REL-1017 (esmethadone hydrochloride), an NMDAR antagonist for the treatment of Major Depressive Disorder

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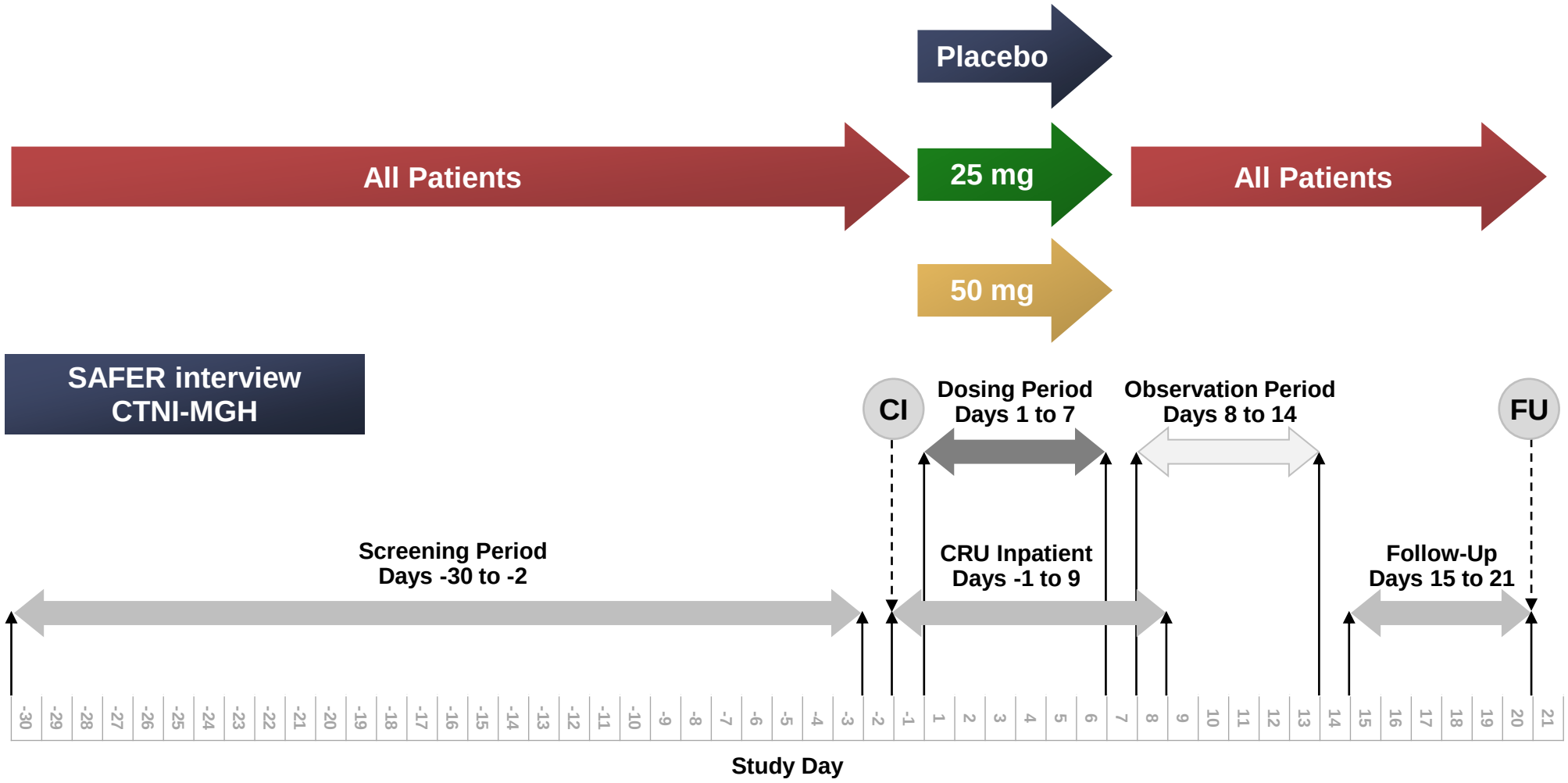
REL-1017 is a novel, low potency, uncompetitive NMDAR channel blocker, currently in Phase 3 Clinical trials for the treatment of MDD

The phase 2 study of REL-1017 showed rapid and robust efficacy, with a favorable safety, tolerability, and pharmacokinetic profile

