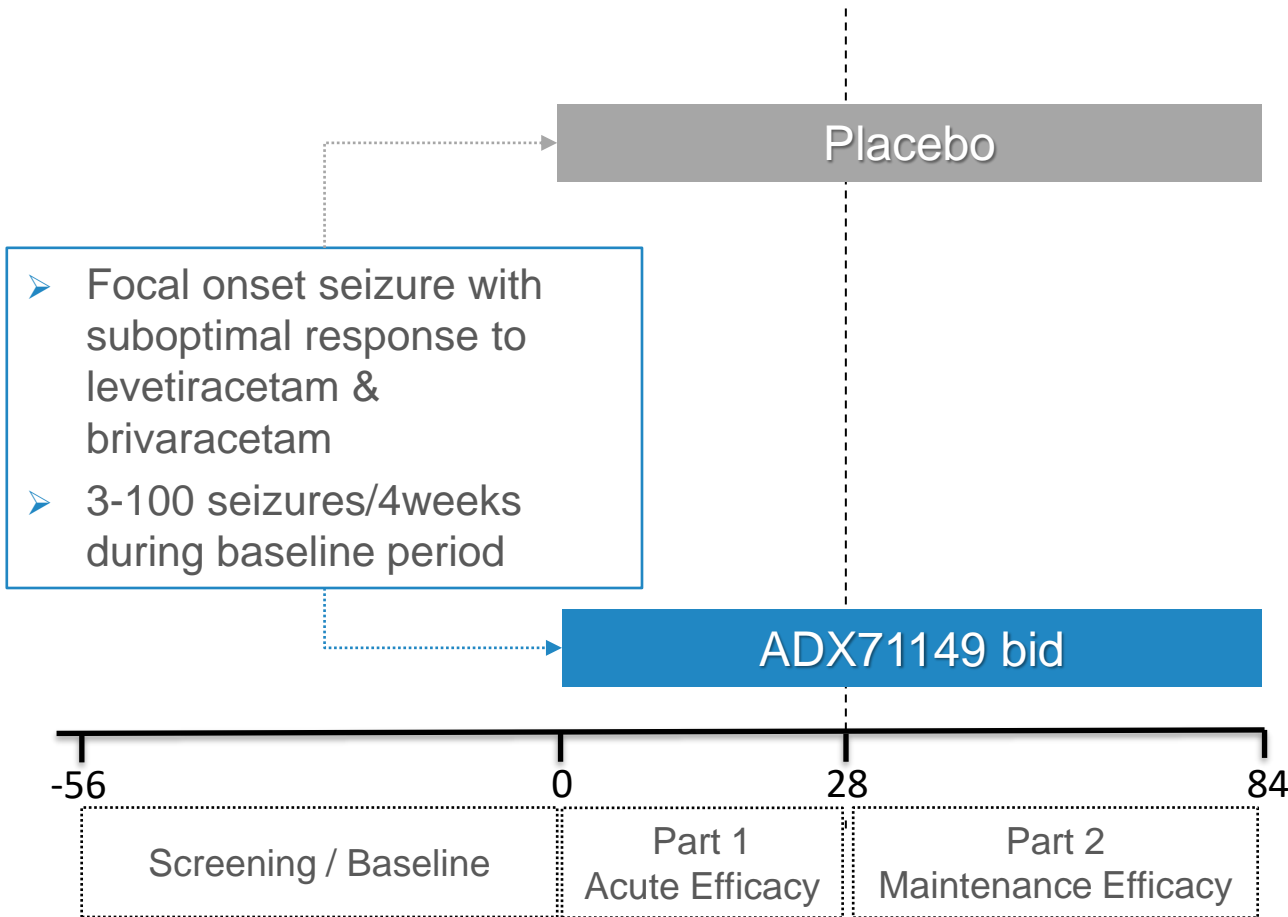


ED₅₀ shift of ADX71149 by adding ED₅₀ dose of LEV



- 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 specific only to SV2A antagonists

ADX71149 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 Part 1 continue double-blind treatment during Part 2
- Evaluating 2 doses in 110 patients
- Cohort 1 (60 patients) completed Part 1 & 2
- Following review of unblinded data of Cohort 1 Part 1 IRC* recommends to continue the study
- Cohort 2 (50 patients): recruitment completed - November 2023

Data expected Q2 2024

GABAB PAM for Substance Use Disorders (Indivior Partnership)

