REL-1017 in Major Depressive Disorder: Phase 2 Clinical Study Results

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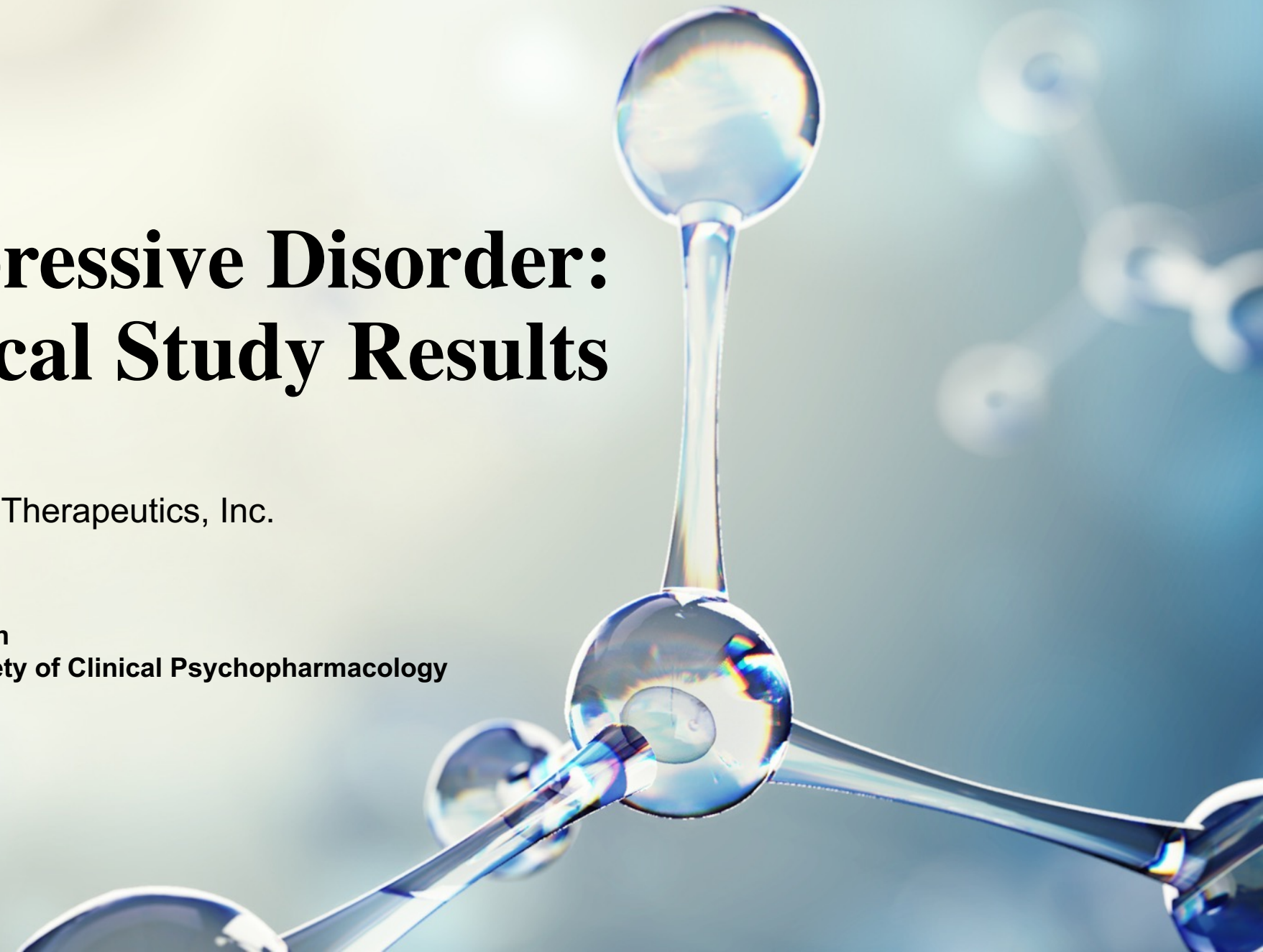
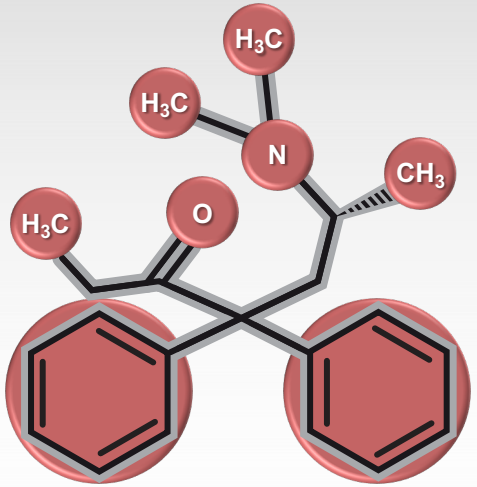


