Relmada THERAPEUTICS

Targeting Major Advances in the Treatment of CNS Disorders

June 6th, 2023

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Investment highlights

CNS focused, with a novel MOA lead program REL-1017 currently in Phase 3 for Major Depressive Disorder (MDD)

Compelling Phase 2 data indicating the robust therapeutic effect of REL-1017 as an adjunctive treatment of MDD

Efficacy and safety profile of REL-1017 potentially address limitations of current MDD treatments options

Significant lessons learned from post-hoc analyses of Phase 3 data provide confidence in the path forward to ongoing and future studies

Highly experienced clinical team with a successful track record advancing CNS programs through NDA approval

CNS= Central Nervous System
**Our fiscal year end is December 31. The periods referred to in this slide are calendar years and quarters.

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Major Depressive Disorder and REL-1017's Novel Mechanism of Action

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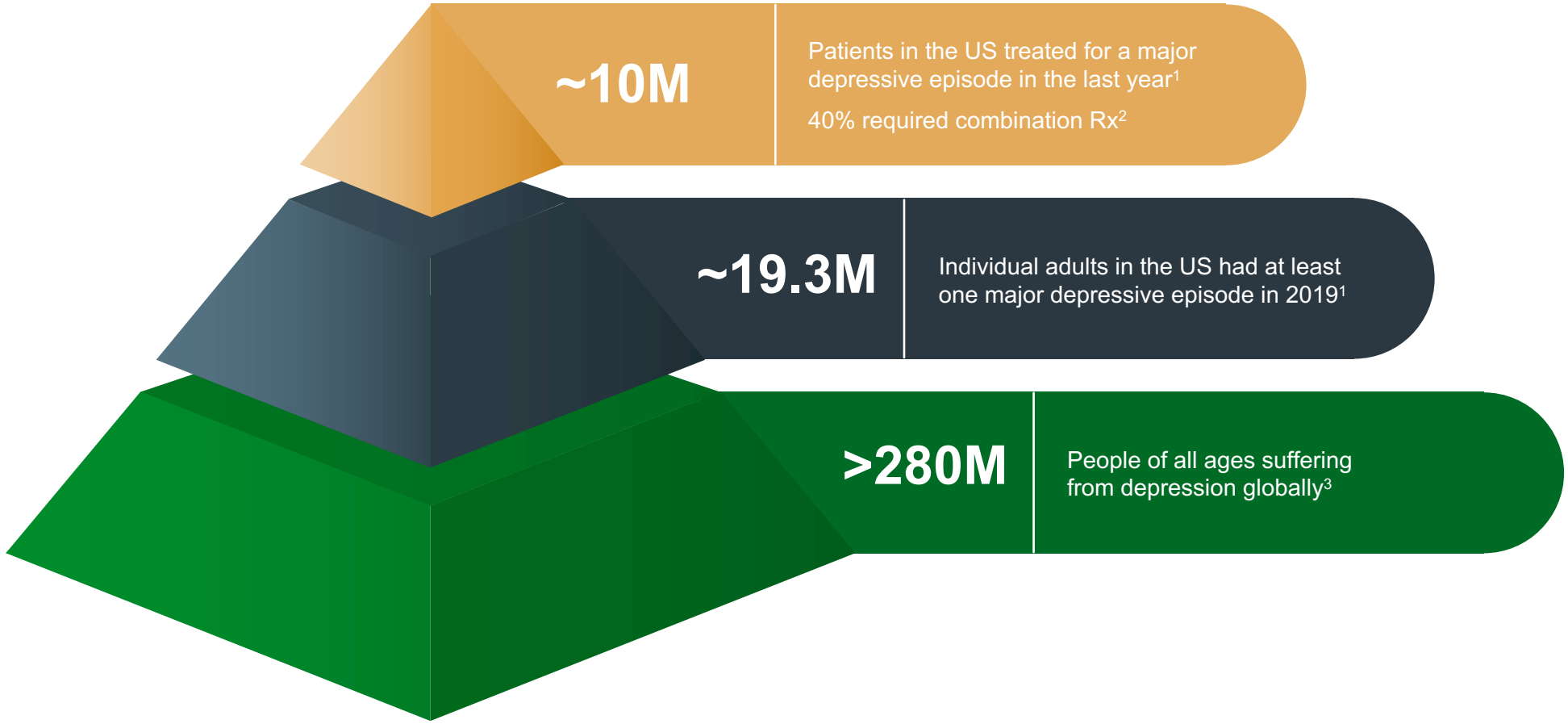
Prevalence of depression



