atai
LIFE SCIENCES

# Healing mental health disorders so that everyone everywhere can live a more fulfilled life.

**R&D Day**
**October 25, 2022**

# Agenda

| | | |
|---|---|---|
| 1 | R&D Strategy and Pipeline Overview | Florian Brand |
| 2 | Fireside chat – Clinical & Regulatory Aspects of Depression | Moderated by Dr. Heather Berlin |
| 3 | PCN-101 / R-ketamine | Dr. Srinivas Rao |
| 4 | COMP360 / Psilocybin | Dr. Srinivas Rao |
| 5 | VLS-01 / DMT | Dr. Glenn Short |
| 6 | GRX-917 / Deuterated etifoxine | Dr. Rolando Gutierrez |
| 7 | RL-007 | Dr. Rolando Gutierrez |
| 8 | KUR-101 / Deuterated mitragynine | Dr. Srinivas Rao |

# R&D Strategy and Pipeline Overview

Florian Brand, Co-Founder and CEO

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**Note: Unless otherwise stated, the information in this presentation is as of October 25, 2022**

# Although mental health has become one of the largest global healthcare challenges, there has been little innovation for patients

## SIGNIFICANT BURDEN

**~1bn** — Global population with mental health disorders[1]

**~4x** — US adults experiencing symptoms of depression and anxiety quadrupled[2]

**2nd** — Depression is the 2nd leading cause of disability worldwide[3]

**$300 bn** — U.S. economic burden from adults with Major Depressive Disorder [4]

## URGENT NEED FOR INNOVATION

**~33%** — of patients with depression respond inadequately or relapse[5]

**4-12 wks** — Frontline treatments for depression and anxiety have slow onset (4-12wks)[6]

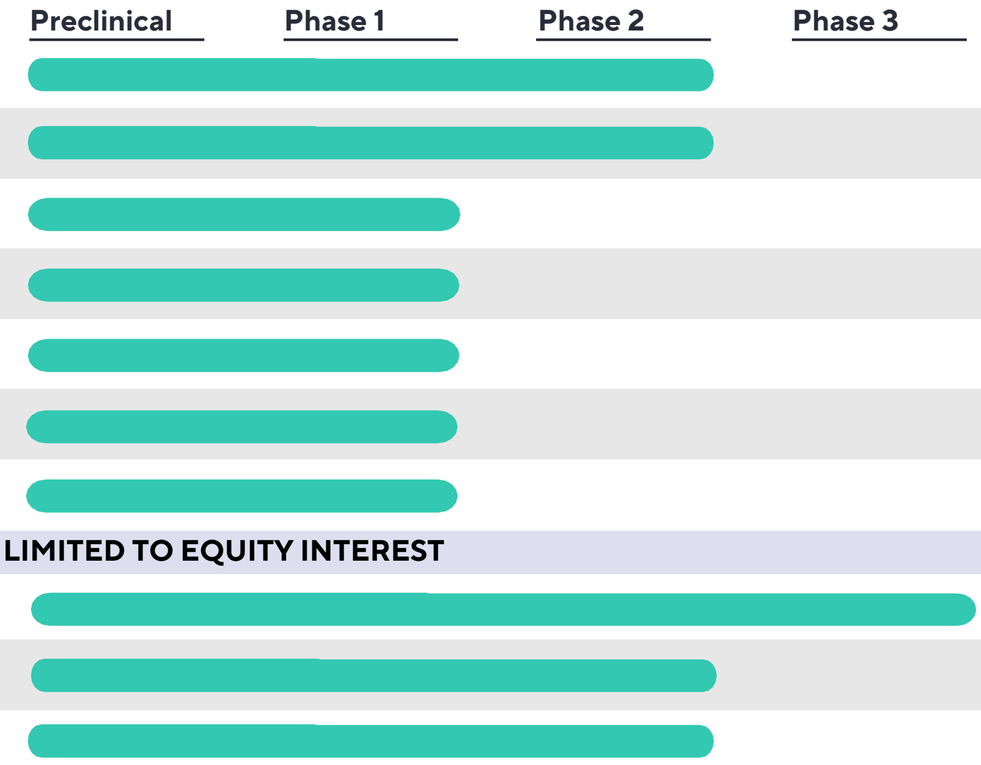
**~75%** — of patients treated for opioid use disorder (OUD) relapse[7]

**7** — Only 7 new compounds approved by FDA for depression since 2017[8]

1. Ritchie, "Global mental health: five key insights which emerge from the data", Our World In Data (2018).
2. Abbott, "COVID's mental-health toll: how scientists are tracking a surge in depression, Nature (2021)
3. WHO source
4. Patel et al., "The Lancet Commission on global mental health and sustainable development", The Lancet (2018).
5. Salzer, "National Estimates of Recovery-Remission From Serious Mental Illness", Psychiatry Online (2018).
6. Tew et al., "Impact of prior treatment exposure on response to antidepressant treatment in late life" Am J Geriatr Psychiatry (2006)
7. Sinha, "New Findings on Biological Factors Predicting Addiction Relapse Vulnerability" (2011)
8. U.S. Food and Drug Administration (as of 5.01.2022). New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products.

# We will deliver on our strategy through a robust pipeline with drug development programs across several mental health indications with large unmet need

| Program | Indication | Affiliate Company[1] |
|---|---|---|
| PCN-101 / R-ketamine | Treatment-Resistant Depression | Perception Neuroscience |
| RL-007 / Compound[2] | Cognitive Impairment Associated With Schizophrenia | Recognify Life Sciences |
| GRX-917 / Deuterated etifoxine | Generalized Anxiety Disorder | GABA Therapeutics |
| VLS-01 / DMT | Treatment-Resistant Depression | Viridia Life Sciences |
| KUR-101 / Deuterated mitragynine | Opioid Use Disorder | Kures |
| DMX-1002 / Ibogaine | Opioid Use Disorder | DemeRx IB |
| EMP-01 / MDMA derivative | Post-Traumatic Stress Disorder | EmpathBio |
| **LIMITED TO EQUITY INTEREST** | | |
| COMP360 / Psilocybin[3] | Treatment-Resistant Depression | Compass Pathways |
| COMP360 / Psilocybin[3] | Post-Traumatic Stress Disorder | Compass Pathways |
| COMP360 / Psilocybin[3] | Anorexia Nervosa | Compass Pathways |




Note: Information as of October 25, 2022, unless otherwise stated. DMT = N,N-dimethyltryptamine; MDMA = 3,4-Methylenedioxymethamphetamine

1. 1. Perception, Recognify, DemeRx IB, and Kures are all variable interest entities; GABA is a non-consolidated VIE with operational involvement through MSA model; EmpathBio and Viridia are wholly-owned subsidiaries; COMPASS Pathways is a non-controlling equity interests
2. RL-007 compound is (2R, 3S)-2-amino-3-hydroxy-3-pyridin-4-yl-1-pyrrolidin-1-yl-propan-1-one(L)-(+) tartrate salts
3. (3) Developing COMP360, a formulation of psilocybin, administered with psychological support from specially trained therapists

# We will build on recent success by delivering several meaningful R&D catalysts anticipated across our key programs through 2024[1] with cash runway into 2025

**Achieved and expected catalysts**

## H2'21 – H1'22

- ✓ **COMP360 Phase 2b results**
- ✓ **RL-007 Phase 2a biomarker results**

## H2'22

- ✓ **KUR-101 Phase 1 results**
- ✓ **GRX-917 Phase 1 results**
- ○ COMP360 Phase 3 initiation
- ○ **PCN-101 Phase 2a PoC results**
- ○ **RL-007 Phase 2b initiation**
- ○ GRX-917 HV[3] PoC Study initiation

## H1'23

- ○ **VLS-01 Phase 1 results**
- ○ **DMX-1002 Phase 1 results**
- ○ PCN-101 Phase 1 SQ rBA[2] study initiation
- ○ VLS-01 Phase 2a PoC initiation

## H2'23

- ○ **EMP-01 Phase 1 results**
- ○ DMX-1002 Phase 2 PoC initiation
- ○ GRX-917 HV[3] PoC Study results

## H1'24

- ○ RL-007 Phase 2b PoC results
- ○ VLS-01 Phase 2a PoC results

**$312M in cash as of June 30, 2022, plus access to up to $175M from Hercules term loan facility, provides runway into 2025**

1 Based on current expectations and projections as of the date of this presentation, and subject to change. 2 Subcutaneous relative bioavailability study. 3 Healthy Volunteers

# Three pioneers & thought leaders provide their views on the clinical & regulatory aspects of depression

## Dr. Heather Berlin

Neuroscientist, clinical psychologist & Associate Professor of Psychiatry and Neuroscience

Icahn School of Medicine at Mount Sinai

HARVARD UNIVERSITY

UNIVERSITY OF OXFORD

## Dr. Gerald Sanacora

Professor of Psychiatry & thought leader in the pathophysiology of mood disorders

Yale University

NIH National Institutes of Health

## Dr. Heddie Martynowicz

Regulatory strategy leader with focus on mood disorders

***NEOKEE PHARMA CONSULTING***

Janssen Pharmaceutical Companies of Johnson & Johnson

MERCK

Bristol Myers Squibb

# Program update

# PCN-101 / R-ketamine

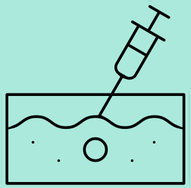
Speaker: Dr. Srinivas Rao

# PCN-101 (R-ketamine) is being developed as a potential rapid-acting treatment for TRD administered in an unsupervised setting at home

**At-home, unsupervised administration** will be based upon a demonstration of an **effective dose** with **good safety** and **tolerability**