Disclosures

- Relmada Therapeutics, Inc.
- CerSci Therapeutics (Acadia Pharmaceuticals)

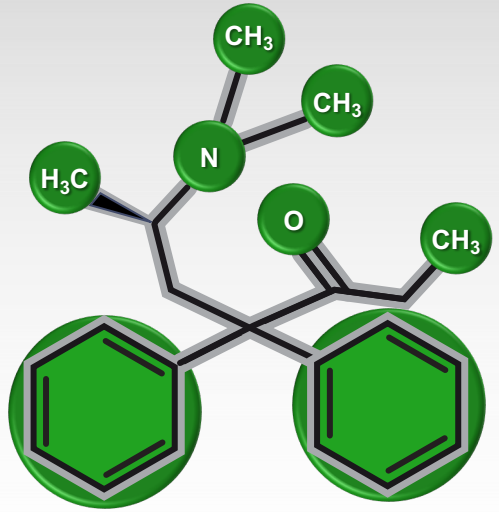
REL-1017 (esmethadone), the opioid-inactive isomer of methadone, is a novel NMDAR channel blocker

Levomethadone
(levo-isomer)



- A full opioid agonist with 20X higher affinity for the mu opioid receptor than esmethadone[1]
- Responsible for the opioid effects associated with racemic methadone, such as euphoria, analgesia and respiratory depression[2,3]

REL-1017 (esmethadone)
(dextro-isomer)



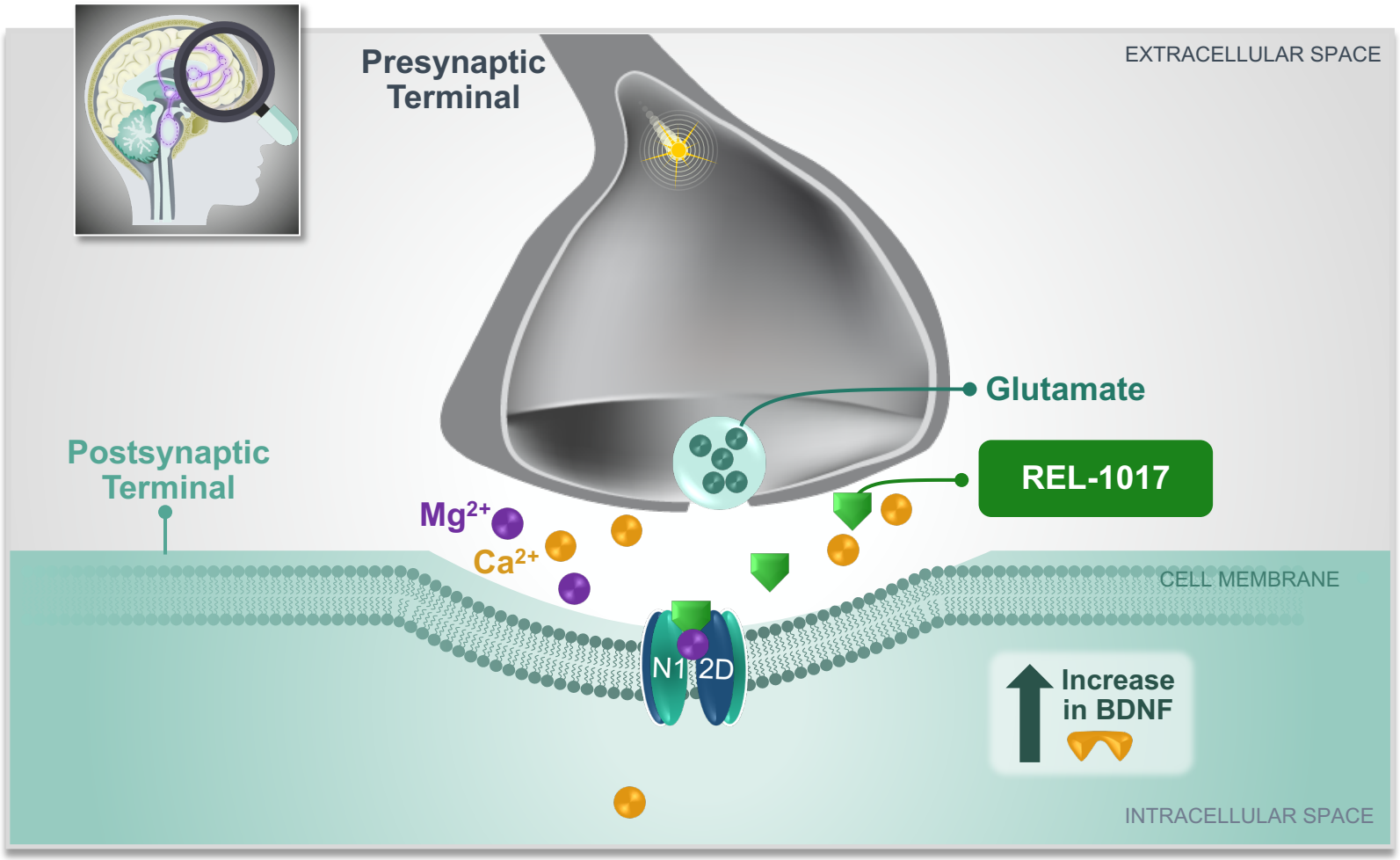
- A novel uncompetitive NMDAR channel blocker[4,5]
- Free from clinically relevant opioid activity at all tested doses: no euphoric, dissociative and respiratory depressant effects and no known addiction liability[2,3,6]