Rx = prescription
1.) Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services (HHS) 2019 National Survey on Drug Use and Health; 2.) Decision Resources Group Unipolar Depression 2020 report; 3.) WHO Depression Fact Sheet

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Limitations of current treatments for MDD

Limited efficacy

~65% MDD patients do not respond to first antidepressant treatment[1]

Slow onset of action

Standard antidepressants, even when effective, may take up to 8 weeks to reach efficacy[2]

Safety and tolerability challenges

Side effects of atypical antipsychotics approved as adjunctive treatments for MDD include tardive dyskinesia, metabolic syndrome, cognitive impairment and stroke[3]

MDD = major depressive disorder

1.) Trivedi MH, et al. Am J Psychiatry. 2006;163:28-40; 2.) Ashton AK, et al. Curr Ther Res. 2005;66(2):97-106; 3.) US Prescribing Information, brexpiprazole, quetiapine, aripiprazole

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Unique profile of REL-1017 addresses limitations of current treatments

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

Novel Mechanism of Action: preferential targeting of NMDAR channels potentially associated with MDD[1,2,3]

Clinical data has demonstrated:

- Robust, rapid, and sustained statistically significant antidepressant effects on all tested scales[4]
- Rapid onset: significant efficacy effects by Day 4[4]
- Favorable safety and tolerability profile consistent across all studies[4,5,6]: no opioid and no psychotomimetic adverse events and no metabolic side effects[4,5,6]
- Orally administered, once-daily tablet

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

1.) Bettini E al. Pharmacological Comparative Characterization of REL-1017 (Esmethadone-HCl) and Other NMDAR Channel Blockers in Human Heterodimeric N-Methyl-D-Aspartate Receptors. Pharmaceuticals (Basel). 2022;15(8):997; 2.) Bettini E et al. The N-Methyl-D-Aspartate Receptor Blocker REL-1017 (Esmethadone) Reduces Calcium Influx Induced by Glutamate, Quinolinic Acid, and Gentamicin. Pharmaceuticals (Basel). 2022;15(7):882; 3.) Stahl SM et al. Esmethadone (REL-1017) and Other Uncompetitive NMDAR Channel Blockers May Improve Mood Disorders via Modulation of Synaptic Kinase-Mediated Signaling. Int J Mol Sci. 2022;23(20); 4.) Fava M et al. REL-1017 (Esmethadone) as Adjunctive Treatment in Patients With Major Depressive Disorder: A Phase 2a Randomized Double-Blind Trial. Am J Psychiatry. 2022;179(2):122-131; 5.) Bernstein et al. 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. J Clin Psychopharmacol. 2019;39(3):226-237; 6.) Relmada data on file

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REL-1017 Phase 1 & 2 Efficacy and Safety Data

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All phase 1 studies for REL-1017 are completed

- ✓ Multiple Ascending Dose (MAD) study
- ✓ Single Ascending Dose (SAD) study
- ✓ Oxycodone Human Abuse Potential (HAP) study
- ✓ Intravenous Ketamine Human Abuse Potential (HAP) study
- ✓ Renal Impairment study and Hepatic Impairment study
- ✓ Drug-Drug Interaction (DDI) study
- ✓ Absorption, distribution, metabolism, excretion (ADME) study

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The results of experimental studies predictive of human abuse potential [1] and the results of human abuse potential studies in recreational opioid users [2] and in recreational ketamine users [3] indicate no meaningful abuse potential and support the DEA statement below:

“The *d*-isomer lacks significant respiratory depressant action and addiction liability...”