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

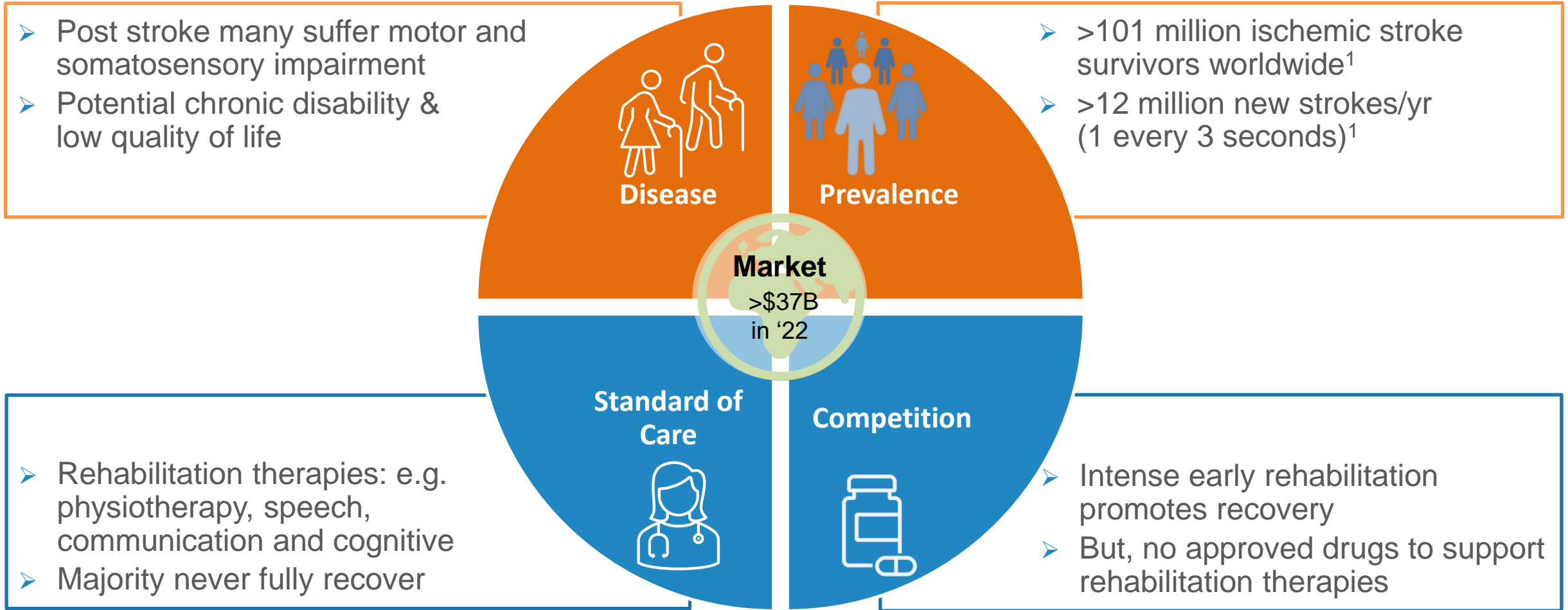
GABAB PAM for Substance Use Disorder

Large market & unmet medical need	<ul style="list-style-type: none">➤ High prevalence; 1.8% of US population¹➤ Current treatments have undesirable side-effects and prone to relapse➤ Burden to society in US is >\$600B annually²
Clinically validated MoA	<ul style="list-style-type: none">➤ Baclofen (GABAB agonist) used off label for alcohol use disorder➤ ADX71441 attenuates alcohol self-administration and relapse to alcohol seeking in rats³ and alcohol consumption in mice⁴➤ ADX71441 reduces cocaine self-administration in non-human primates⁵
Status of program and near-term milestone	<ul style="list-style-type: none">➤ 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 2024
Strategic partnership with Indivior	<ul style="list-style-type: none">➤ 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<ul style="list-style-type: none">– Right to select compounds for development in reserved indications

Dipraglurant (mGlu5 NAM) for Post-Stroke Recovery

Targeting neuroplasticity early in rehabilitation to promote recovery

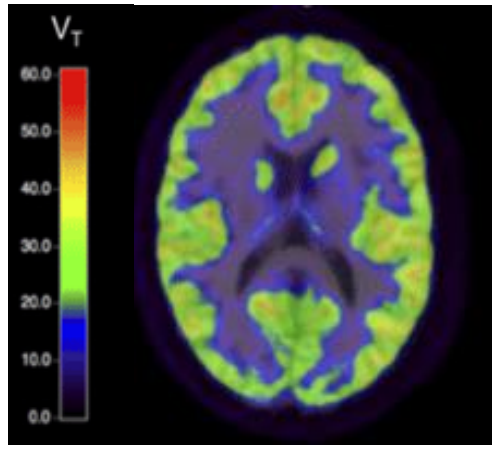
Post Stroke Recovery - Unmet Medical Need & Commercial Opportunity



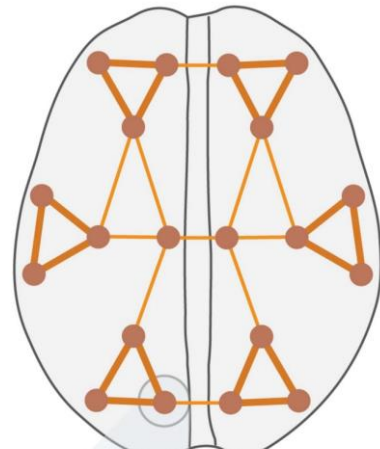
Urgent medical need to promote sensorimotor recovery in post-stroke patients