Phase 2 study of REL-1017 trial design

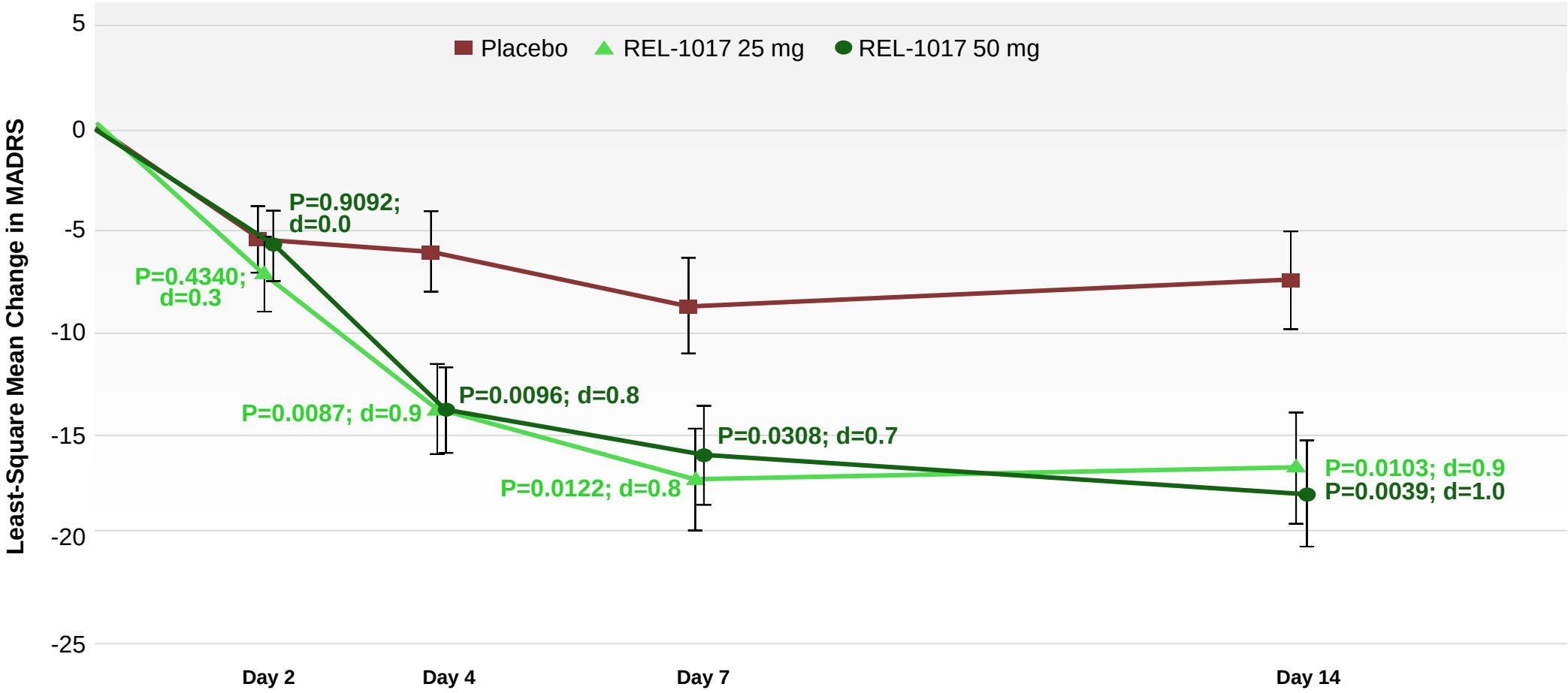
A 7-day inpatient, randomized, double-blind, placebo-controlled study