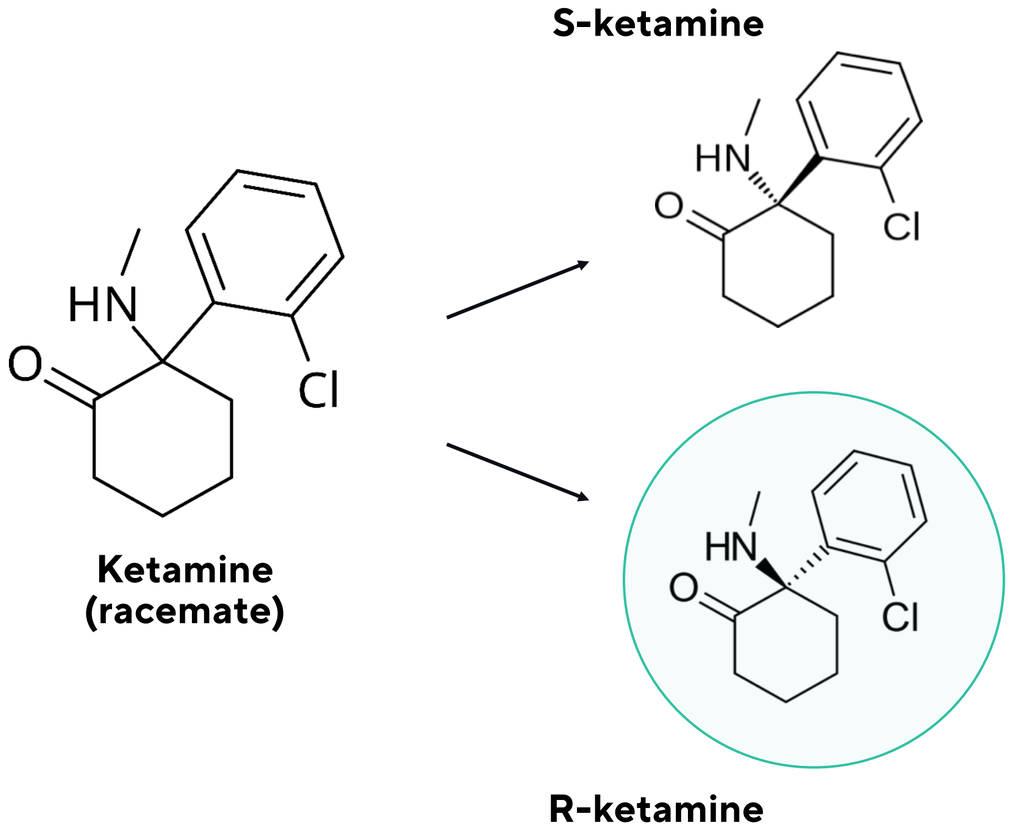
**Phase 2a POC results** anticipated around end of year 2022

Safety, tolerability & efficacy of single dose administration with **PCN-101-IV** in TRD



Phase 1 study of **subcutaneous formulation** relative bioavailability initiating in H1 2023

# R-ketamine vs. S-ketamine: Differentiated profiles with R-ketamine found to have greater antidepressant potency in animal models

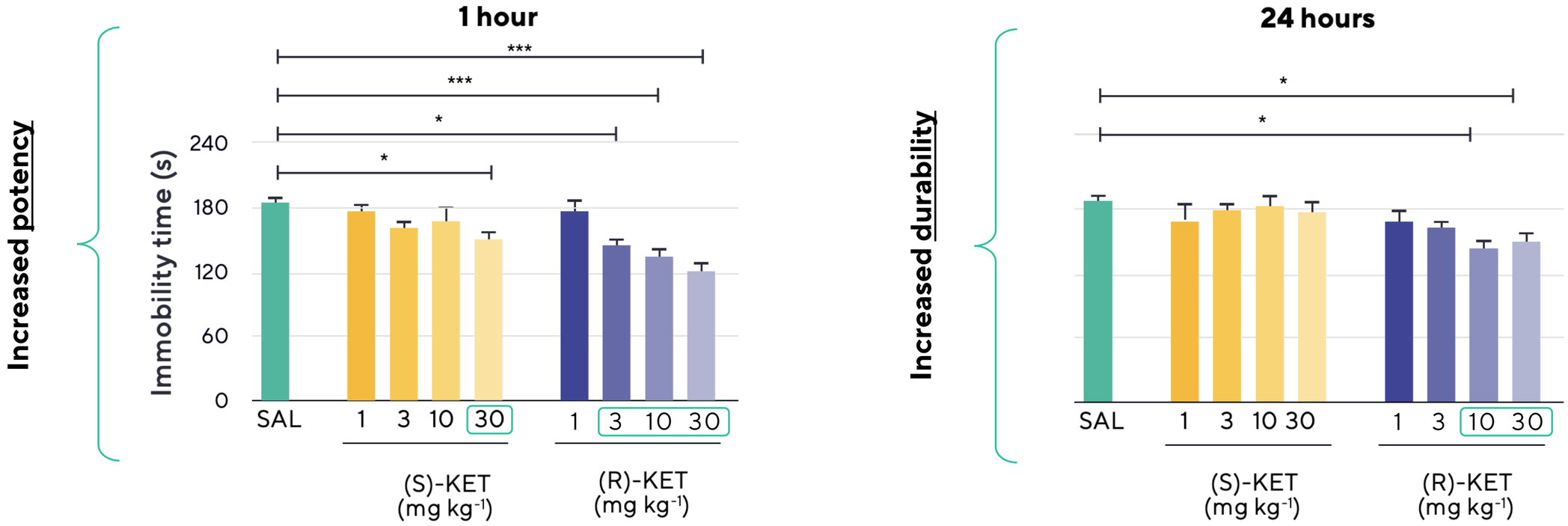



- R-ketamine shows an **improved therapeutic index** in preclinical studies and in a pilot, third-party clinical trial
- R- and S-ketamine may demonstrate **neuroplastic effects through different mechanisms**

1. Wei et al., "A historical review of antidepressant effects of ketamine and its enantiomers" (2020);
2. Chang et al., "Comparison of antidepressant and side effects in mice after intranasal administration of (R,S)-ketamine, (R)-ketamine, and (S)-ketamine Pharmacology Biochemistry and Behavior " (2019)

# R-ketamine vs. S-ketamine in preclinical models: More potent and durable antidepressant activity

**Forced swim test**[1] (third party study)

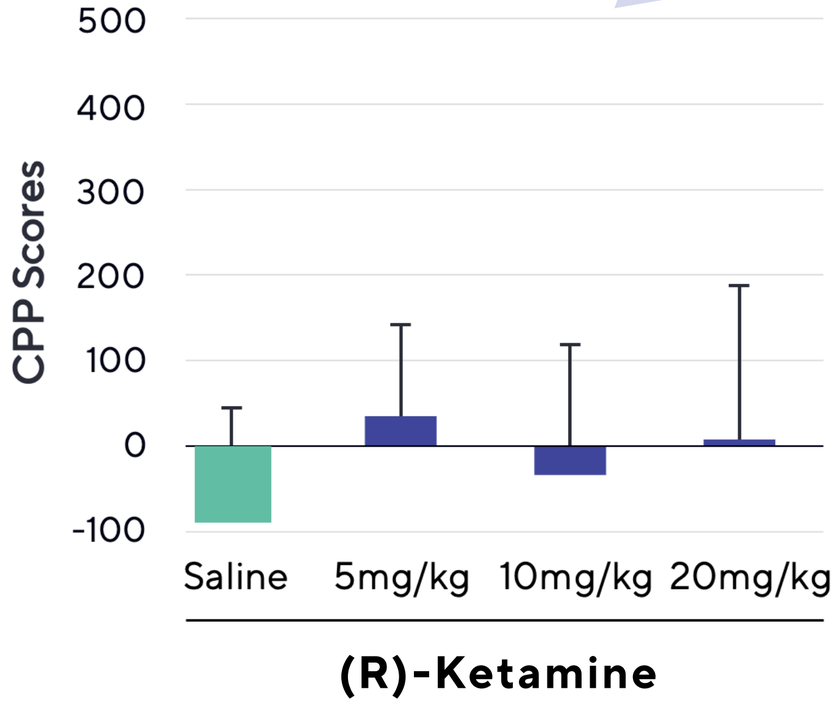



1. Zanos et al., "NDMAR inhibition-independent antidepressant actions of ketamine metabolites" (2016)

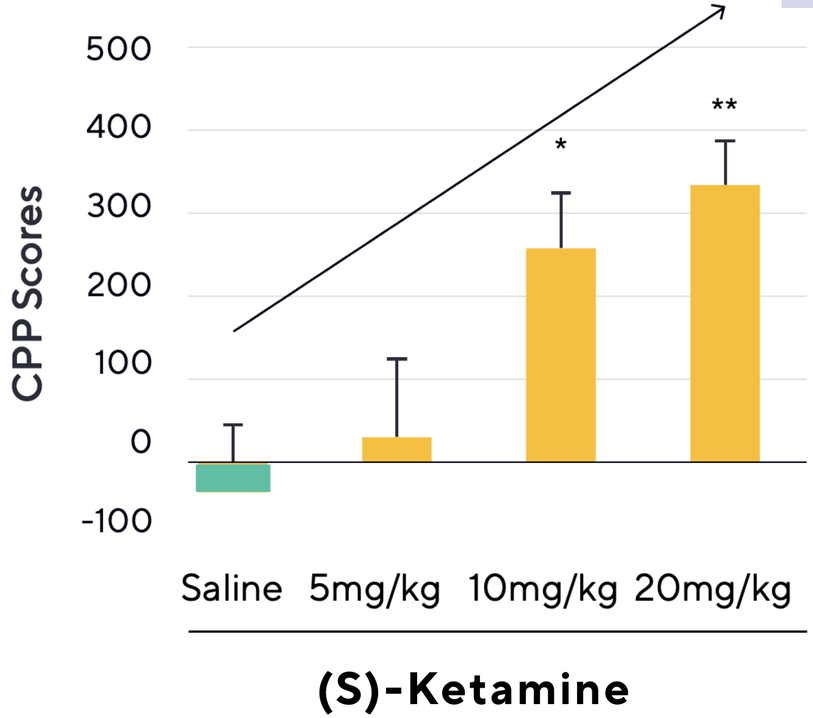
# R-ketamine vs. S-ketamine in preclinical models: Reduced abuse liability potential at effective doses suggest a superior therapeutic index of R-ketamine