mGlu5: An Innovative Target for Post-Stroke Recovery

Healthy brain



mGlu5 brain distribution

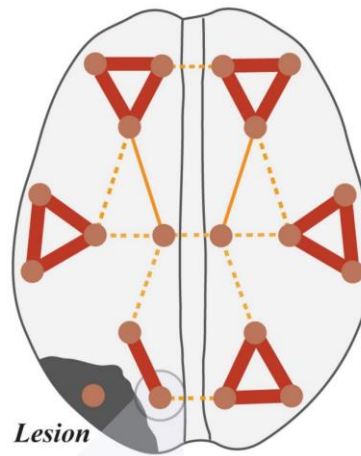


Good inter & intra-nodal connectivity

mGlu5

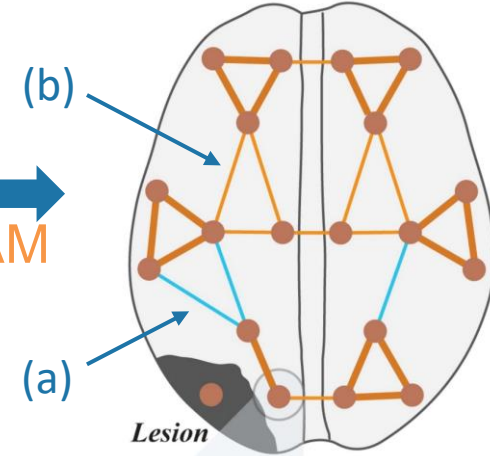
- Densely expressed in the brain