CI=Check-In; CRU=Clinical Research Unit; FU=Follow-Up

Phase 2 study of REL-1017 primary efficacy endpoint

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

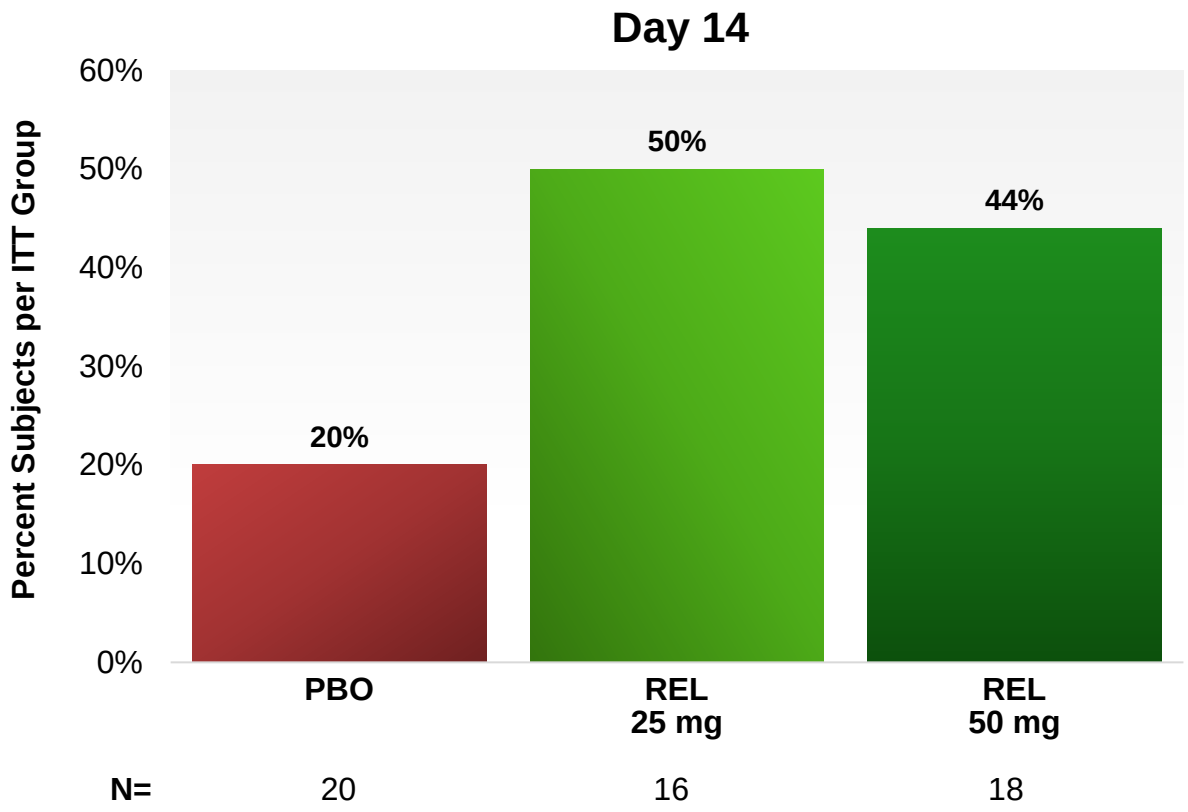


ΔMADRS REL-1017 vs Placebo				
25mg	-1.9	**-7.9***	**-8.7***	**-9.4***
50mg	-0.3	-7.6*	-7.2*	-10.4*