NMDAR=N-methyl-D-aspartate receptor; CH_3=Methyl Group; O=Oxygen; N=Nitrogen

1.Codd EE, et al. *J Pharmacol Exp Ther.* 1995;274:1263-1270; 2. DEA: Diversion Control Division. December 2019. Accessed April 2021. https://www.deadiversion.usdoj.gov/drug_chem_info/methadone/methadone.pdf; 3. Bernstein, et al. *J Clin Psychopharmacology.* 2019 May/Jun;39(3):226-237. 4. Gorman et al. *Neuroscience Letters. 1997;*223:5-8; 5. Bettini et al. *Biological Psychiatry. 2021;*89(9), S294; 6. Fava, et al. 2021.

REL-1017: A Novel, NMDAR Channel Blocker

Preclinical and clinical studies have indicated a differentiated mechanism of action



- REL-1017 is a novel safe and well-tolerated NMDAR channel blocker that preferentially targets hyperactive NMDAR channels associated with MDD[1,2]
  - Specifically, REL-1017 has a preferential affinity for NMDARs containing the GluN2D subunit[1]
- Blocking NMDAR channels with REL-1017 reduces Ca^{2+} influx[1]
- REL-1017 significantly increased plasma levels of BDNF, a neurotrophin with effects on neural plasticity[3]
- REL-1017 was effective in all tested models of depressive-like behavior[4,5]

MDD=major depressive disorder; NCE=new chemical entity; NMDAR=N-methyl-D-aspartate receptor; BDNF=brain-derived neurotrophic factor; Ca^{2+}=calcium; Mg^{2+}=magnesium; GluN2D=receptor channels potentially involved in the pathophysiology of MDD

1. Bettini et al. *Biological Psychiatry. 2021;*89(9), S294; 2. Bernstein, et al. *J Clin Psychopharmacology.* 2019 May/Jun;39(3):226-237; 3. De Martin, et al. 2021 *Front. Pharmacol.* 12:671859; 4. Hanania, et al. *Exp Clin Psychopharmacol* 2020; 28(2):196–201; 5. Fogaca, et al. *Neuropsychopharmacology* 2019; 44(13):2230–8.

REL-1017 Phase 1 SAD & MAD Studies

Single Ascending Dose (SAD) Study Design
Parallel group, double-blind, placebo-controlled

Objectives

Establish PK, PD and safety of single dose administration

Treatment Administration

- 6 Cohorts: 5, 20, 60, 100, 150, 200 mg
- N = 42

Study Conclusions

- Maximum Tolerated Dose (MTD) = 150 mg
- PK demonstrated linear proportionality of C_{max}, $AUC_{0\text{-}inf}$ vs. dose
- **No opioid or NMDA AESI signal observed**

Multiple Ascending Dose (MAD) Study Design
Parallel group, double-blind, placebo-controlled

Objectives

Establish PK, PD and safety of once daily, 10-day administration

Treatment Administration

- 3 Cohorts: 25, 50, 75 mg
- N = 24

Study Conclusions

- Doses up to max does studied 75 mg per day well tolerated
- No unexpected adverse effects
- **No opioid or NMDA AESI signal observed**

PK=pharmacokinetics; PD=pharmacodynamics; MTD=maximum tolerated dose; C_{max}=maximum plasma concentration; $AUC_{0\text{-}inf}$=area under the curve 0 to infinite time; AUC_t=area under the curve to the end of dosing period; N=number of patients; NMDA=N-methyl-D-aspartate receptor antagonist; AESI=adverse event of special interest

Bernstein G, et al. *J Clin Psychopharmacology*. 2019 May/Jun;39(3):226-237.