- Involved in neural plasticity
- Modulates excitation/inhibition equilibrium

mGlu5 NAM supports post-stroke recovery



Lesion

Recovery
+ mGlu5 NAM



(a)

(b)

Lesion

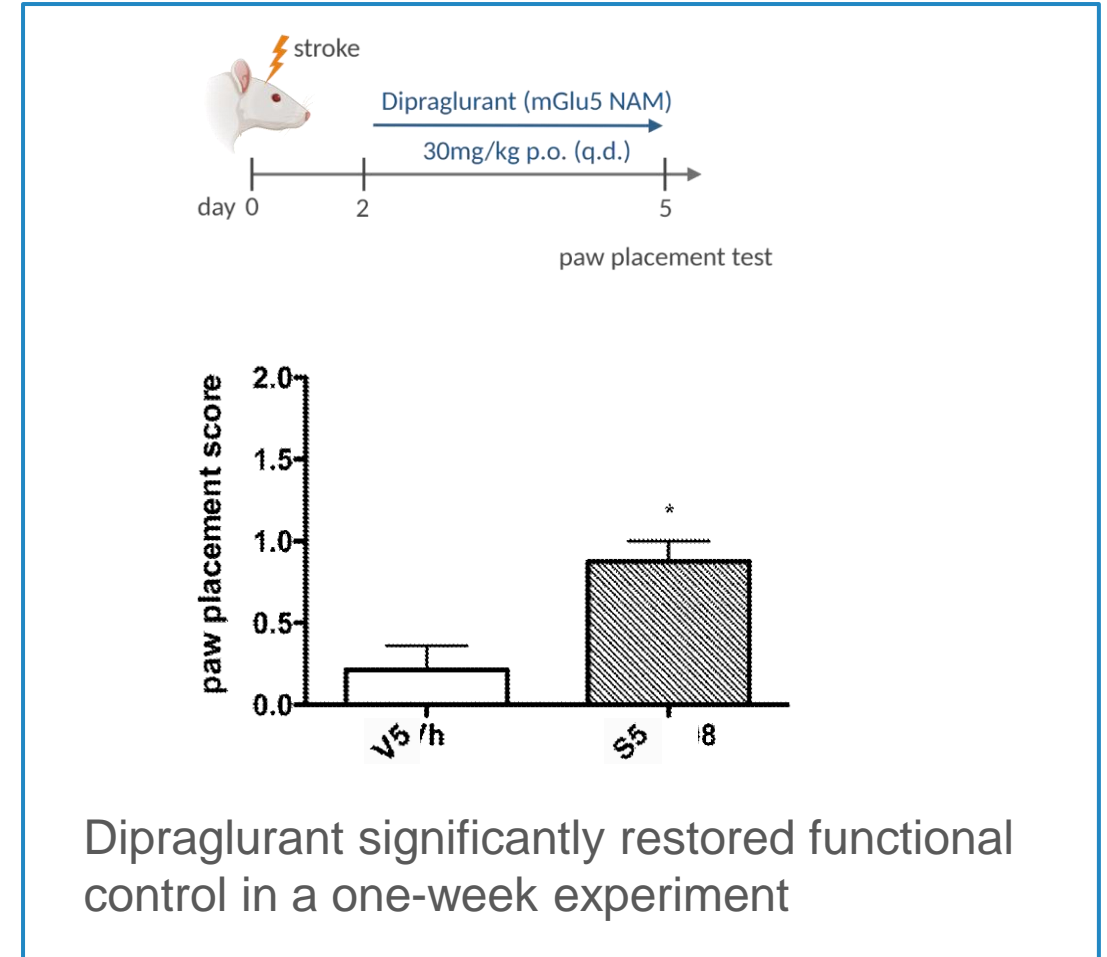
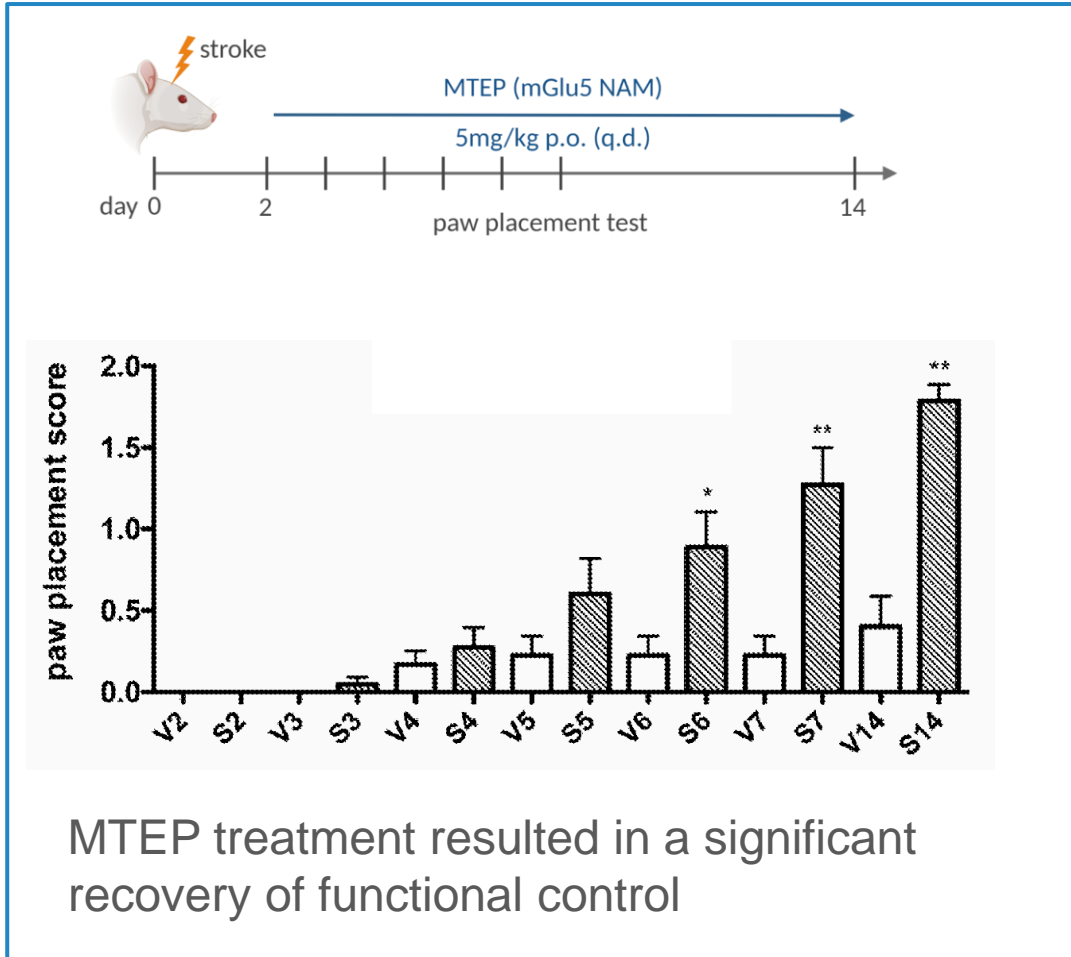
Lesion effects:

- 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

Preclinical Data: mGlu5 Inhibition Promotes Post-Stroke Recovery



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

Dipraglurant Development Status

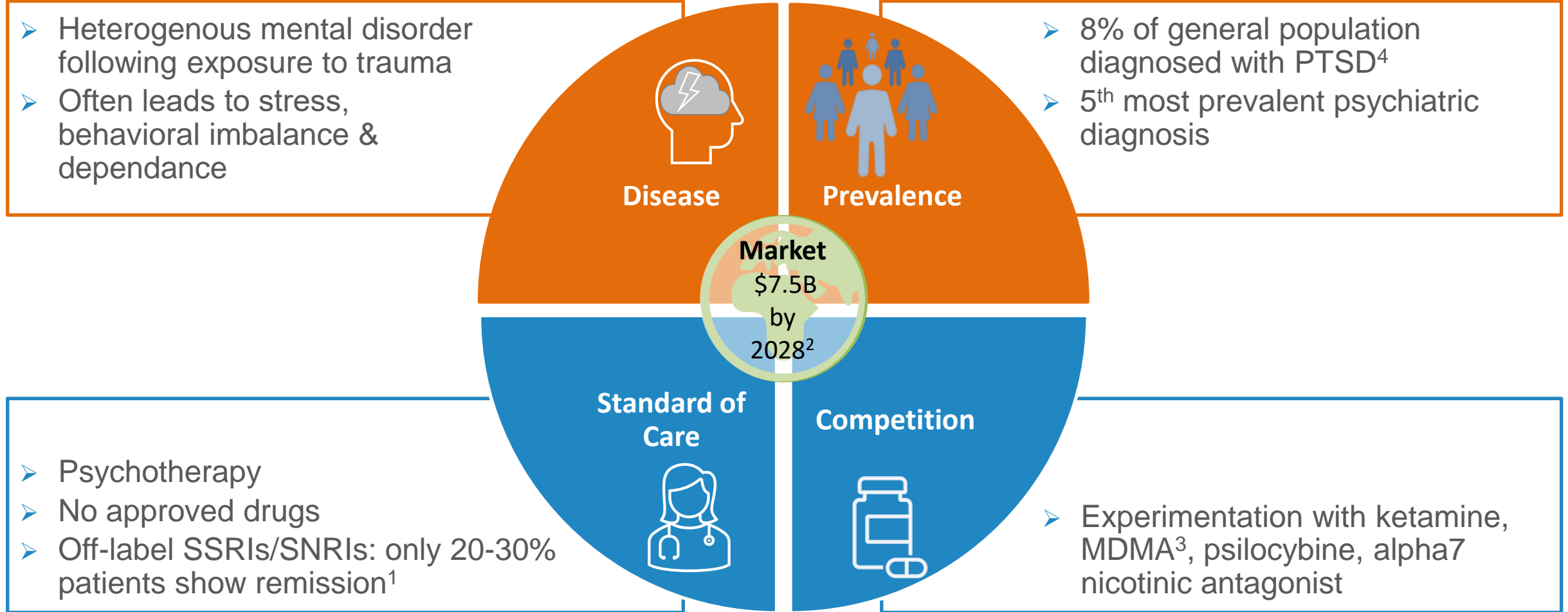
- Fast onset of action and short half-life
 - Ideally suited for concurrent dosing with rehabilitation
- Extensively profiled Phase 1 studies
 - 5 studies with >100 patients
 - Including receptor occupancy (PET ligand study)
- Phase 2 studies conducted
 - Safe and well tolerated in patients suffering 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
 - 90kg 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

mGlu7 NAM for Stress Related Disorders - PTSD

Innovative approach targeting neuronal circuit in stress and fear to deliver an effective and safe treatment for patients with stress-related disorders

Medical Need & Commercial Opportunity in Stress Disorders - PTSD



Urgent medical need for efficacious and safe treatment of PTSD

Selective mGlu7 NAM - Differentiated Approach to Treat Stress Disorders

- Current treatments are primarily based on psychotherapy
 - Marginal efficacy and high relapse rate
- Medication is non-specific
 - Usually ineffective
 - Hindered by numerous side effects
- Experimental use of ketamine & MDMA
 - Efficacy unknown
 - Risks of serious side effects

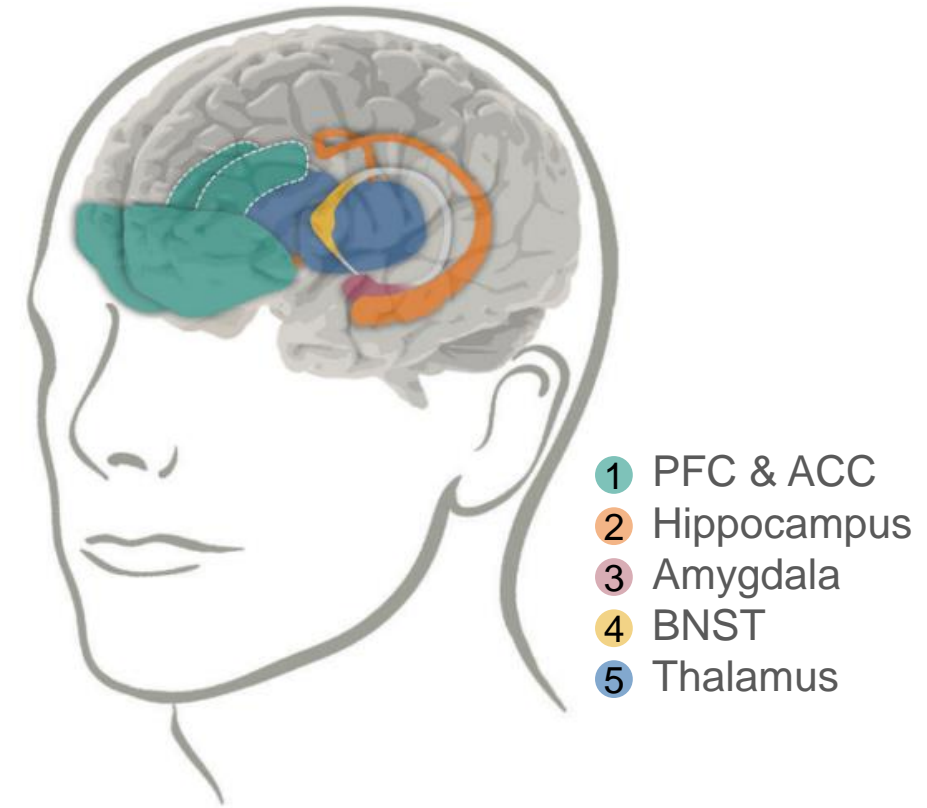
Side-effects	SSRI / SNRI	Ketamine	MDMA	mGlu7 NAM
Withdrawal syndrome	Yes ^{1,2}	No	Yes ³	No
(Neuro)toxicity	No	Yes ^{4,5}	Yes ⁶	No
Cognitive impairment	No	Yes ⁷	Yes ⁸	No
Suicide ideation / risk	Yes	No	Yes ⁹	No