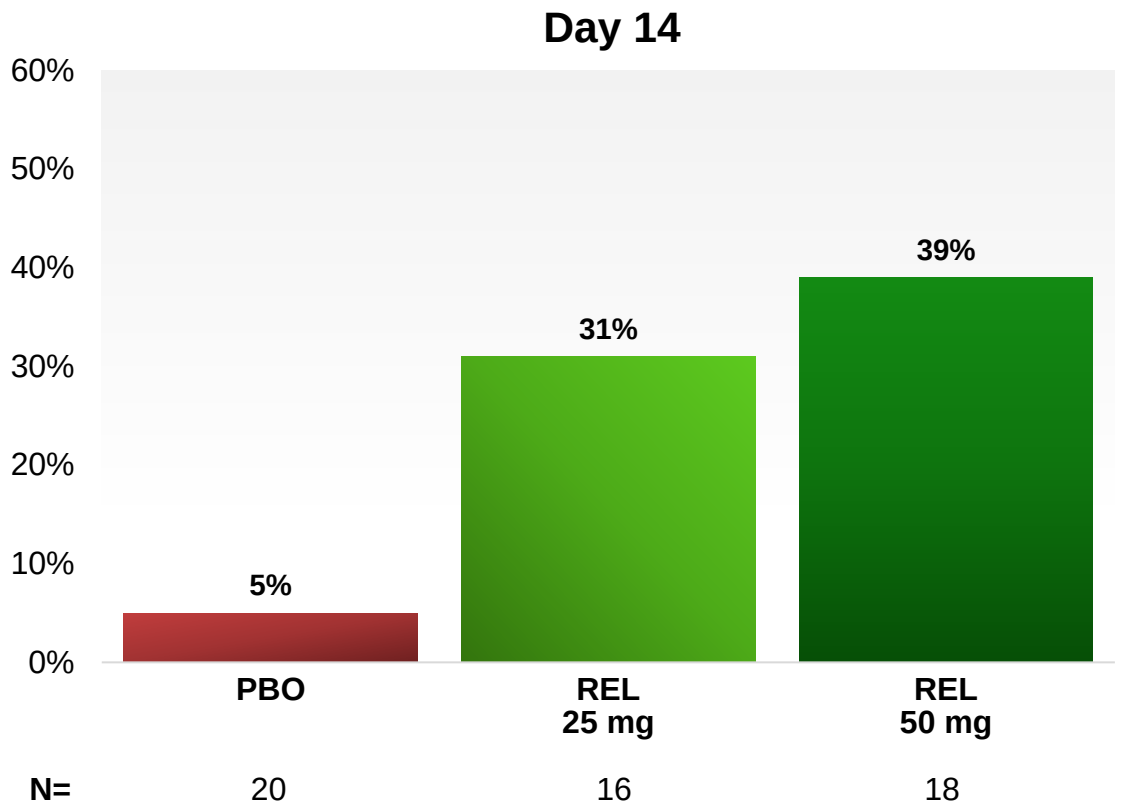
- P-value <.05; d=Cohen's effect size

Phase 2 study of REL-1017 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
MADRS=Montgomery-Asberg Depression Rating Scale
Source: Relmada Data on File

Phase 2 study of REL-1017 safety: treatment emergent adverse events

Treatment-emergent adverse events by preferred term in patients with MDD in the safety analysis set*

Variable	Placebo (N = 22)		REL-1017 25 mg (N=19)		REL-1017 50 mg (N=21)	
	N	%	N	%	N	%
Patients with a serious adverse event	0	0.0	0	0.0	0	0.0
Patients with a severe treatment-emergent adverse event	0	0.0	0	0.0	0	0.0
Treatment-emergent adverse events occurring in three or more patients						
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	0.0	0	0.0
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
Back Pain	0	0.0	1	5.3	2	9.5

Source: Fava, M., et al. (2022). American Journal of Psychiatry 179(2):122-131
*Treatment-emergent adverse event was defined as an adverse event that started or worsened after treatment with the trial drug

REL-1017 shows no meaningful opioid or ketamine-like abuse potential

Table 1. Drug Liking (E_{max}) "at this moment" bipolar Visual Analog Scale (VAS): REL-1017 vs Oxycodone in study completers

Drug Liking (E_{max}) "at this moment" (VAS)++	Placebo N=47	REL-1017 25 mg N=47	REL-1017 75 mg N=47	REL-1017 150 mg N=47	Oxycodone 40 mg N=47
Mean (SD)	52.7 (6.5)	54.2 (10.3)	58.7 (15.0)	64.9 (16.6)	83.2 (16.6)
Median	50	50	50	58	85
OXYCODONE vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	<0.001	--
REL-1017 vs PLACEBO (equivalence), p-value#	--	<0.001	<0.001	0.036	--

Table 2. Drug Liking (E_{max}) "at this moment" bipolar Visual Analog Scale (VAS): REL-1017 vs Ketamine in study completers

Drug Liking (E_{max}) "at this moment" (VAS)++	Placebo N=51	REL-1017 25 mg N=51	REL-1017 75 mg N=51	REL-1017 150 mg N=51	Dextromethorphan 300 mg N= 51	Ketamine 0.5 mg/kg N=51
Mean (SD)	50.9 (2.2)	51.4 (3.3)	54.9 (9.6)	59.2 (14.4)	68.4 (18.4)	90 (14.5)
Median	50	50	50	51	60	100
KETAMINE vs REL-1017 (difference), p-value	<0.001	<0.001	<0.001	<0.001		--
REL-1017 vs PLACEBO – (equivalence) p-value#	--	<0.001	<0.001	0.003		--