**Conditioned place preference (CPP) score test**[1] (third party study)

R-Ketamine: **lower abuse potential**



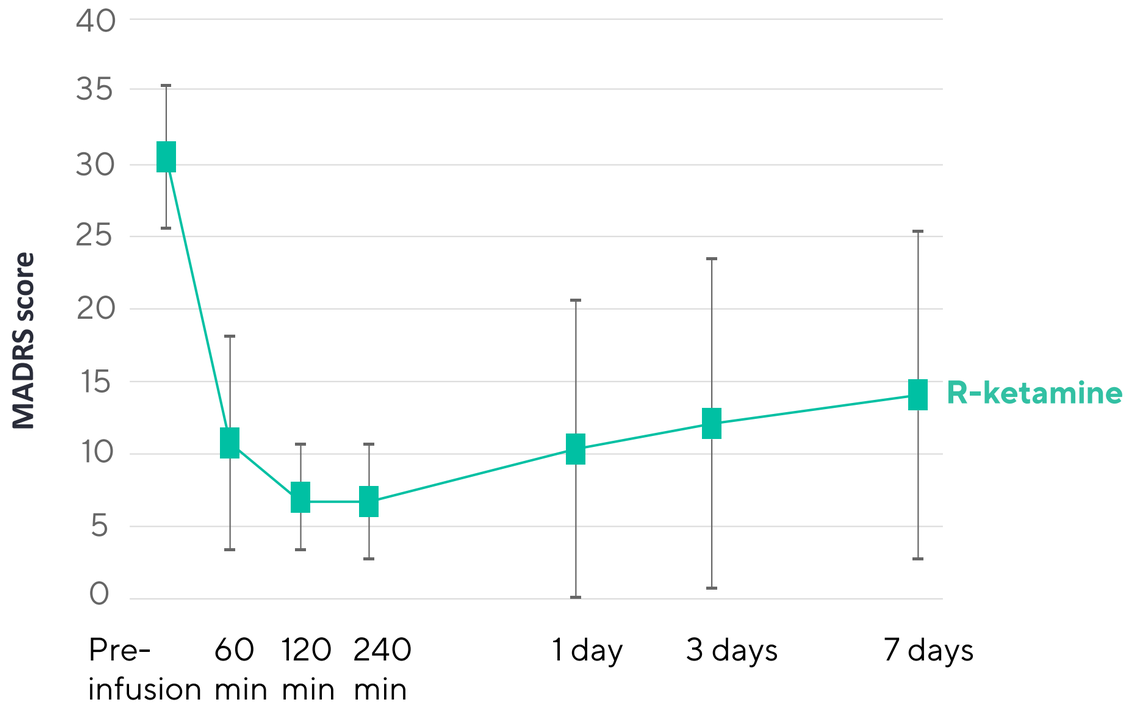

S-Ketamine: **greater abuse potential**

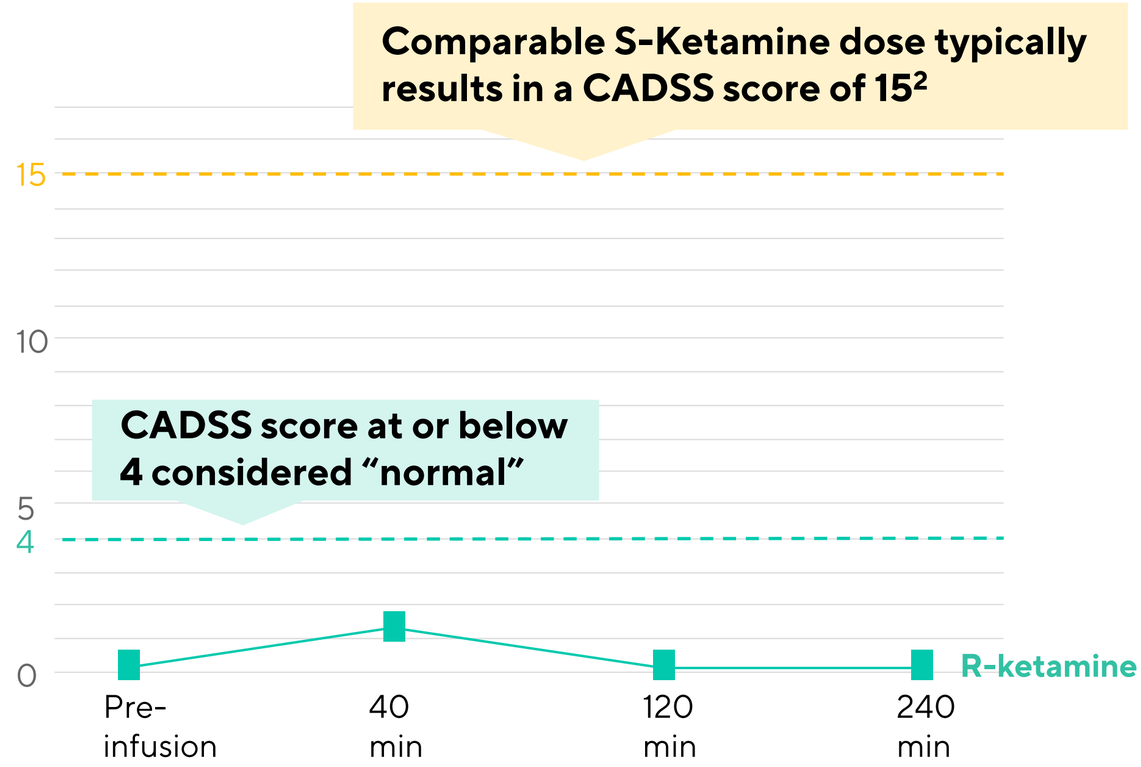



1. Yang et al., "R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects" (2015).

# Prior evidence in humans further reinforces the superior therapeutic index of R-ketamine: Rapid reduction in depressive symptoms with lack of dissociation

**Prior evidence in humans** (third party, open label study[1])

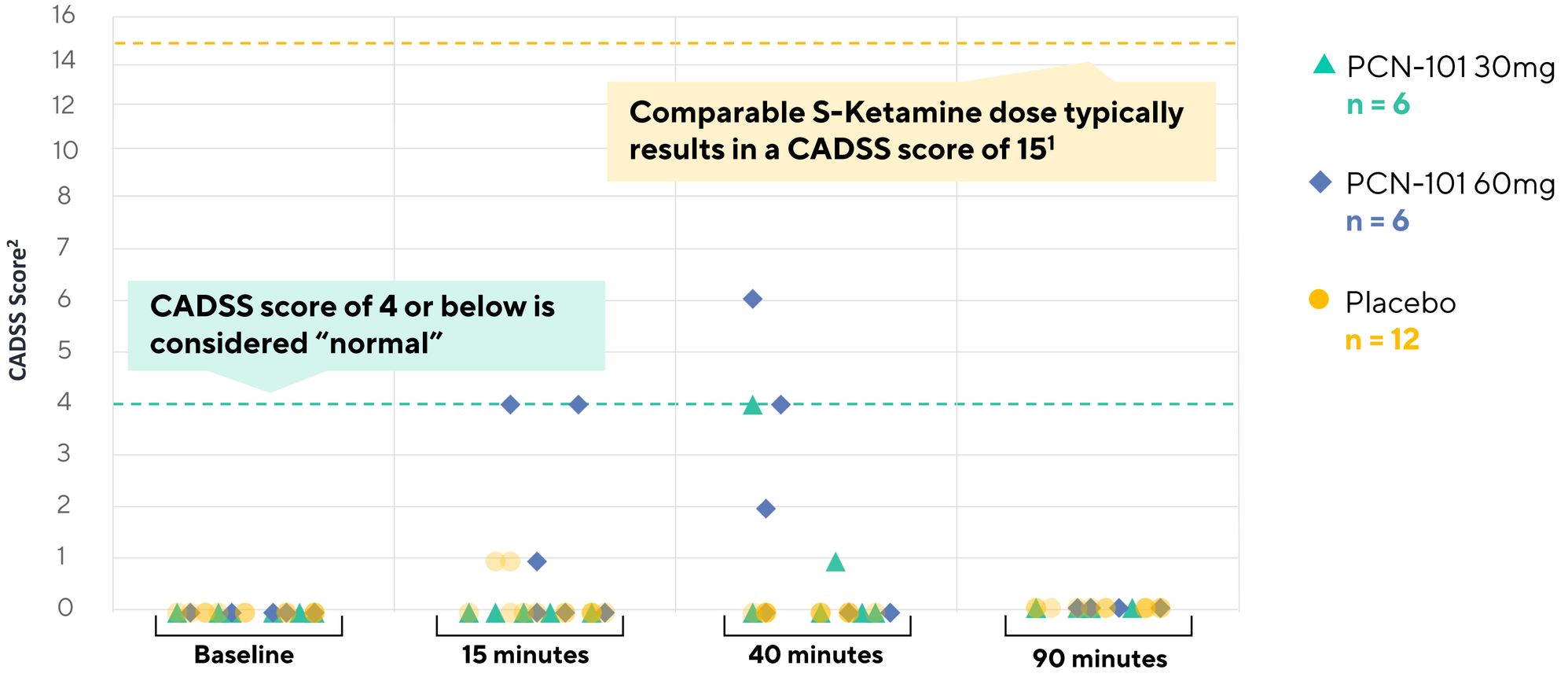



Note: MADRS = Montgomery-Asberg Depression Rate Scale, CADSS = Clinician-administered dissociative states scale, IV = Intravenous, PBO = Placebo.