REL-1017 Phase 2 Trial Design

Multicenter, randomized, double-blind, placebo-controlled, 3-arm study to assess the safety, tolerability, PK profile, and symptom response of a 7-day dosing with REL-1017 25 mg daily and 50 mg daily as adjunctive therapy in the treatment of patients diagnosed with Major Depressive Disorder

7 Days of Daily Dosing in-patient &
7 Days of Observation after last dose

Randomized
QD Dosing, Days 1 to 7

- **Placebo**
- **REL-1017 25 mg**
- **REL-1017 50 mg**

(n=62)

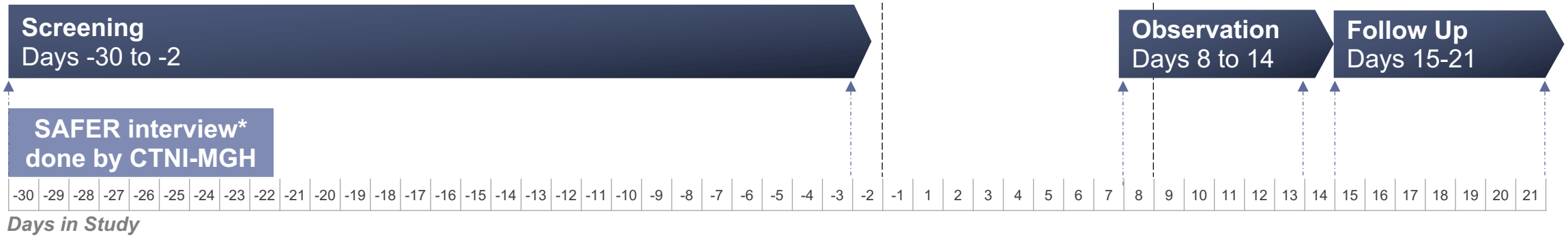
Inpatient Days -1 to 9

Primary Efficacy Endpoints:

- Change from BSL at Day 2, 4, 7 and 14 on:
  - MADRS
  - SDQ
  - CGI-S
- Difference in CGI-I Day 2 to 14

Safety Endpoints:

- Day 14
- Day 21



MDD=major depressive disorder; RDPC=randomized double-blind placebo controlled; MADRS=Montgomery-Asberg Depression Rating Scale; SDQ=Symptoms of Depression Questionnaire; CGIs=Clinical Global Impression scales; PK=pharmacokinetics; BSL=baseline; QD=Once a Day; MGH CTNI=MGH Clinical Trials Network and Institute

*SAFER interview confirms that the illness is a specific state, and excludes patients with any symptoms that are nonspecific or not readily assessable

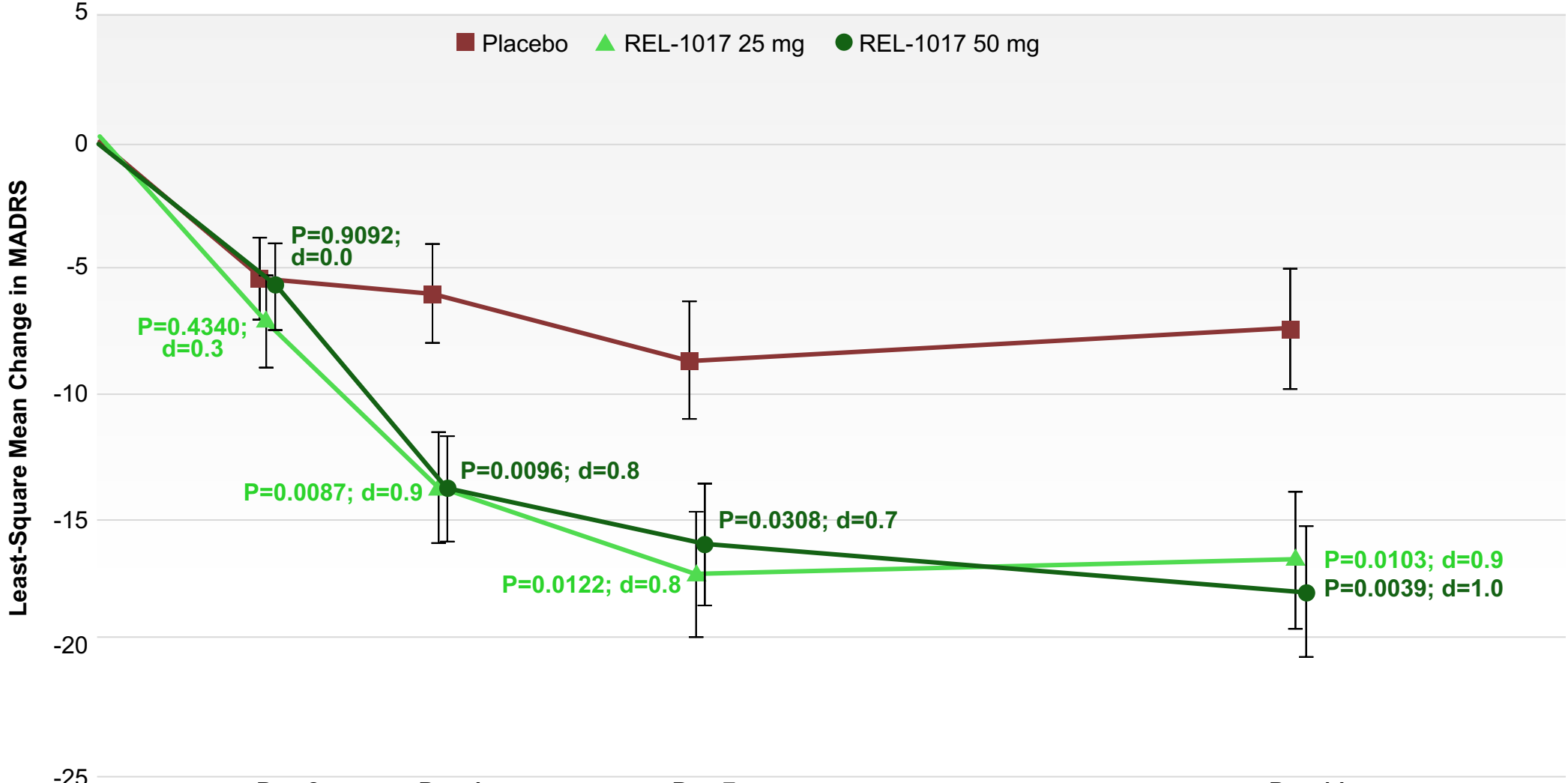
REL-1017 Phase 2 Study – Baseline Patient Characteristics