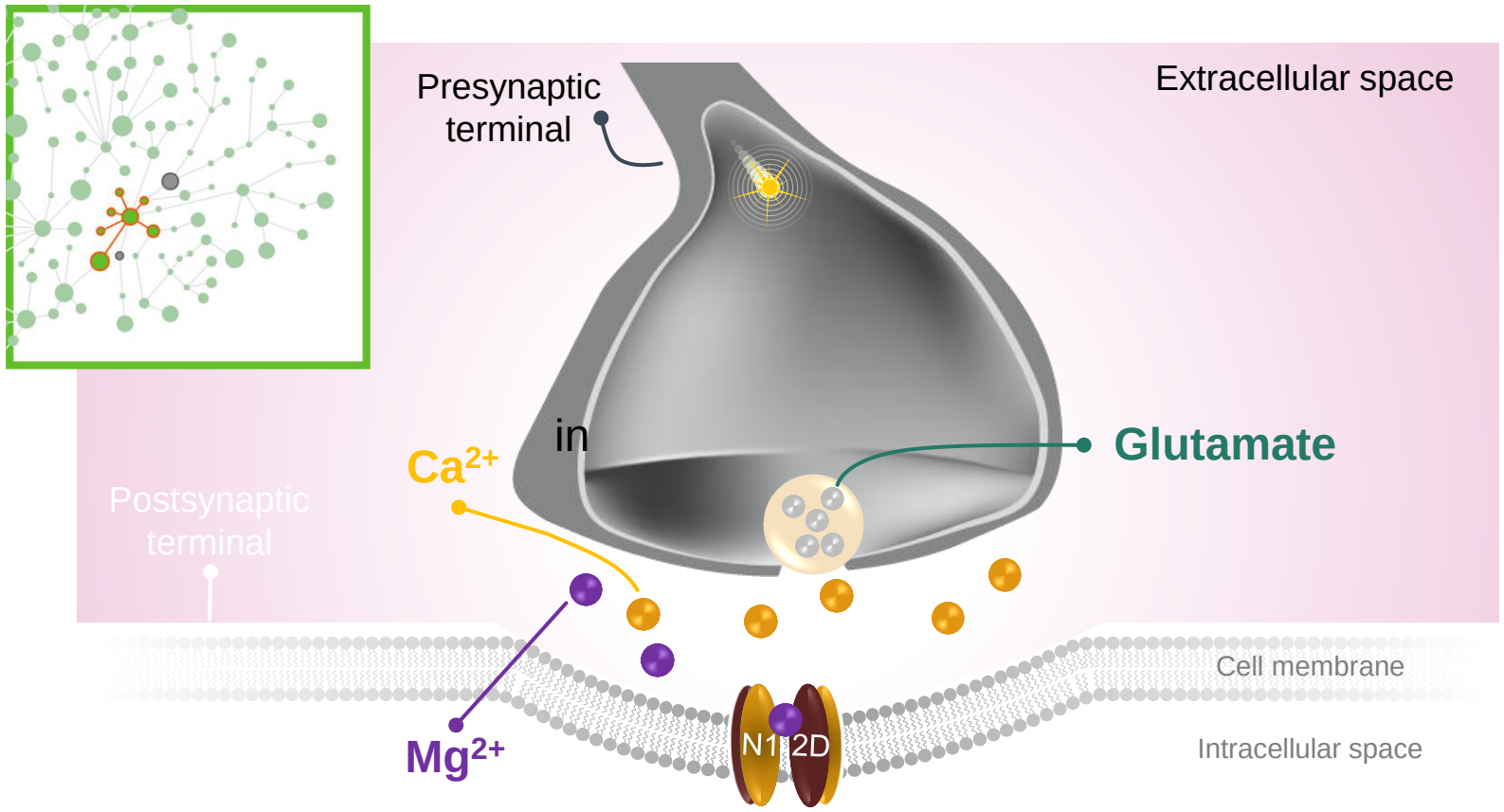
++ The primary endpoint of the study was the maximum effect (E_{max}) for Drug Liking ("at this moment"), assessed with a bipolar (0 to 49 = dislike; 50 = neutral; 51-100 = like) visual analog scale (VAS).
# Interpretation of p-value: p-values ≤0.05 indicate that REL-1017 is statistically equivalent to placebo (i.e., within 11 points)

- The E_{max} for oxycodone 40 mg was greater than all 3 doses of REL-1017 (p<0.001).
- Comparison of REL-1017 to placebo, using the FDA suggested equivalence analysis, indicated equivalency to placebo at p<0.05 at all tested doses.

- The E_{max} for ketamine was greater than all 3 doses of REL-1017 (p<0.001).
- Comparison of REL-1017 to placebo, using the FDA suggested equivalence analysis, indicated statistical equivalency to placebo at p<0.05 at all tested doses.