Selective mGlu7 NAM - potential to deliver better efficacy and tolerability

mGlu7 NAM in Stress Related Disorders

- mGlu7 expressed throughout the stress/fear neural circuit
- mGlu7 KO mice exhibit
 - Reduced conditioned fear and anxiety¹
 - Reduced aggressivity and increased pro-social behaviors²
- mGlu7 NAM treatment results in
 - Reduces expression of fear conditioning in rodents⁴
 - Reduced anxiety and panic-like reactivity³ in rodents
 - Antipsychotic-like efficacy in rodent models of psychosis^{5, 6}

Brain regions involved in fear memory



**mGlu7 NAM blocks the reconsolidation of traumatic memory
and decreases its expression**

Target Product Profile, Project Status and Development Plan

- A first-in-class mGlu7 NAM to treat PTSD
 - Once-a-day oral dosing suitable for chronic treatment
 - Reduction in symptoms and improvement in quality of life (social interaction, anxiety, depression, irritability/aggressivity)
 - Can be combined with psychotherapy
 - Superior tolerability (lack of withdrawal, cognitive impairment, suicide ideation, etc)
- Status of program: Ready to start IND enabling studies
 - In vivo POC in PTSD rat models, without any impact on recognition & spatial memory and no side effects after 5 days treatment (rotarod and mini-Irwin)

Development Plan

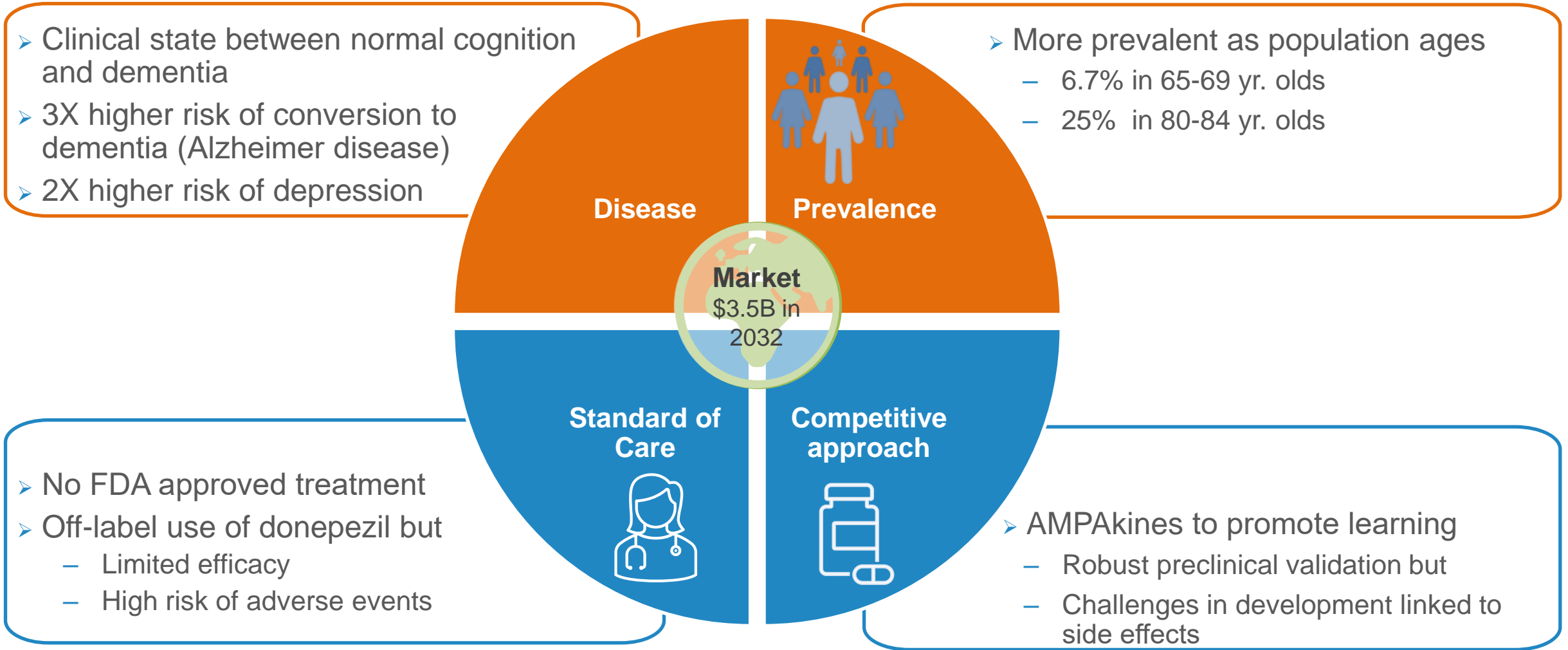


Addex mGlu7 NAM Ready to enter IND enabling studies

mGlu2 NAM for Mild Neurocognitive Disorders

Innovative Approach for Treatment of Mild Neurocognitive Disorder (mNCD)