	Placebo	REL-1017 25 mg	REL-1017 50 mg	All Subjects
Randomized Subjects	22	19	21	62
Completed All Visits (Day 21)	20	18	19	57
Received All Doses	21	19	21	61
Age: Mean Years (SD)	49.7 (11.1)	49.4 (12.4)	48.6 (10.9)	49.2 (11.3)
Females	11 (50%)	8 (42.1%)	9 (42.9%)	28 (45.2%)
Subjects ITT	22	19	21	62
Subjects PPP	21	19	21	61
Screening HAMD – Mean (SD)	25.6 (3.5)	25.1 (3.5)	25.0 (3.8)	25.3 (3.6)
Baseline MADRS – Mean (SD)	33.8 (4.0)	32.9 (6.0)	35.2 (3.9)	34.0 (4.7)

ITT=Intent-To-Treat; PPP=Per-Protocol-Population; HAMD=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale

Phase 2 Study REL-1017: Primary Efficacy Endpoint

REL-1017 showed rapid, robust, and sustained differences in MADRS change vs. placebo

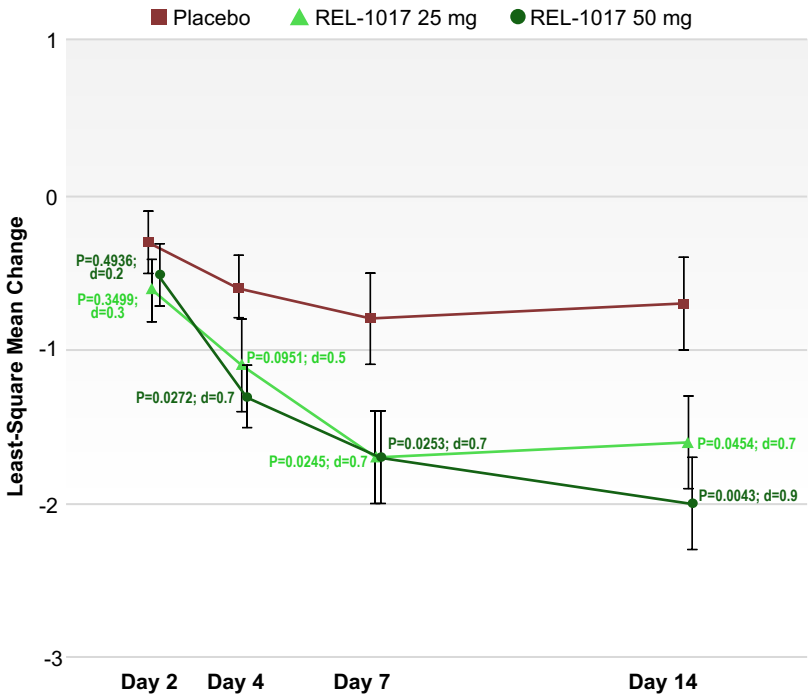


		Day 2	Day 4	Day 7	Day 14
ΔMADRS vs Placebo	25 mg		7.9	8.7	9.4
	50 mg		7.6	7.2	10.4