Preclinical trials conducted to date showed that REL-1017 has a preference for the GluN2D subtype, which may be an important variable in understanding its clinical actions

Excessive tonic Ca^{2+} influx through hyperactive GluN2D-containing NMDA receptors may impair neural plasticity and contribute to MDD pathology



GluN2D-containing NMDARs are physiologically prone to exhibit a higher glutamate affinity and a lower sensitivity to Mg2+ blockade [6-8]

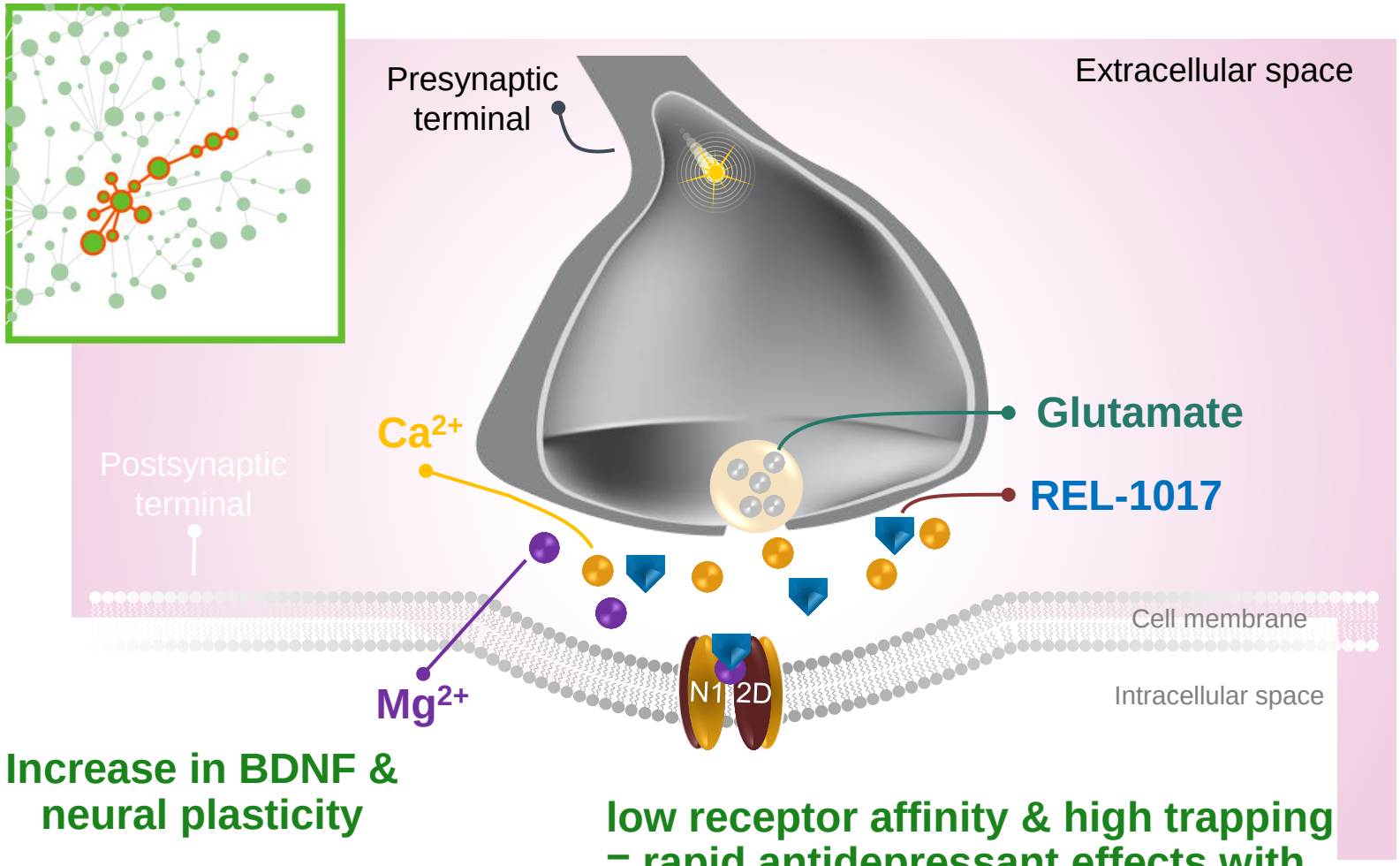
<u>Our MOD hypothesis</u> is that in MDD GluN2D-containing NMDARs may become tonically and pathologically hyperactive, and this state would lead to intracell Ca^{2+} overload and neurotoxicity with impairment of transcription and production of synaptic proteins and BDNF, followed by decreased neural and memory plasticity[1-5]