1. Leal et al., "Intravenous arketamine for treatment-resistant depression: open-label pilot study" (2020)
2. Singh et al. "Intravenous Esketamine in Adult Treatment-Resistant Depression", Biological Psychiatry (2016)

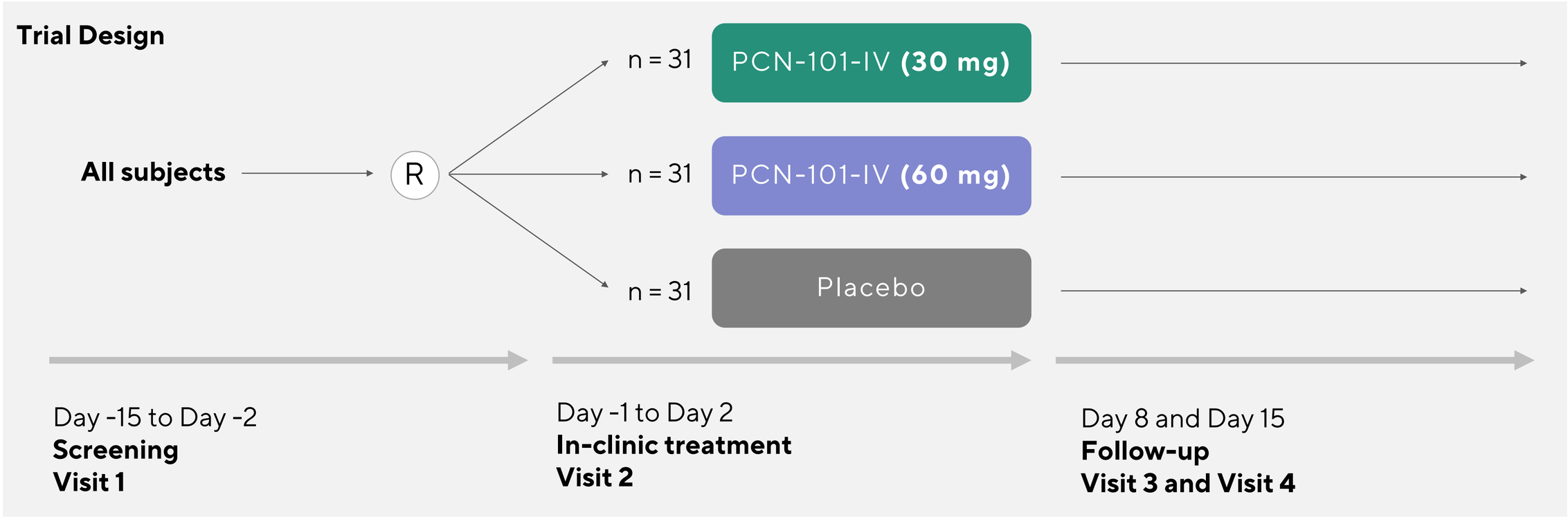
# PCN-101 Phase 1 data: 30 & 60 mg doses that were selected for Phase 2a showed minimal to no dissociation




Note: CADSS = Clinician administered dissociative states scale ; GHB = Gamma Hydroxybutyrate, used to treat Narcolepsy

1. Singh et al. "Intravenous Esketamine in Adult Treatment-Resistant Depression", Biological Psychiatry (2016)

# Randomized Phase 2 study of PCN-101 is expected to establish human proof-of-concept and on track read out around year-end 2022




**Primary Endpoint**:
MADRS at 24h

**Last patient anticipated to be dosed this week, with total number of patients expected to be around 100. Topline results expected around year-end 2022.**

Note: Information as of October 25, 2022, unless otherwise stated.

# PCN-101 Phase 2a singe dose study designed to test the therapeutic index of R-ketamine against dissociation and severe sedation

## Safety/tolerability

**Internal Product Goal**

Differentiation from other TRD therapies with **at-home, unsupervised use**

**Objective for this trial**

Sedation (MOAA/S) and dissociation (CADSS) comparable to placebo, operationalized as risk ratio of < 2

## Efficacy

**Internal Product Goal**

**Rapid and sustained efficacy** with ~2x/week dosing (comparable to other TRD therapies)

**Objective for this trial**

Improvement in MADRS vs. placebo at 24 hours of ≥ 5 for a single dose

## PCN-101 - Important to note:

- Redosing may increase magnitude of effect over time, as seen for example in ketamine studies in TRD[1]
- Doses may be adjusted in future trials to further optimize the balance of efficacy and tolerability
- Potentially less functional unblinding vs. ketamine/S-ketamine studies due to improved tolerability

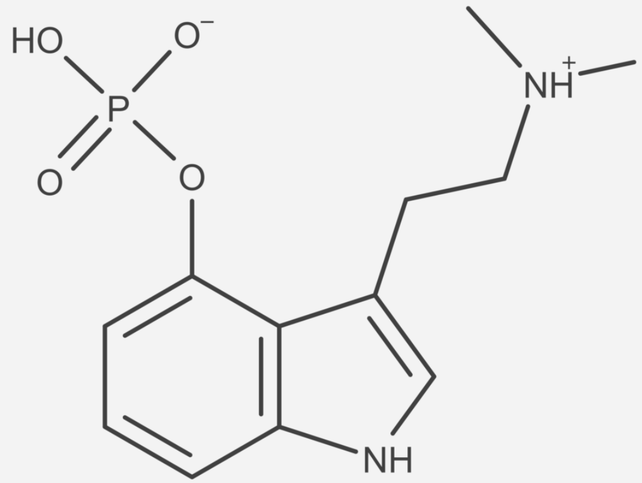
Note: MOAA/S = Modified Observer's Assessment of Alertness/Sedation

1. Such as Singh et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression", Am J Psychiatry (2016)

# COMP360 / Psilocybin

Speaker: Dr. Srinivas Rao

# Latest developments at COMPASS Pathways include positive topline results from phase 2 and announcement of phase 3 program design




Compass' lead asset is **COMP360**, a proprietary formulation of synthetic **psilocybin**

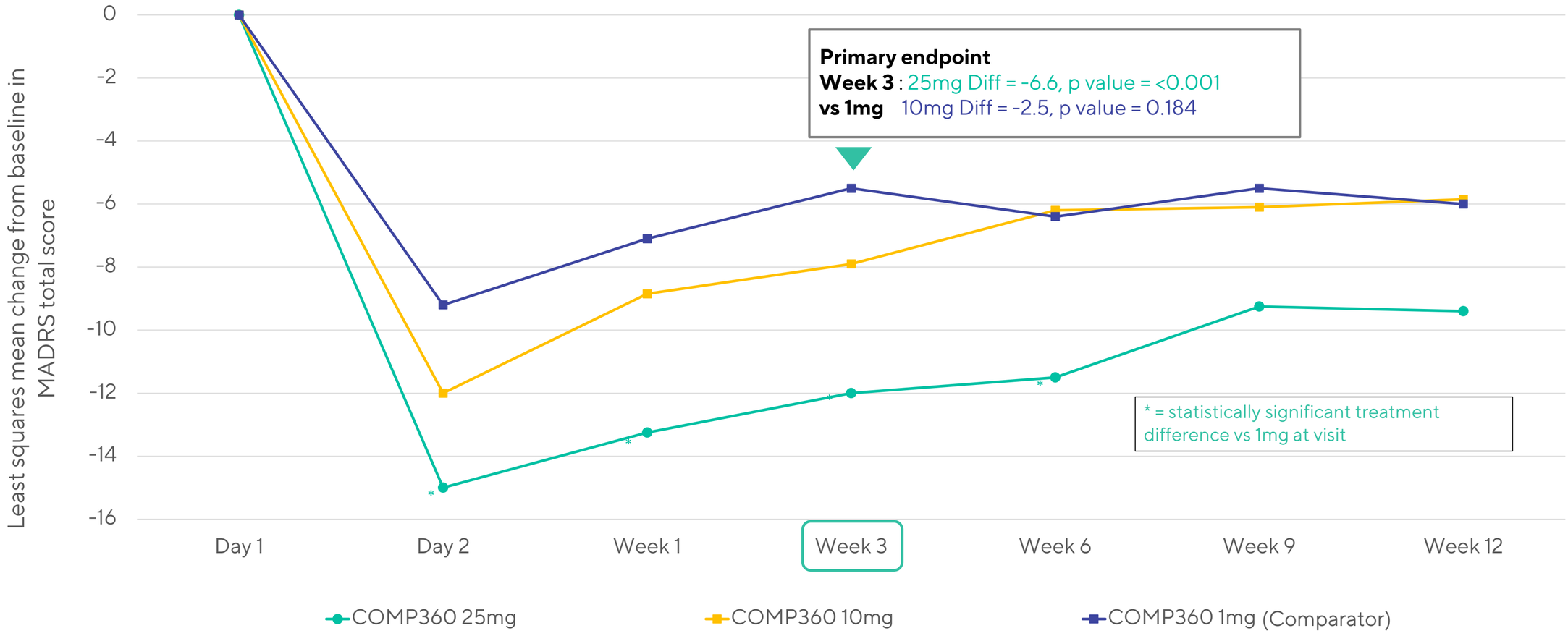
## LAST YEAR

- ✓ **Phase 2b trial completed (n = 233)**
  - Positive topline results

## THIS YEAR

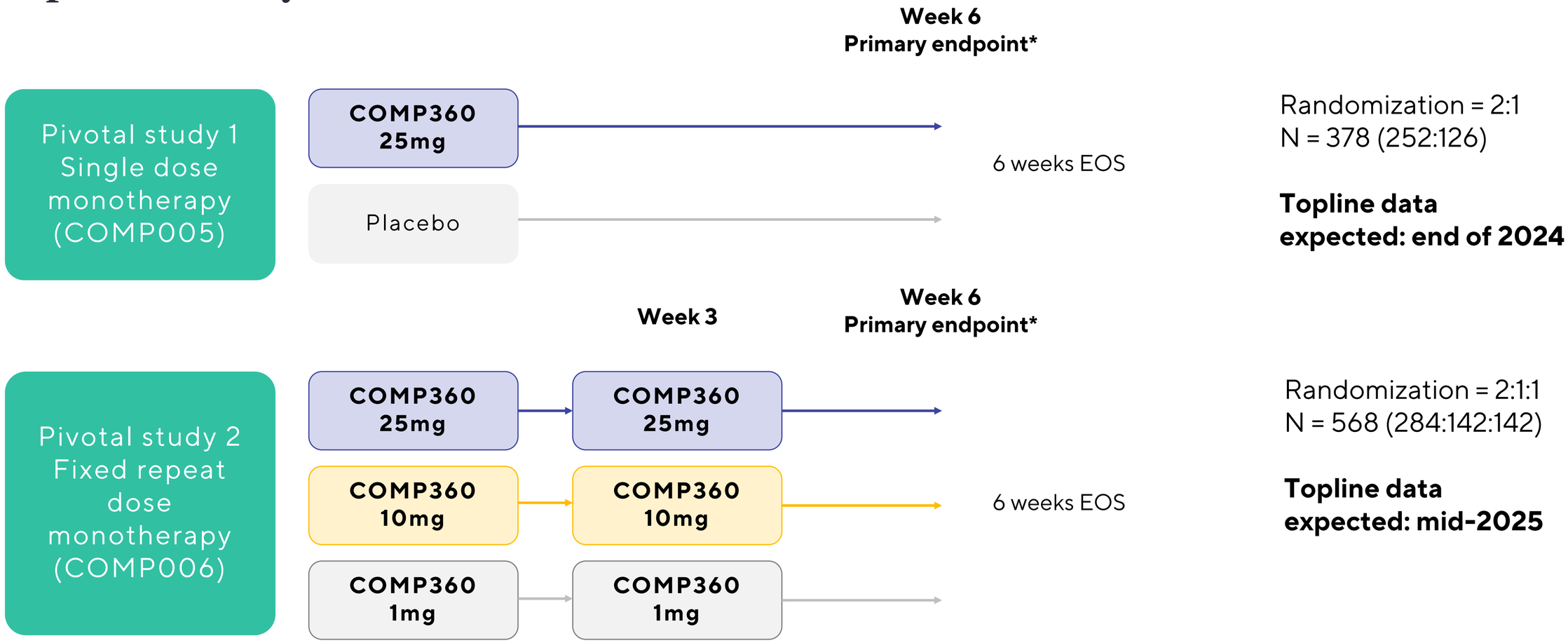
- ✓ **Phase 3 program design announced**
  - First Phase 3 to start this quarter
  - Topline data expected by end of 2024 and mid-2025