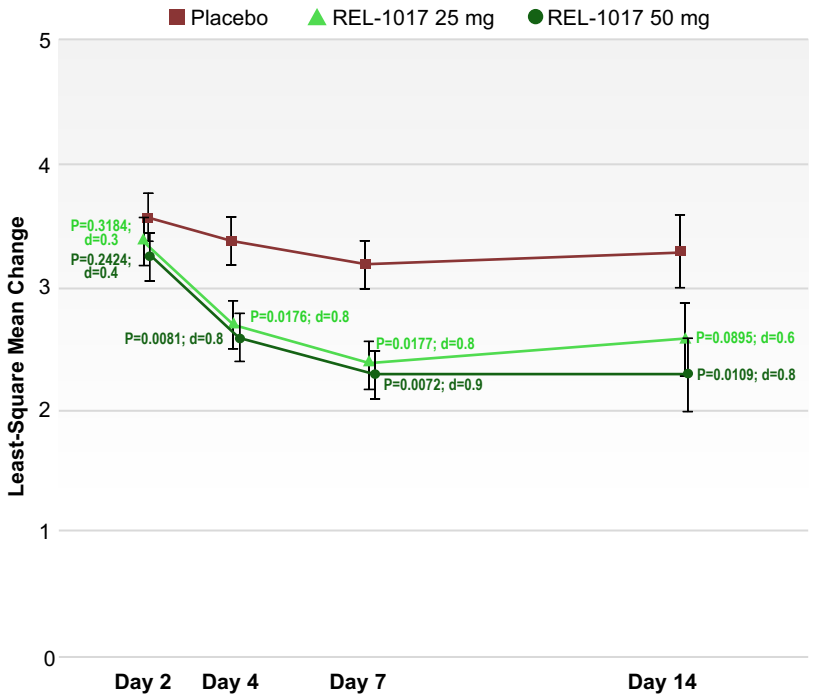
REL-1017 Phase 2 Additional Efficacy Endpoint Results

Statistically significance vs. placebo achieved on all efficacy endpoints

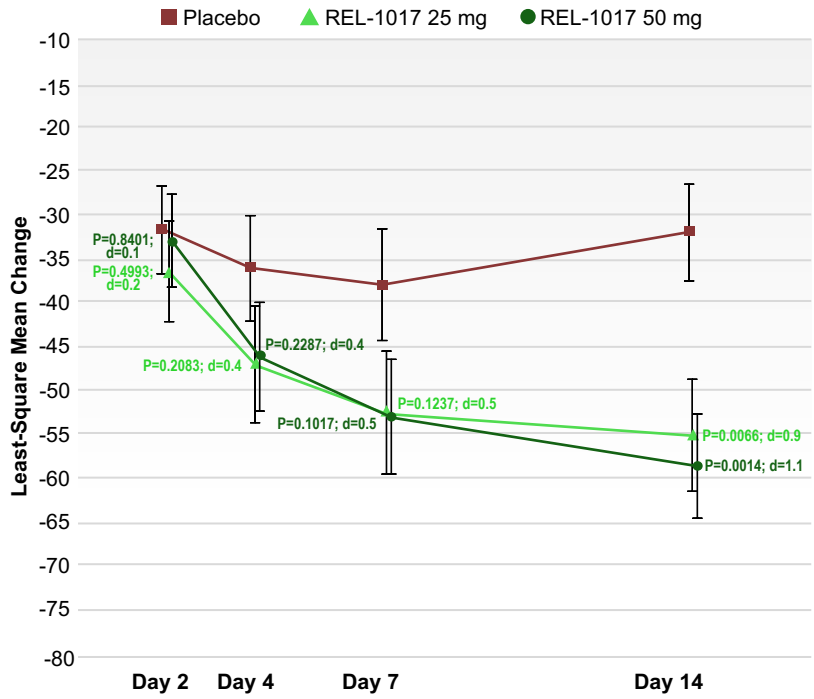
Clinical Global Impression of Severity (CGI-S)



Clinical Global Impression of Improvement (CGI-I)



Symptoms of Depression Questionnaire (SDQ)