Tonically hyperactive GluN2D-containing NMDARs may be a novel target for modulating excessive Ca^{2+} signaling and for positively impacting on neural plasticity in MDD[1-5]

MDD=major depressive disorder; NMDAR=N-methyl-D-aspartate receptor; Ca^{2+}=calcium; Mg^{2+}=magnesium

1. Bettini, et al. (2021) Biological Psychiatry, 89(9), S294; 2. Bettini et al.(2021) Biological Psychiatry, 89(9), S198-S199; 3. Fogaca et al. (2019) Neuropsychopharmacology, 44(13):2230-2238; 4. De Martin, et al. (2021) Frontiers in Pharmacology 12:973-978; 5. Fava, M., et al. (2022). American Journal of Psychiatry 179(2):122-131; 6 .Cull-Candy et al. 2001; 7. Misra et al. 2000; 8. Siegler Retchless et al. 2012

REL-1017 preferentially blocks GluN2D-containing NMDARs



Increase in BDNF & neural plasticity

low receptor affinity & high trapping = rapid antidepressant effects with no dissociative symptoms

Once REL-1017 blocks the pore of pathologically hyperactive GluN2D-containing NMDARs, intraneuronal tonic Ca^{2+} influx [1,2] is downregulated

Phase 1 studies have showed that REL-1017 can rapidly increase BDNF serum levels [2]

The block of GluN2D subtypes by REL-1017 would restore neural plasticity by promoting transcription and production of synaptic proteins, including BDNF[3]

Upon physiological AMPAR mediated depolarization, both Mg^{2+} and REL-1017 are expelled from the NMDAR pore; REL-1017 has low receptor affinity and high trapping, which results in no dissociative symptoms, unlike other higher potency NMDAR antagonists[1,2]

BDNF=brain-derived neurotrophic factor; NMDAR=N-methyl-D-aspartate receptor; Ca^{2+}=calcium; Mg^{2+}=magnesium

1. Bettini et al.(2021) Biological Psychiatry, 89(9), S198-S199; 2. De Martin, et al. (2021) Frontiers in Pharmacology 12:973-978;3. Fogaca et al. (2019) Neuropsychopharmacology, 44(13):2230-2238

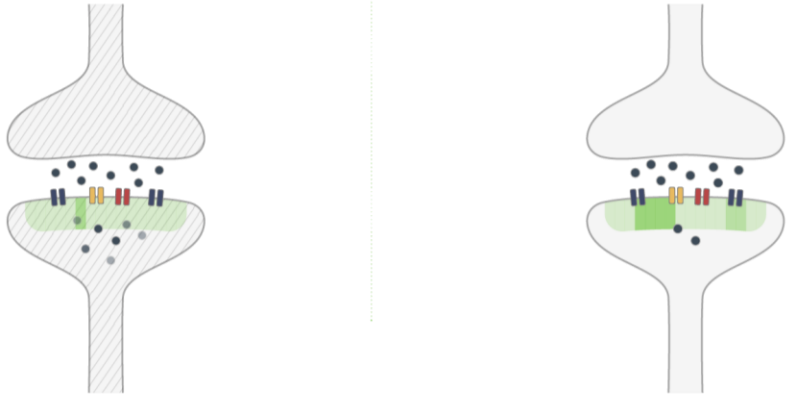
Tonic NMDAR activity before and after REL-1017

GluN2D-containing NMDA RECEPTORS with TONIC HYPERACTIVITY in MDD

NORMALIZATION of NMDAR ACTIVITY with REL-1017

RESTORATION OF PHYSIOLOGIC PHASIC ACTIVITY with REL-1017

Artistic rendition—not actual data



Before REL-1017 treatment, NMDARs are pathologically excessively open at resting membrane potential: **chronic glutamate excitotoxicity due Ca^{2+} overload impairs neural plasticity and causes MDD.**