# COMP360 Phase 2b trial showed a rapid, sustained reduction in depressive symptoms in 233 patients with TRD




Source: Schedule 13D filed with the SEC as of November 29th, 2021
Note: MADRS = Montgomery-Åsberg Depression Rating Scale;; COMP360 = a proprietary high-purity, polymorphic crystalline formulation of psilocybin; In COMPASS's model of psilocybin therapy, COMP360 is administered in conjunction with psychological support from specially trained therapists.
1. Ownership percentage as of June 30th, 2022

# COMPASS Pathways pivotal phase 3 studies are expected to deliver topline data by 2024 and 2025




*Primary endpoint = Change from baseline in MADRS total score at week 6
The participant population (TRD definition and core inclusion / exclusion criteria) remains unchanged compared to phase 2b

Source: Compass Pathways Capital Markets Day presentation as of October 12, 2022

# COMP360's Phase 3 study design informs the development of our 2nd generation psychedelic compounds

Placebo inclusion in COMP 005 suggests **agreement of agency with both placebo and dose-controlled pivotal trials** and the potential implications of functional unblinding in the former

Assumable **acceptance by agency of psychological and elements of digital support as an integral part of the therapeutic approach for psychedelics**. No requirement of factorial trials to tease out drug effect vs. the effect of these supporting tools

Design of COMP 006 involving 2 doses suggests that **agency is comfortable with repeat dosing** in the context of psychedelic drug development

If these trials are successful, COMP360 will **pave the way for the other drugs in atai's pipeline** developed for TRD, especially VLS-01 (DMT)

# VLS-01 / DMT

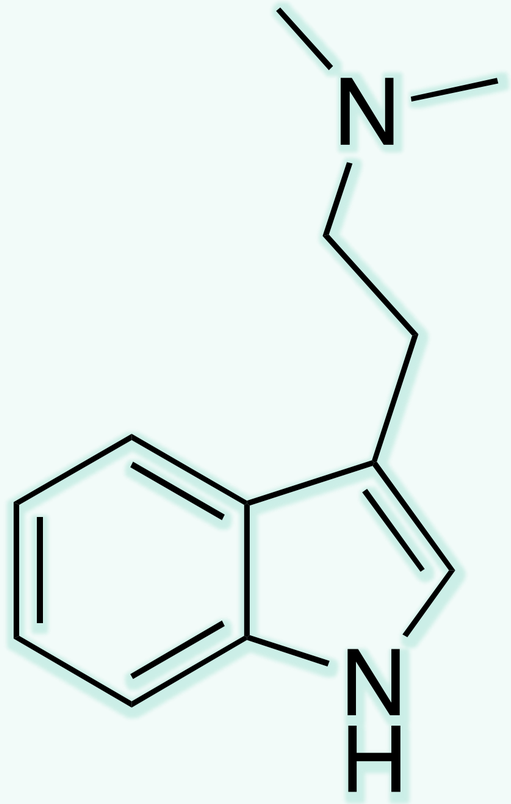
Speaker: Dr. Glenn Short

# VLS-01, also known as N,N-dimethyltryptamine (DMT), is a psychoactive indole alkaloid

DMT is the psychedelic moiety in ayahuasca, a substance with antidepressant properties

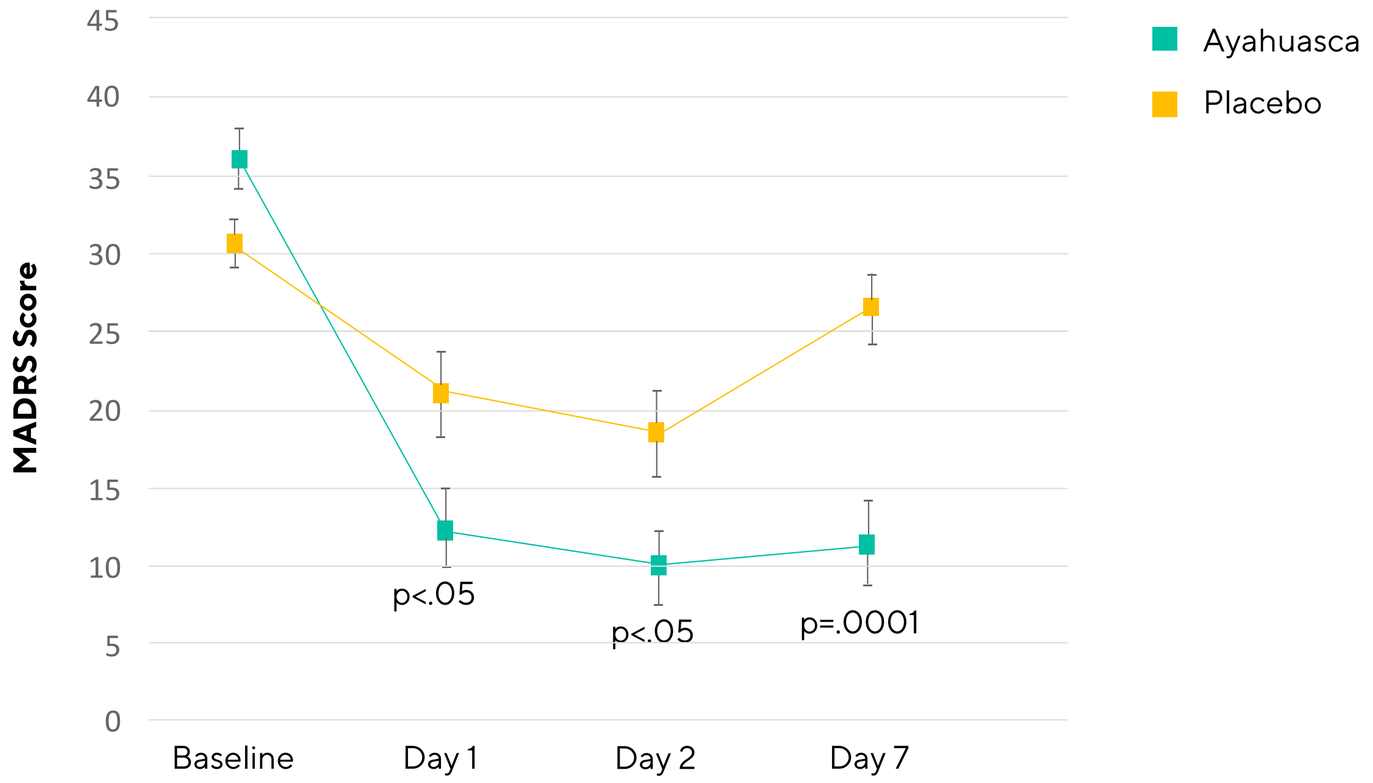
VLS-01 being developed as an oral transmucosal film for TRD

First subject dosed with transmucosal film in Phase 1 trial in October



# Evidence of efficacy in the administration of ayahuasca highlights the potential of VLS-01 as a rapid-acting antidepressant

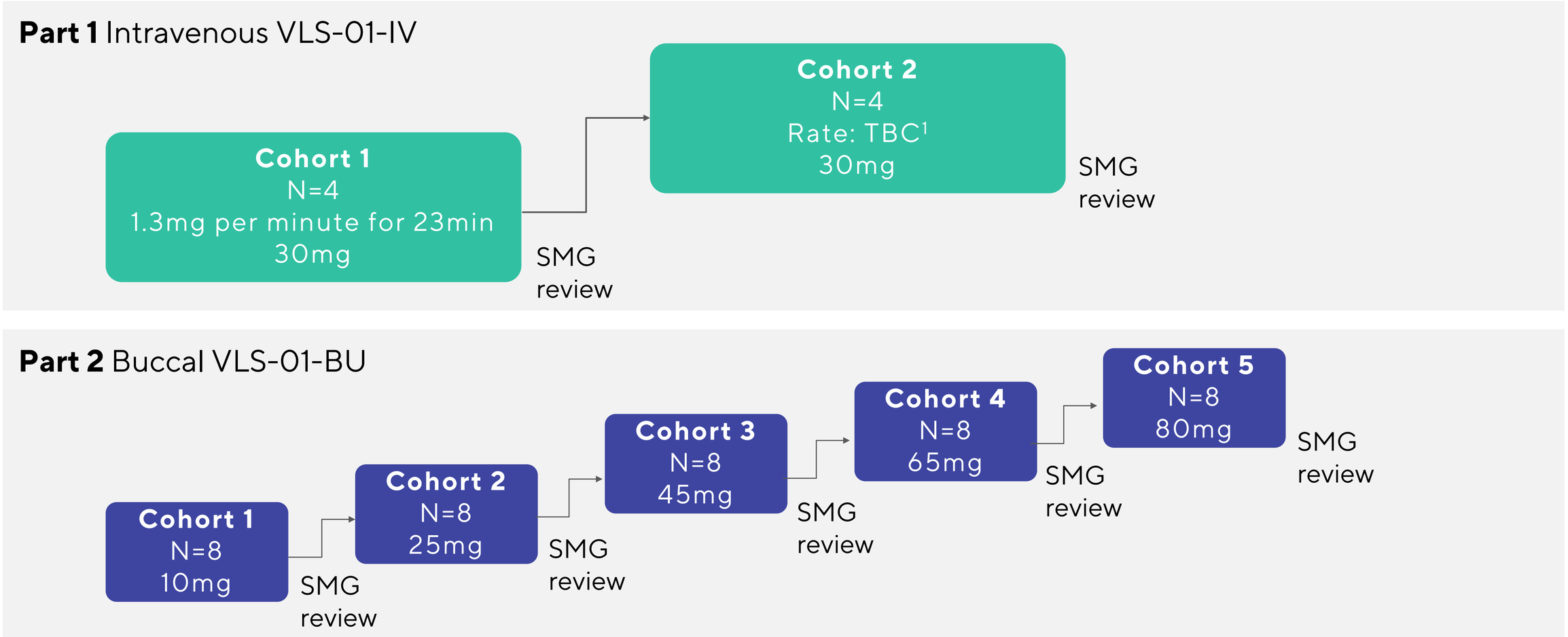
**Prior evidence in humans** (third party study[1]):
**Double-blind, randomized placebo-controlled trial with Ayahuasca in 29 patients with TRD**




Note: MADRS: Montgomery-Asberg Depression Rate Scale.