US Drug Enforcement Administration
December 2019 [4]

1.) Henningfield, et al. REL-1017 (esmethadone; D-methadone) does not cause reinforcing effect, physical dependence and withdrawal signs in Sprague Dawley rats. Sci Rep 12, 11389 (2022); 2.) Shram M, et al., No meaningful abuse potential in recreational opioid users of REL-1017 (esmethadone hydrochloride), a new NMDAR antagonist and potential rapid-acting antidepressant American Society of Clinical Psychopharmacology (ASCP) 2022; 3.) Shram M, et al., No meaningful abuse potential in recreational ketamine users of REL-1017 (esmethadone hydrochloride), a new NMDAR antagonist and potential rapid-acting antidepressant. American Society of Clinical Psychopharmacology (ASCP) 2022; 4.) US DEA Statement on Methadone, December 2019

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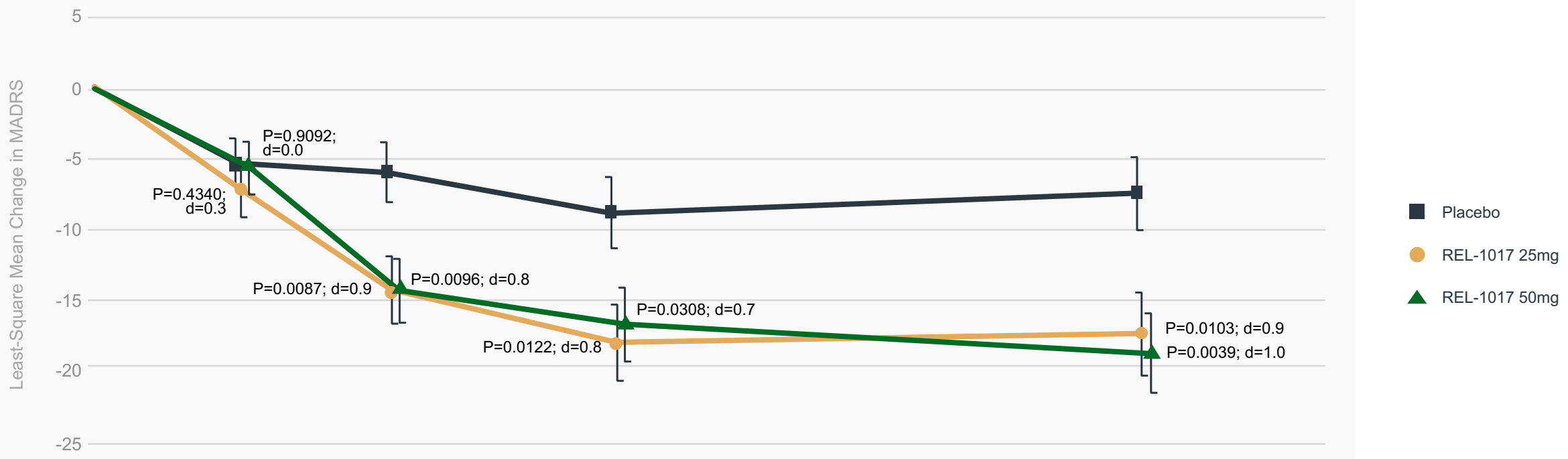
Phase 2 study REL-1017: primary efficacy endpoint

REL-1017 25 and 50 mg (Day 1 loading dose 75 and 100 mg, respectively) showed rapid and sustained differences in MADRS change vs. placebo



ΔMADRS	Day 2	Day 4	Day 7	Day 14
25mg	-1.9	-7.9*	-8.7*	-9.4*
50mg	-0.3	-7.6*	-7.2*	-10.4*