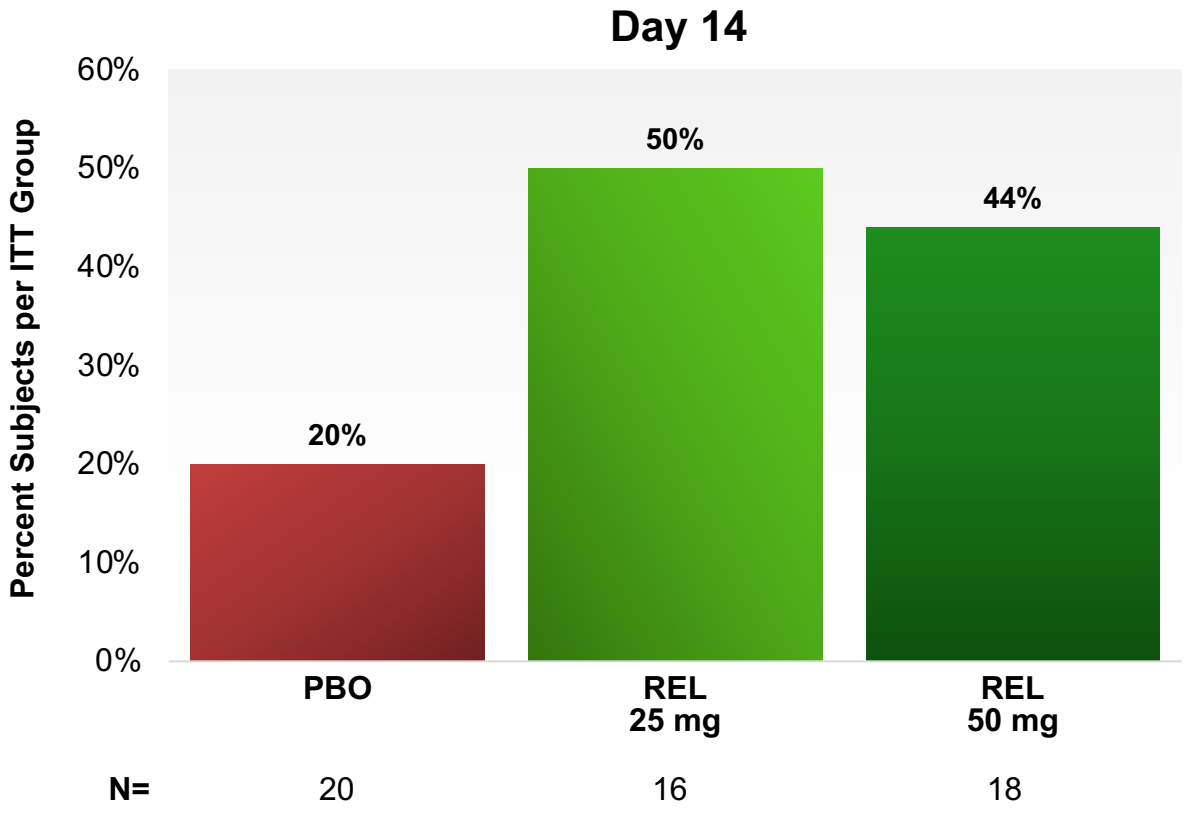


CGI-S=Clinical Global Impression of Severity; CGI-I=Clinical Global Impression of Improvement; SDQ=Symptoms of Depression Questionnaire; Error Bars=Standard Errors P and d values as Treatment vs Placebo; d=Cohen's effect size

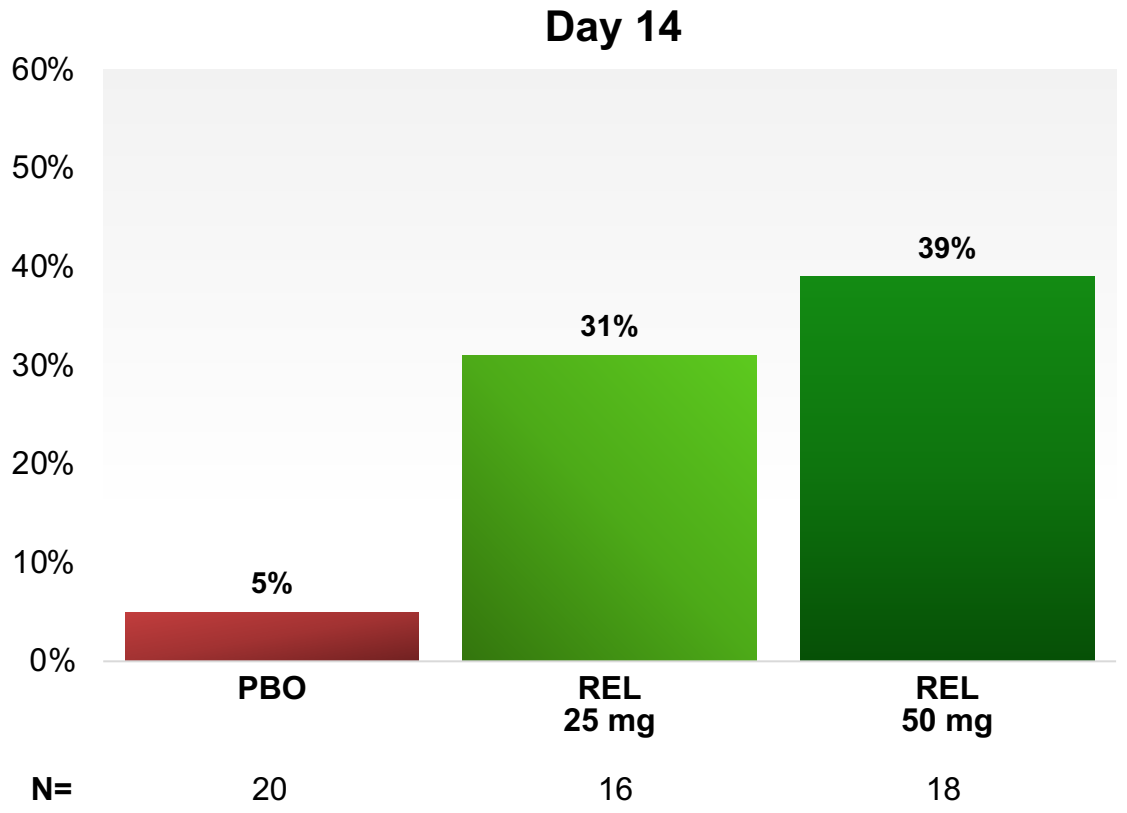
Source: Relmada Data on file

REL-1017 Phase 2 Study Efficacy: Response & Remission

% of Subjects Achieving Response
(≥ 50% MADRS Improvement from Baseline)