1. Palhano-Fontes et al. "Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression", Psychol Med (2019)

# The VLS-01 phase 1 study is designed to evaluate the safety, tolerability, and PK of VLS-01 administered via the IV or buccal route




Abbreviations: BU = Buccal, IV = Intravenous, SMG = Safety Monitoring Group, TBC = To be confirmed after SMG review of all available safety, tolerability, and PK data.
Note: Sentinel dosing will be used throughout the study. In each cohort, 2 participants will be administered VLS-01 prior to the remaining participants in that cohort. The remaining participants in the dose cohort will be administered VLS-01 at least 24 hours after the sentinel participants if no safety concerns are identified.
1. In Part 1, if the IV infusion rate is adjusted for Cohort 2, sentinel dosing will be used. If the IV infusion rate does not change, sentinel dosing will not be used for Cohort 2.

# GRX-917 / Deuterated etifoxine

Speaker: Dr. Rolando Gutierrez

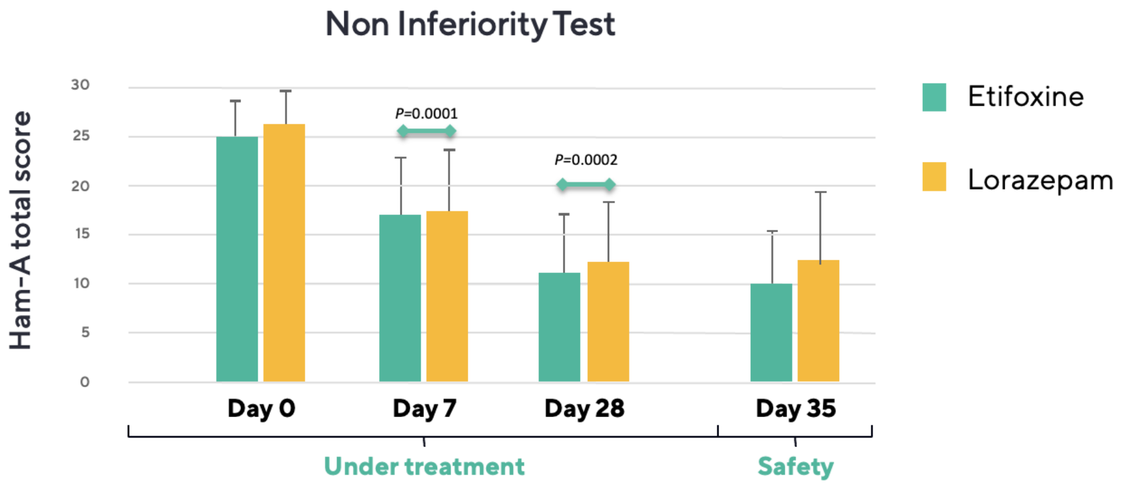
# GRX-917 has the potential for benzodiazepine-like efficacy with improved safety and tolerability

## Etifoxine has been approved for anxiety disorder since 1979 with 14m+ prescriptions in France[1]

**Etifoxine works as rapidly as lorazepam**, with etifoxine continuing its effects beyond treatment, while lorazepam shows rebound

**Etifoxine** has a **strong safety** record: a review of over **14m prescriptions** between 2000 and 2012 in France found no cases of abuse, misuse or dependence[1]

## Third party study[2]




Note: HAM-A = Hamilton Anxiety Rating Scale

1. Cottin et al., "Safety profile of etifoxine: A French pharmacovigilance survey" (2016)
2. Nguyen et al., "Efficacy of etifoxine compared to lorazepam monotherapy" (2006)

# Single and multiple ascending doses were administered to healthy subjects to evaluate safety, tolerability and pharmacokinetics of GRX-917

## Phase 1 study design

Prospective, randomized, double-blind, placebo-controlled study of single and multiple ascending doses of GRX-917 (n = 100)

### Part 1: Single Ascending Dose

**TREATMENT** | **SAFETY/PK/PD**

**Up to 40 healthy subjects:**
Up to 5 cohorts
25mg to 500mg

**PD Endpoint:**
qEEG

### Part 2: Multiple Ascending Dose

**TREATMENT** | **SAFETY/PK/PD**

**Up to 36 healthy subjects:**
Up to 3 cohorts
100mg to 300mg every 12 hours for 7 days

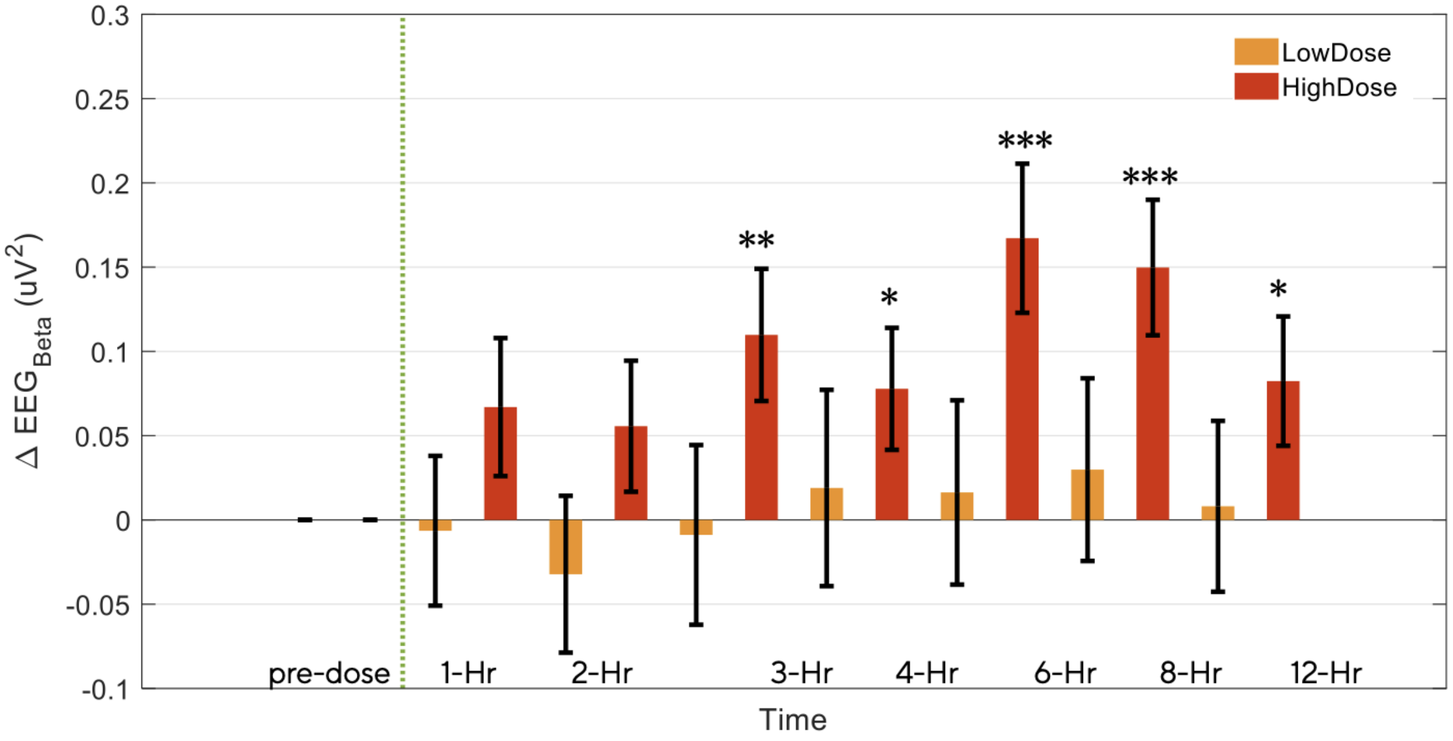
**PD Endpoint:**
qEEG

Adverse events were mild in most cases with no severe or serious adverse events, or dose-relation, with minimal sedation or dizziness.

Note: PD = Pharmacodynamics; qEEG = Quantitative electroencephalography

# Pharmacodynamic effect: The EEG beta effect is dose-dependent and time-dependent, showing a rapid onset of efficacy, with a delayed PD curve

**Group average changes in Beta power for low dose and high dose groups per time point***




* p<.05 ** p<.01 *** p<..001

- **Changes in beta power averaged over each channel from pre-dose to each time point (pre-dose power subtracted from post dose at each point).**
- Average differences in each time point is compared to zero and time points with significant changes (t-test, p<.05) were marked with asterisk.