P-value <.05
MADRS=Montgomery-Asberg Depression Rating Scale

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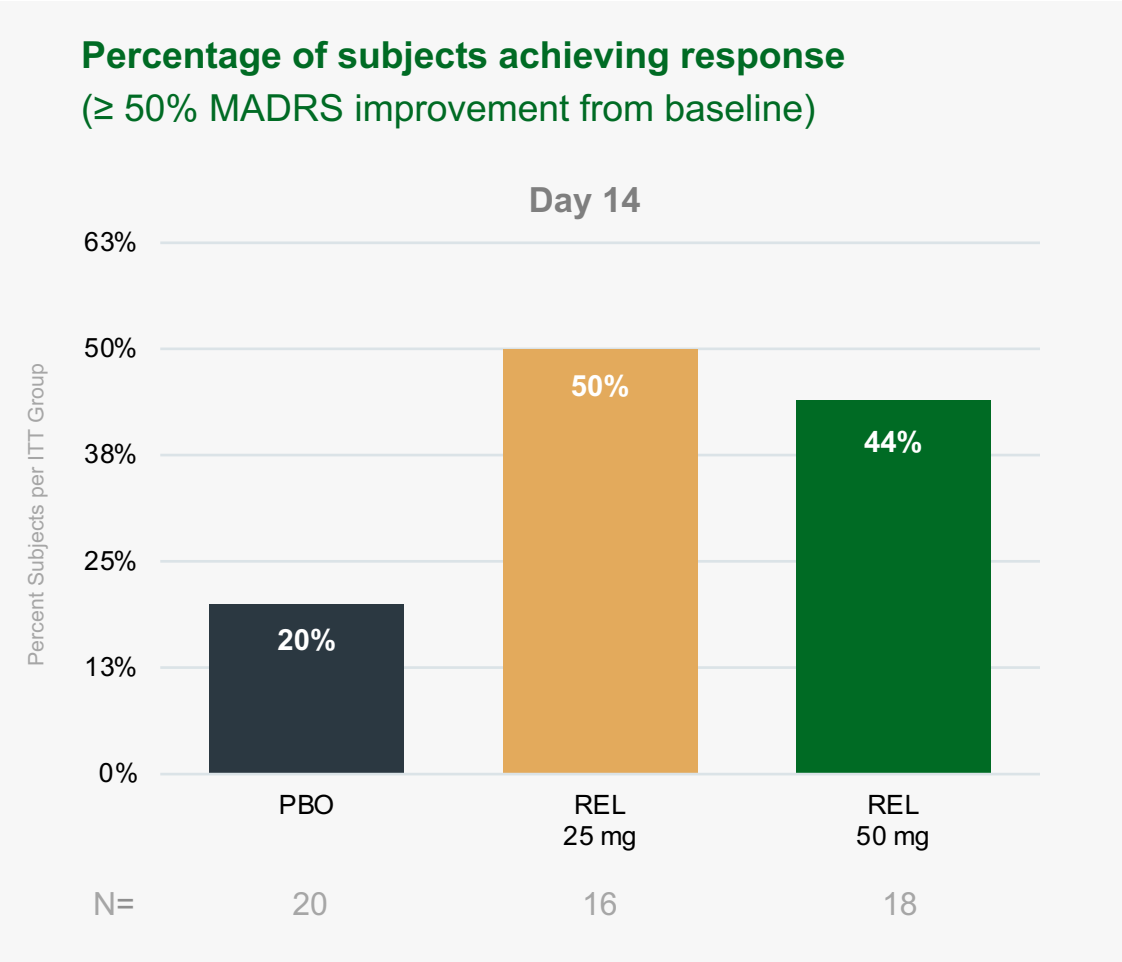
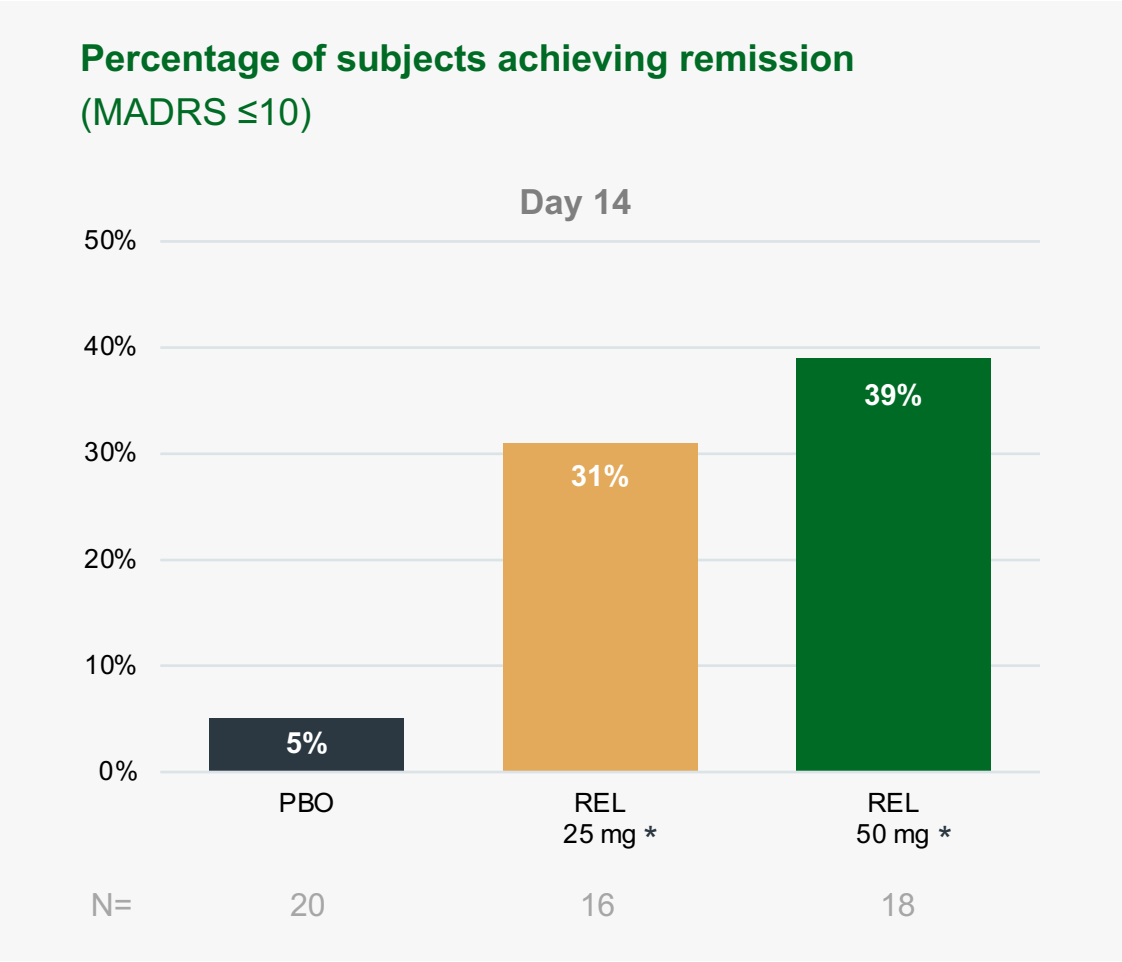
REL-1017 phase 2 study efficacy: response & remission