% of Subjects Achieving Remission
(MADRS ≤10)



Day 14: last efficacy assessment, 7 days after last dose of study drug
Statistical analysis: p values for treatment groups tested vs. placebo, Fisher Exact Test p-value
MADRS=Montgomery-Asberg Depression Rating Scale
Source: Relmada Data on File

REL-1017 Phase 2 Safety Findings

Adverse event rates were comparable to placebo across both 25mg and 50mg doses

System Organ Class/Preferred Term	Placebo (N=22)	REL-1017 25 mg (N=19)	REL-1017 50 mg (N=21)
Subjects With Any Treatment-Emergent Adverse Event	12 (54.5%)	9 (47.4%)	15 (71.4%)
Gastrointestinal Disorders	8 (36.4%)	5 (26.3%)	5 (23.8%)
Constipation	3 (13.6%)	1 (5.3%)	3 (14.3%)
Nausea	2 (9.1%)	1 (5.3%)	2 (9.5%)
Diarrhea	3 (13.6%)	0	0
Abdominal Discomfort	2 (9.1%)	0	0
Dyspepsia	0	2 (10.5%)	0
Flatulence	0	1 (5.3%)	0
Vomiting	0	1 (5.3%)	0
Nervous System Disorders	6 (27.3%)	4 (21.1%)	6 (28.6%)
Headache	3 (13.6%)	2 (10.5%)	3 (14.3%)
Somnolence	2 (9.1%)	1 (5.3%)	1 (4.8%)
Dizziness	1 (4.5%)	1 (5.3%)	1 (4.8%)
Sedation	1 (4.5%)	1 (5.3%)	0
Infections and Infestations	2 (9.1%)	1 (5.3%)	1 (4.8%)
Upper Respiratory Tract Infection	2 (9.1%)	0	0
Urinary Tract Infection	0	1 (5.3%)	0
Musculoskeletal and Connective Tissue Disorders	0	1 (5.3%)	3 (14.3%)
Back Pain	0	1 (5.3%)	2 (9.5%)
General Disorders and Administration Site Conditions	0	1 (5.3%)	2 (9.5%)
Fatigue	0	1 (5.3%)	0
Investigations	0	0	3 (14.3%)
Weight Decreased	0	0	2 (9.5%)
Cardiac Disorders	0	1 (5.3%)	0
Palpitations	0	1 (5.3%)	0
Renal and Urinary Disorders	0	1 (5.3%)	0
Pollakiuria	0	1 (5.3%)	0
Skin and Subcutaneous Tissue Disorders	0	1 (5.3%)	0
Pruritus	0	1 (5.3%)	0

- Across all groups, there were no Serious Adverse Events (SAEs) or Adverse Events of Special Interest (AESIs)
- Also, no signs of euphoric, dissociative or opioid like effects

REL-1017 Clinical Program for Major Depressive Disorder (MDD)

Completed

- ✓ Preclinical Proof-of-Concept in MDD
- ✓ Phase 1: Single Ascending Dose & Multiple Ascending Dose
- ✓ Phase 2: Adjunctive Treatment

Ongoing

- Phase 3 for Adjunctive Treatment:
  - RELIANCE I
  - RELIANCE II
  - RELIANCE-OLS

Planned

- RELIANCE-III Monotherapy Treatment

MDD=major depressive disorder; OLS=open label study

Conclusions

- REL-1017 is a novel NMDAR channel blocker that preferentially targets hyperactive channels associated with MDD
  - More specifically, REL-1017 appears to particularly target channels containing the GluN2D subunit
  - REL-1017 (esmethadone) is the opioid-inactive isomer of methadone
- The Phase 2 study evaluating REL-1017 as an adjunctive treatment for MDD demonstrated:
  - Robust, rapid and sustained statistically significant efficacy with large effect size
  - Remission (MADRS < =10) rates were 31% and 39% at day 14 for 25 and 50 mg REL-1017, respectively
- Phase 1 and Phase 2 studies showed consistent and favorable safety and tolerability results
  - No opioid or NMDA AESI at any dose

The Phase 3 **RELIANCE Clinical Research Program** for REL-1017 in MDD is actively enrolling

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Thank you!

Questions?

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