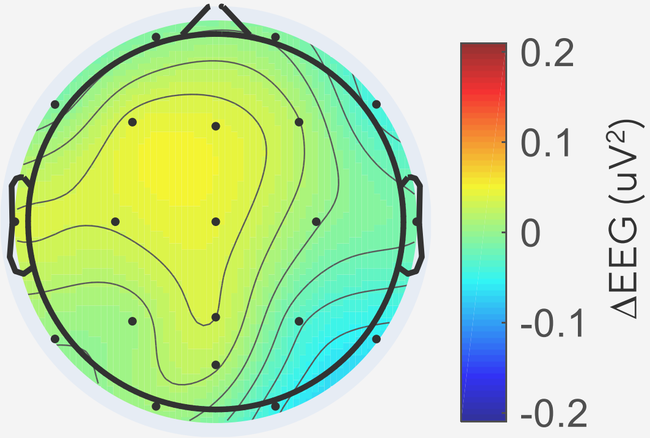
**Preliminary data, subject to change**

Notes: PD = Pharmacodynamics; qEEG = Quantitative electroencephalography, *Preliminary draft data, subject to change

# Pharmacodynamic effect: Changes in Beta power (13-30 Hz) (unit: $uV^2$) from pre-dose to 3-hour post-dose*

**Placebo**

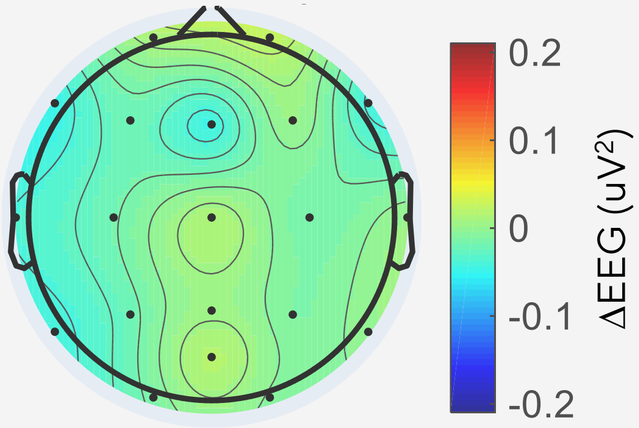
N = 25




P = 0.477

**LowDose**

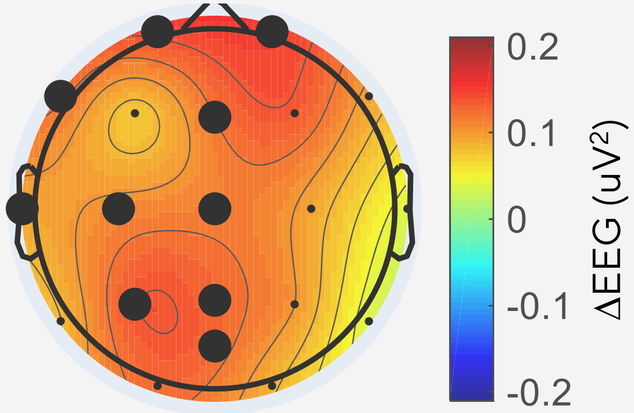
N = 37




P = 0.252

**HighDose**

N = 37




P = 0.005

**No significant change**

**Significant increase**

Channels with significant differences (paired t-test; $p<0.05$, after FDR correction for multiple comparison) are marked with black circles. Topographical maps show distribution of beta power (13-30 Hz) across the scalp. Power is NOT in log scale and the unit of measurement is $uv^2$

*Preliminary draft data, subject to change

**Preliminary data, subject to change**

# The combination of the dose-dependent pharmacodynamic effect along with lower incidence and severity of adverse events shows favorable profile

GRX-917 was **well-tolerated** with no dose-limiting toxicities identified up to the highest dose of 300mg given every 12 hours for 7 days

There were **no serious adverse events reported** nor discontinuations due to adverse events and both single- and multiple-ascending dose (SAD and MAD) regimens showed **only mild adverse events** that were **comparable to placebo-treated subjects**

**No evidence of sedation or other benzodiazepine side effects** at any doses tested

Dose-dependent increase in frontal beta power was demonstrated in subjects receiving GRX-917 but not with placebo **providing evidence of target engagement and mechanism of action**

These results show potential use for GRX-917 as a clinically superior treatment for generalized anxiety disorder (GAD) compared to SSRIs/SNRIs and benzodiazepines

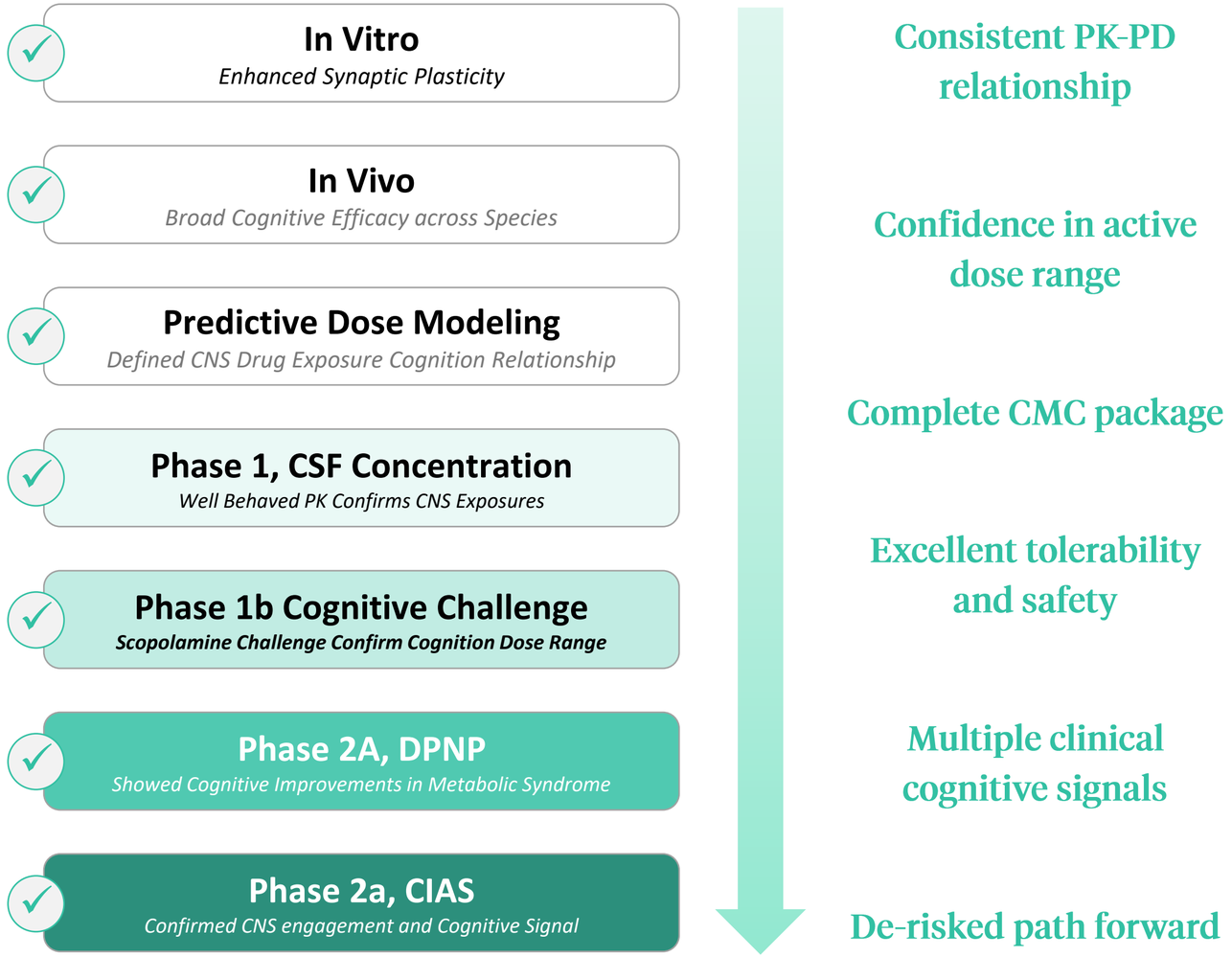
# RL-007

Speaker: Dr. Rolando Gutierrez

# RL-007: a de-risked pro-cognitive neuromodulator with excellent tolerability in humans

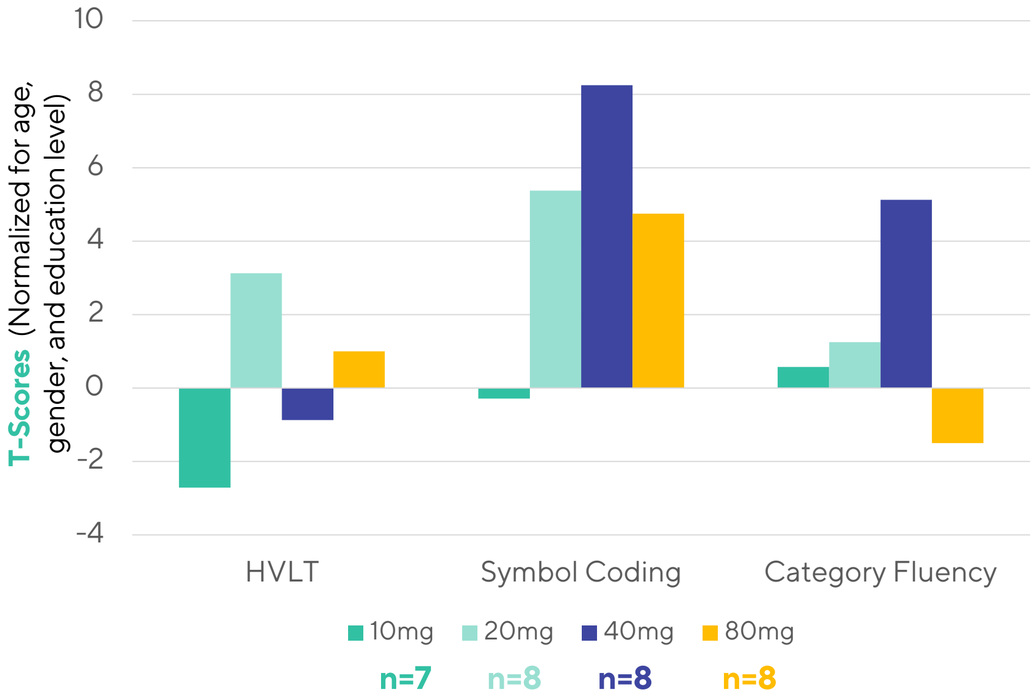
## RL-007: demonstrated pro-cognitive treatment for CIAS