Day 14: last efficacy assessment, 7 days after last dose of study drug
* p = < .05
MADRS=Montgomery-Asberg Depression Rating Scale
Source: Fava et al. Rapid and Sustained Antidepressant Effects of REL-1017 (dextromethadone) as an Adjunctive Treatment for Major Depressive Disorder

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Reliance: The Phase 3 Program for REL-1017

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REL-1017 phase 3 program for the treatment of MDD

Reliance I + II

Randomized two-arm, placebo-controlled pivotal studies in patients with MDD and inadequate response to ongoing standard antidepressant treatment. These are two studies conducted one after the other.

In MDD patients with inadequate response to 1-3 ADT in the current MDE

Primary Endpoint: Change in MADRS at Day 28

Key Secondary Endpoints:

- Change in CGI-S score at Day 28
- Change in MADRS score at Day 7

Reliance III

Randomized, two-arm, placebo-controlled pivotal study as a monotherapy treatment for patients with MDD.

In patients experiencing an untreated MDE (patients receiving no ADT)

Primary Endpoint: Change in MADRS at Day 28

Key Secondary Endpoints:

- Change in CGI-S score at Day 28
- Change in MADRS score at Day 7

Reliance OLS

Long-term, open-label safety study.

Patients continuing from Reliance I, II & III

Patients new to REL-1017

Reliance

Additional phase 3 adjunctive MDD trial

Trial design in preparation with consideration of the lessons learned from Reliance I and III

MDD = major depressive disorder; ADT = antidepressant treatment ; OLS = open label study;
MADRS = Montgomery-Asberg Depression Rating Scale; CGIs = Clinical Global Impression scales; MDE = major depressive episode

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Reliance I and Reliance III results overview

- Reliance I and Reliance III did not reach primary endpoint, however, post-hoc analyses show a positive efficacy signal
- Reliance I showed a significant 40% response rate compared to placebo (p=0.044)
- Reliance I and Reliance III confirmed REL-1017's favorable safety profile consistent with data from Phase 2
- REL-1017 demonstrated a lack of abuse potential consistent with data from the HAP studies
- Lessons learned have been taken into consideration for Reliance II amendments and an additional Phase 3 study