mNCD - Unmet Medical Need and Commercial Opportunity



High unmet need for better treatment options

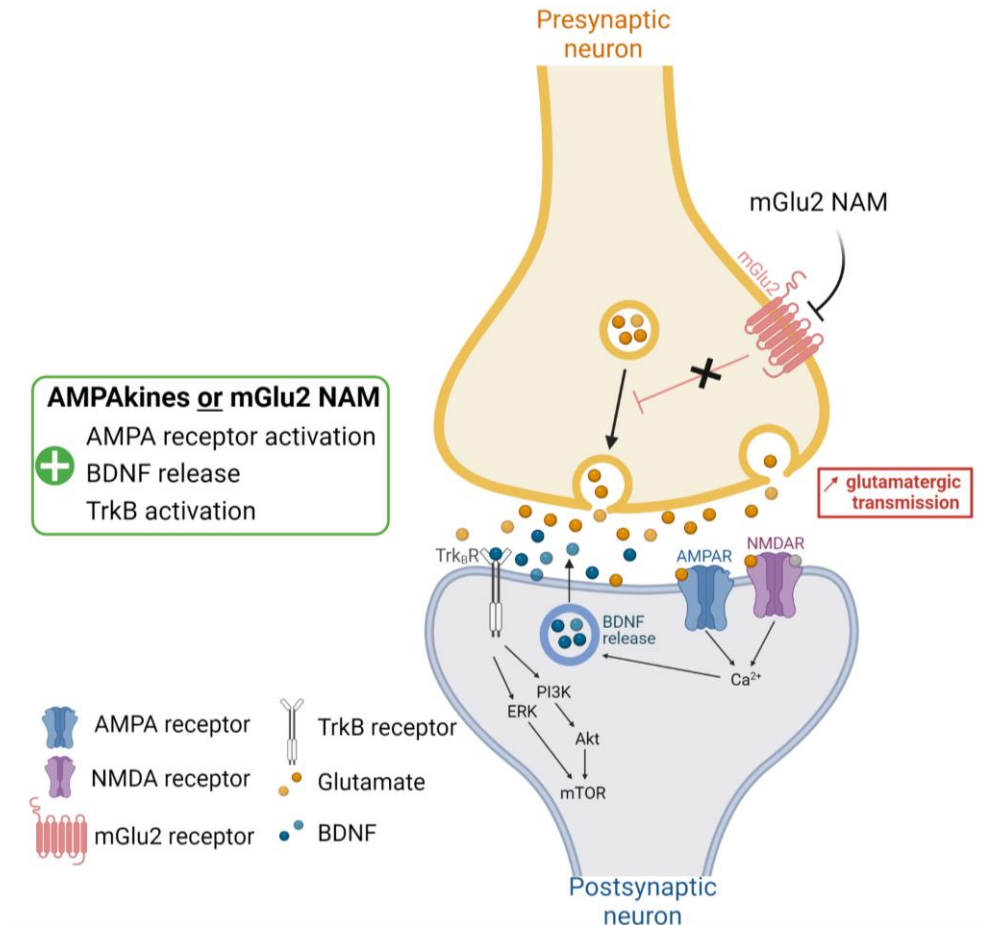
mGlu2 NAM Mode of Action in mNCD

AMPAkines and mGlu2 NAM shared molecular pathways

- By increasing the excitability of neural circuits, AMPAkines/mGlu2 NAMs could counteract the synaptic deficits seen in mNCD

This mechanism directly affects the strength of synaptic connections between neurons, potentially leading to more significant improvements in cognitive function

- AMPAkines: strong preclinical validation but no validation in human studies, due to side effects
- mGlu2 NAMs offer potential to break the paradigm:
 - Highly selective
 - Bioavailable
 - Brain Penetrant



mGlu2 NAM has the potential to offer chronic treatment with best-in-class tolerability

Depression a Major Co-morbidity in mNCD

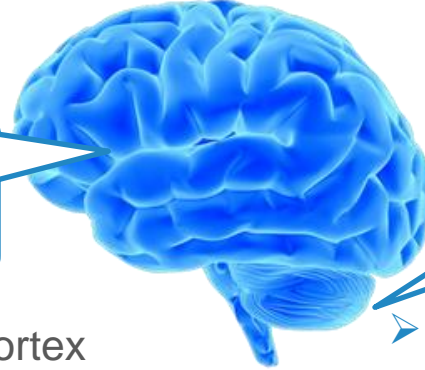
Depression is often associated to mNCD and linked to a poorer prognosis

- mNCD patients with depression > more cognitive deficits
- Lower scoring in memory – executive/ lexicosemantic functions - immediate/delayed memory
- mNCD patients with depression > higher conversion rates to dementia
- Conversion rates in mNCD patients with stable depression = 31%
- Conversion rates in mNCD patients without depression = 13.5%

mGlu2 in Depression

Increased expression of mGlu2/3 receptors in the prefrontal cortex of patients diagnosed with Major Depressive Disorder