1. Pharma developed product in-licensed with extensive pre-clinical & clinical data package
2. Human Phase 1 + 2 data show replicated, clinically significant learning and memory effects, consistent with broad pre-clinical pro-cognitive data
3. Well tolerated ( >500 subjects dosed), centrally acting oral drug
4. Initial indication: cognitive impairment associated with schizophrenia (CIAS) is characterized by episodic learning & memory deficits – no approved treatment



# RL-007 has previously shown pro-cognitive effects in human clinical studies & CIAS Phase 2a biomarker study showed wide-spread beneficial qEEG changes

**Phase 2a Efficacy data**




Improved

**Cohen's d* (Symbol Coding):**
20 mg: 0.79
40 mg: 0.56
80 mg: 0.38
*Day 4 vs Day 2

EEG data confirmed CNS activity in schizophrenia population

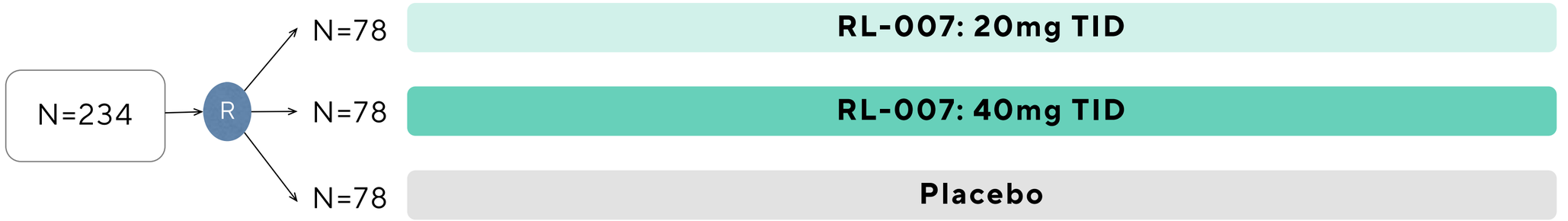
**Dose dependent, widespread qEEG changes observed across brain regions**

EO - Increased alpha/ASI (middle & high doses)
decreased beta (lowest dose)

EC - Observed elevations in resting state alpha increased ASI and
decreased TBR

**Suggesting a relaxed wakeful state without drowsiness at the mid to high dose levels**

# Phase 2b randomized 6-week study of RL-007 20mg and 40mg vs placebo in 234 patients with CIAS




| | V1 **Screening** | V2 **Randomizing** | V3-7 **Week 1-5** | V8 **Week 6 End of trial** | MCC **Week 8 Exit** |
|---|---|---|---|---|---|
| Efficacy | MCCB[1] | MCCB | Safety and tolerability, Conmeds, Compliance | MCCB | Phone call: Safety and tolerability ConMeds Compliance |
| Function | VRFCAT[2] | VRFCAT | | VRFCAT | |

**Primary Endpoint**: MCCB at week 6

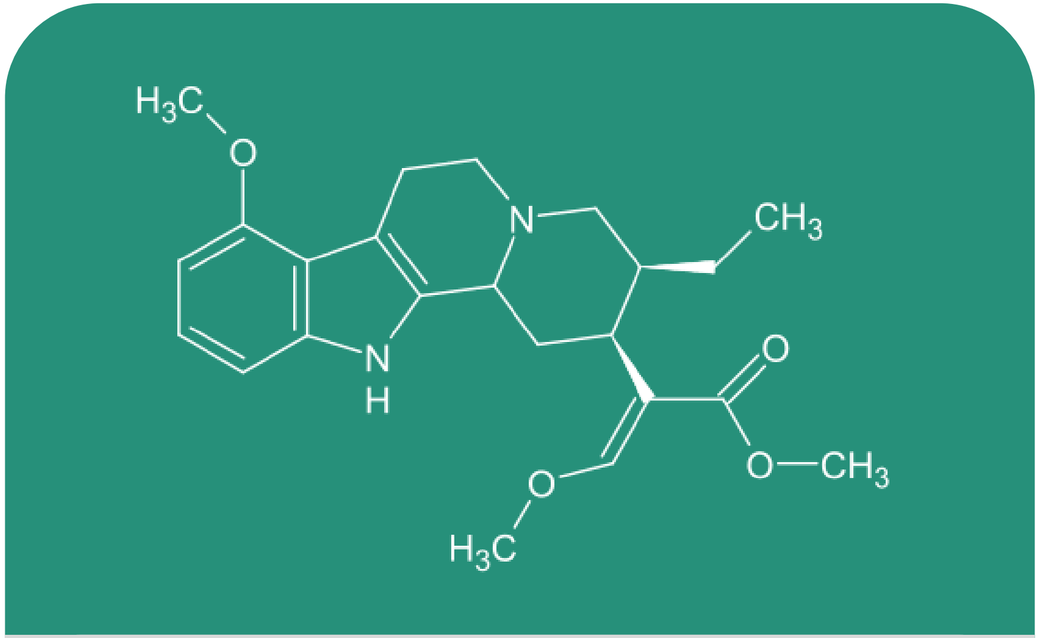
Adaptive design: 2 interim analyses for futility of one or both doses, success, sample size re-estimation

Note: Chart updated as of 8/11/2022; 1. MATRICS Consensus Cognitive Battery 2. Virtual Reality Capacity Assessment Tool

# KUR-101 / Deuterated mitragynine

Speaker: Dr. Srinivas Rao

# KUR-101 is a potentially safer alternative for both opioid maintenance therapy and pain management




**Deuterated mitraginyne**
Active moiety in *kratom*

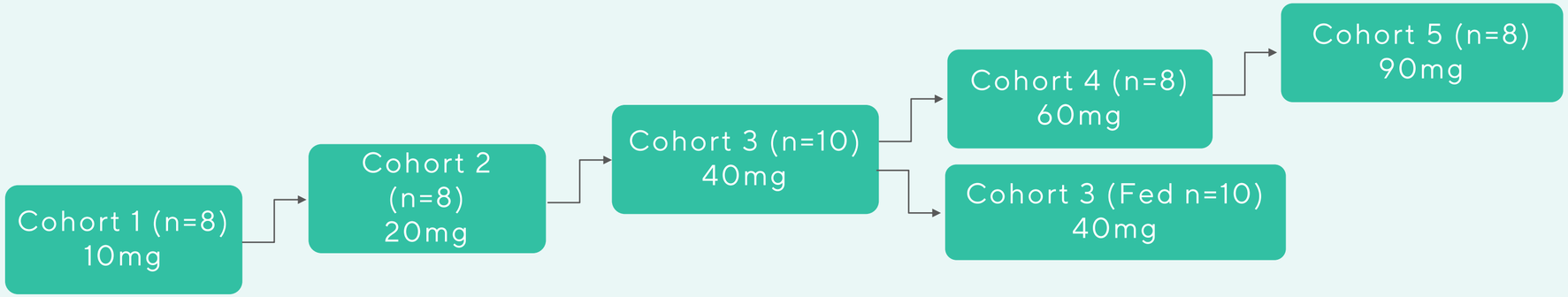
**Mitraginyne** acts as a **mu opioid receptor agonist** with anecdotal reports suggesting reduced potential for respiratory depression, constipation, and/or addictive potential compared to strong opioids

- *Extensive use in East Asia*
- *Use in US for OUD and the treatment of pain*
- *Not a controlled substance in US*

# This Phase 1 study is designed to unlock the therapeutic potential and improved safety profile of KUR-101

**Part 1** SAD study completed August 2022

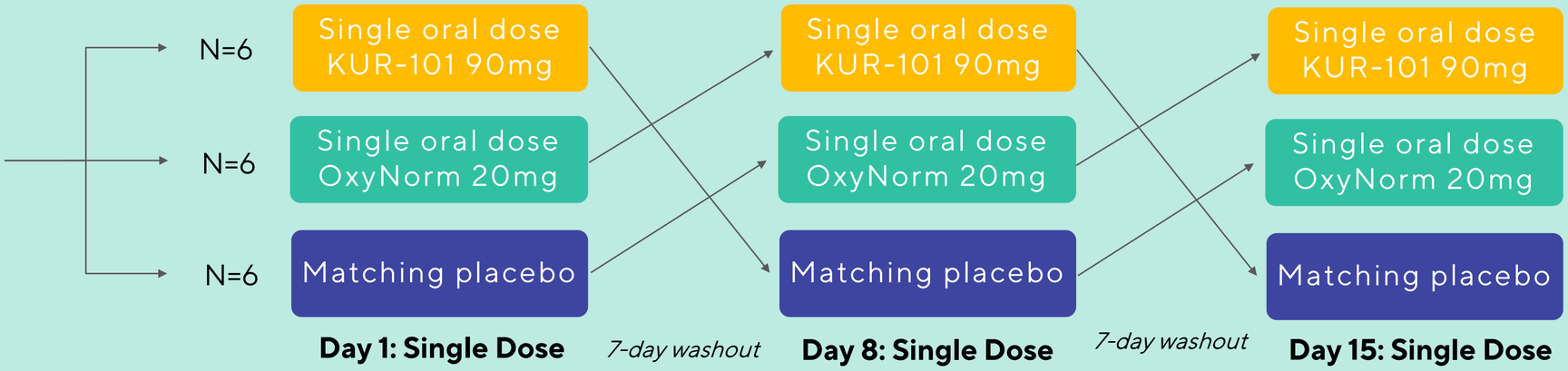
Healthy adult participants (n=42)




**In addition to safety (including respiratory) and PK assessments, evoked pain tests were administered to all cohorts**

**Part 2** comparator study results by EOY 2022

Healthy male participants (n=18)



# Initial results showed single ascending oral dosing of KUR-101 produces dose-dependent analgesia (pain relief) with placebo-like effects on respiration

- Initial results indicate that KUR-101 is safe and generally well-tolerated
- Results also showed a dose-proportional pharmacokinetic (PK) profile that was unaffected by food
- In the single ascending oral dose portion of the trial, no severe or serious adverse events were reported, with most treatment-related adverse events being mild
- Changes in respiratory rate following treatment with KUR-101 were comparable to that of placebo-treated patients for the doses tested and comparable across doses
- Analysis of part 2 of the trial continues and we expect topline results from a portion of the trial by year’s end

atai
LIFE SCIENCES

# Thank you

**R&D Day**
**October 25, 2022**