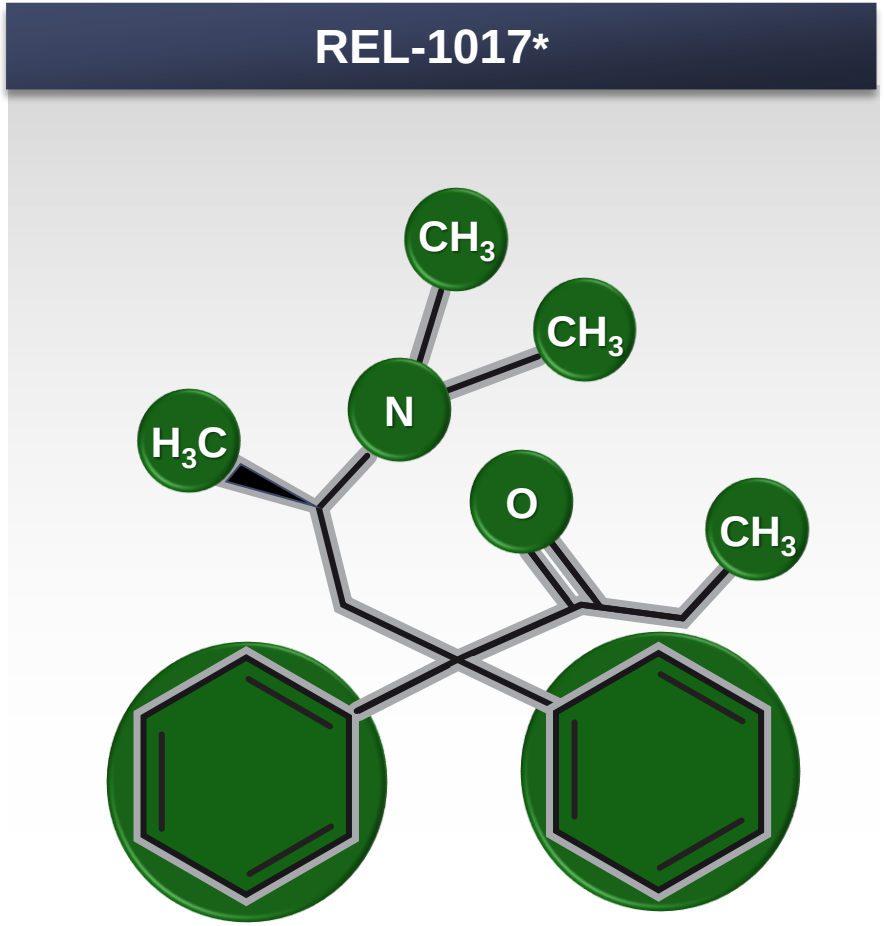
After REL-1017 treatment, NMDARs are physiologically operating at resting membrane potential: **tonic Ca^{2+} influx is normalized, excitotoxicity reverses and physiologic neural plasticity resumes.**

REL-1017, similarly to Mg^{2+}, is expelled from the channel pore during phasic activity and thus REL-1017 does not interfere with stimulus-triggered neural plasticity. Phasic Ca^{2+} influx activates downstream signaling cascades that direct neural plasticity. New or enhanced connections are formed and MDD goes into remission.

Unique profile of REL-1017

Potential as a rapid, oral, once-daily antidepressant for MDD, if approved

- Novel mechanism of action: preferential targeting of N2D-containing NMDA receptors potentially associated with MDD[1]
- Available clinical data demonstrated:
  - Favorable safety and tolerability profile consistent across Phases 1 & 2 studies with no metabolic side effects and with no opioid or psychotomimetic adverse events[2,3]
  - No meaningful abuse potential confirmed by preclinical and clinical HAP studies vs oxycodone and ketamine
  - Robust, rapid, and sustained statistically significant antidepressant effects on all tested scales[2]
  - Orally administered, once-daily tablet
  - REL-1017 Ph 3 clinical trials for the treatment of MDD in progress



MDD = major depressive disorder; NMDAR = N-methyl-D-aspartate receptor

*Diagram reflects chemical structure of REL-1017 (esmethadone); molecules are CH_3 = Methyl Group, O = Oxygen, N = Nitrogen

1. Bettini et al. (2021) Biological Psychiatry, 89(9), S198-S199. 2. Fava, M., et al. (2022). American Journal of Psychiatry 179(2):122-131; 3. Bernstein, G., et al. (2019). J Clin Psychopharmacol 39(3): 226-237.

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Bernstein, G., et al., (2019). “Characterization of the safety and pharmacokinetic profile of d-methadone, a novel N-methyl-D-aspartate receptor antagonist in healthy, opioid-naive subjects: Results of two Phase 1 studies” *Journal of Clinical Psychopharmacology*, 39(3): 226-237. https://doi.org/10.1097/jcp.0000000000001035.

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Questions?

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Thank you!

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