- mGlu2 inhibition > ↗ levels of serotonin in rat cortex > antidepressant effects
- mGlu2/3 NAM (RO4491533) antidepressant effect validated in multiple depression models in rodents



mGlu2 in Cognitive Disorder

Increased mGlu2 expression in the hippocampus of Alzheimer's disease patients

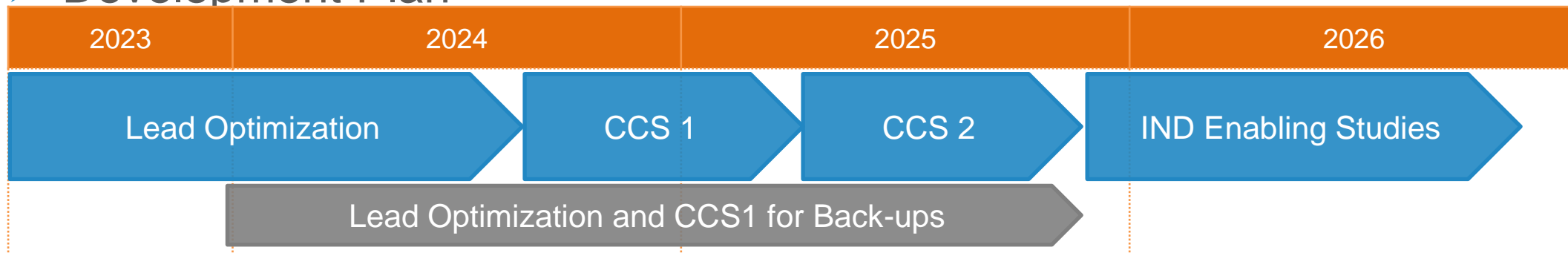
- mGlu2 NAM MK-8768 ↗ attention and executive function in Rhesus monkeys treated with scopolamine
- mGlu2/3 inhibition (in WT but not mGlu2/3 KO mice) > ↗ memory and spatial learning
- mGlu2/3 inhibition > ↗ cognitive performance in age-impaired rats and in model of AD

mGlu2: therapeutic target in both cognition and depression => unique added value

mGlu2 NAM in mNCD - TPP and Development Plan

- A novel mGlu2NAM to treat mild neurocognitive disorder
 - Once daily oral dosing
 - Better efficacy and tolerability than donepezil and AMPAkines
 - Effect on comorbidities such as depression
- Status
 - Our program is in lead optimization
 - Addex led consortium awarded €4 million Eurostars grant to deliver clinical candidates

➤ Development Plan



Innovative novel treatment for mNCD

Addex Financials, Stock and Milestones

Financials and Stock

- Cash at June 30, 2023: CHF 7.2M (USD 8.0M)
- No debt
- Traded on SIX Swiss Exchange: ADXN (ISIN:CH0029850754)
- ADS representing 120 shares traded on Nasdaq: ADXN (ISIN: US00654J107; CUSIP: 00654J107)
- 98.37M outstanding shares
 - Armistice Capital LLC – 43.36%^{*/**}
 - New Enterprise Associates – 7.67%*
- 142.49M shares incl. treasury shares (232.30M fully diluted)
 - Management & board holds – 18.09% (fully diluted basis)
- Analyst coverage:
 - HC Wainwright - Raghuram Selvaraju
 - valuationLab - Bob Pooler
 - Baader Helvea AG - Leonildo Delgado
 - ZKB - Laurent Flamme

Milestones

Milestone	Timing
ADX71149 for epilepsy (Janssen funded) – results expected	Q2 2024
GABAB PAM for chronic cough - start IND enabling studies	H1 2024
M4 PAM for schizophrenia - start IND enabling studies	H2 2024
Dipraglurant for post-stroke recovery – start Phase 2a in stroke patients	2024
GABAB PAM for SUD (Indivior funded) - start IND enabling studies	H2 2024
mGlu7 NAM for stress-related disorders – start IND enabling studies	H1 2024
mGlu2 NAM for cognition - start clinical candidate selection	H2 2024

Achievement of milestones is subject to securing funding or decision of partners

Summary

Multiple high value programs

- Phase 2 epilepsy study (J&J) ongoing
- GABAB PAM for cough and substance use disorder (Indivior)
- M4 PAM for schizophrenia and other psychosis
- Dipraglurant - post-stroke recovery phase 2 ready to start

Technology and capabilities to deliver

- Pioneering allosteric modulation drug development
- Proprietary screening assays and unique chemical library
- All programs developed in-house, protected with >170 patents

Solid foundation

- Partnerships with industry leaders - JnJ & Indivior
- Top tier US investors - Armistice Capital, NEA and NLV
- Dual listed SIX Swiss exchange & US Nasdaq

Promising outlook

- Data from Phase 2 epilepsy study - data expected Q2 2024
- GABAB PAM and M4 PAM programs - start IND enabling studies in 2024
- Dipraglurant Phase 2 post-stroke recovery study expected to start in 2024
- Solid pipeline delivering value and addition partnering potential



ALLOSTERIC MODULATORS FOR HUMAN HEALTH

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