* Center-specific factors in these top-enrolling centers yielded paradoxical results: placebo robustly outperformed REL-1017. The top enrolling center in Reliance III had a mean placebo response of 23 MADRS points

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Pivotal phase 3 trial design for adjunctive therapy

Reliance I

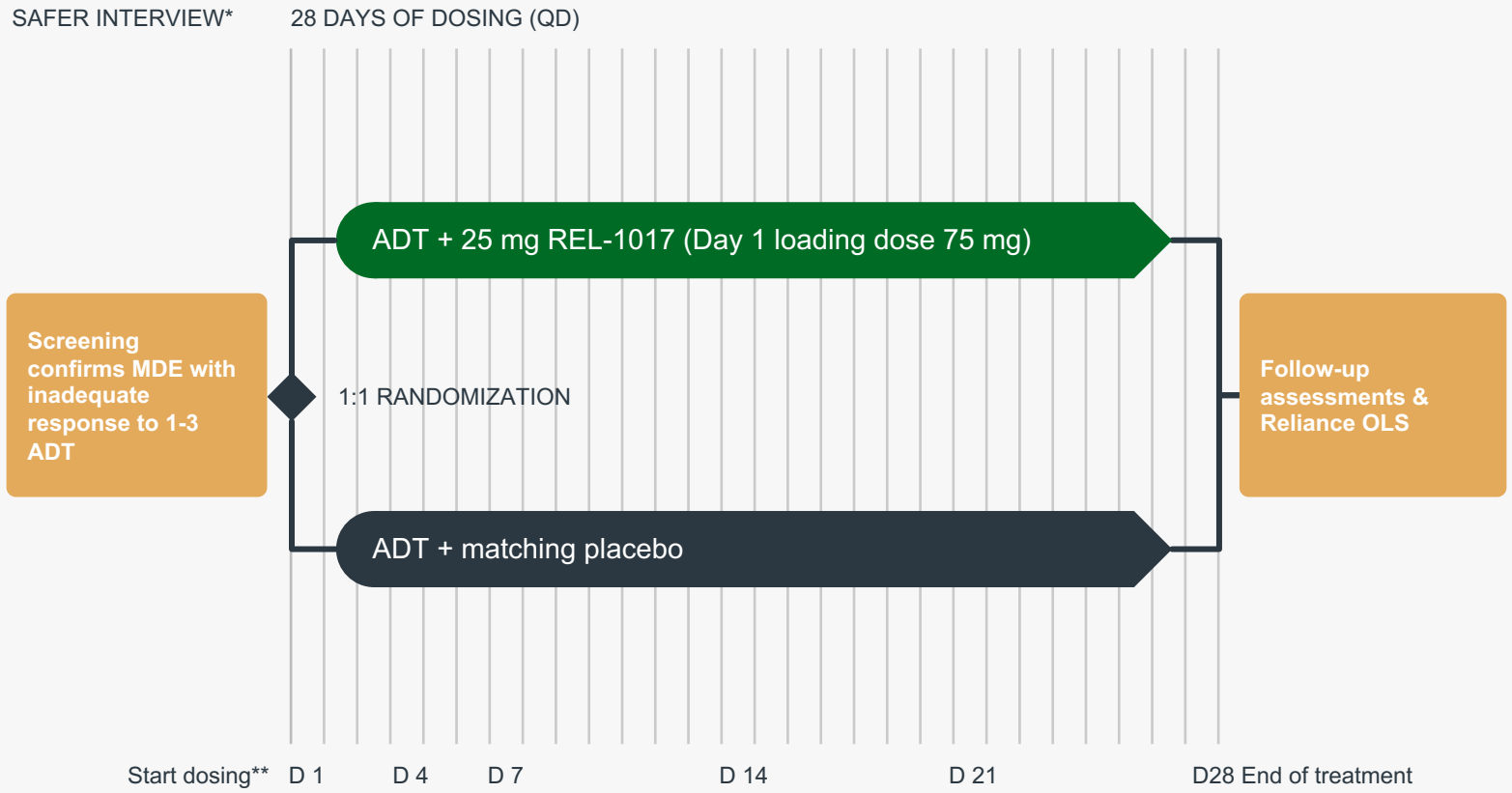
ADJUNCTIVE THERAPY

Primary endpoint:

- Change in MADRS at Day 28

Key secondary endpoints:

- Change in MADRS score at Day 7
- Change in CGI-S score at Day 28



MADRS = Montgomery-Asberg Depression Rating Scale; CGIs = Clinical Global Impression scales; MDE = major depressive episode; ADT = antidepressant treatment; QD = once daily; OLS = open label study
*SAFER interview confirms that the illness is a specific state and excludes patients with any symptoms that are nonspecific or not readily assessable. Desseilles M, et al 2013. Massachusetts General Hospital SAFER criteria for clinical trials and research. Harv Rev Psychiatry. Sep-Oct;21(5):269-74.
**75mg loading dose on Day 1 of REL-1017

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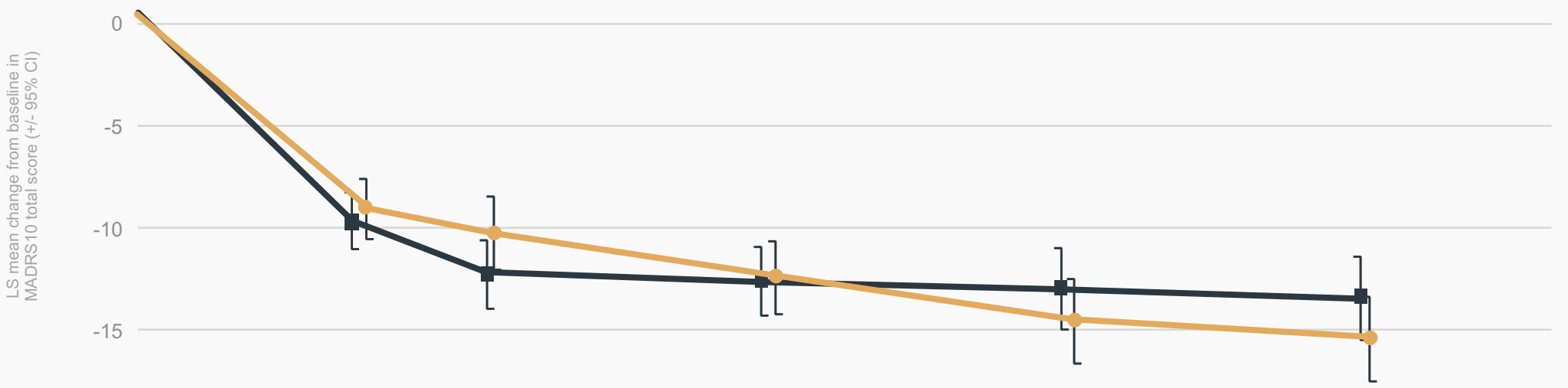
Reliance I primary efficacy endpoint: REL-1017 showed a clinically meaningful -2.3 MADRS point difference vs. placebo at Day 28 in the full analysis set



ΔMADRS (N=227) Placebo N=114, 25 mg N=113, 43 sites	Day 4	Day 7	Day 14	Day 21	Day 28 End of Treatment
Placebo Mean (SD)	-9.3 (7.3)	-11.8 (9.9)	-12.2 (10.9)	-13.0 (11.2)	**-12.9** (10.4)
25 mg Mean (SD)	-8.3 (8.9)	-10.2 (9.5)	-12.4 (9.4)	-14.4 (10.4)	**-15.1** (11.3)
Placebo LSMean (SE), MMRM	-8.5 (0.8)	-11.9 (0.9)	-12.4 (1.0)	-13.0 (1.0)	-13.4 (1.1)
25 mg LSMean (SE), MMRM	-8.3 (0.8)	-10.2 (0.9)	-12.6 (1.0)	-14.2 (1.0)	-15.1 (1.1)
REL-1017 vs Placebo LSMean Diff (SE); p-value, MMRM	0.2 (1.2); 0.85	1.7 (1.3); 0.20	-0.2 (1.4); 0.88	-1.2 (1.5); 0.42	-1.7 (1.5); 0.26

-2.3 diff.
REL-1017
vs. placebo
p=0.15
ES=-0.21

Day 28: last efficacy assessment
Total N=227; * p= <0.05
MADRS=Montgomery-Asberg Depression Rating Scale; Source: Relmada Data on File

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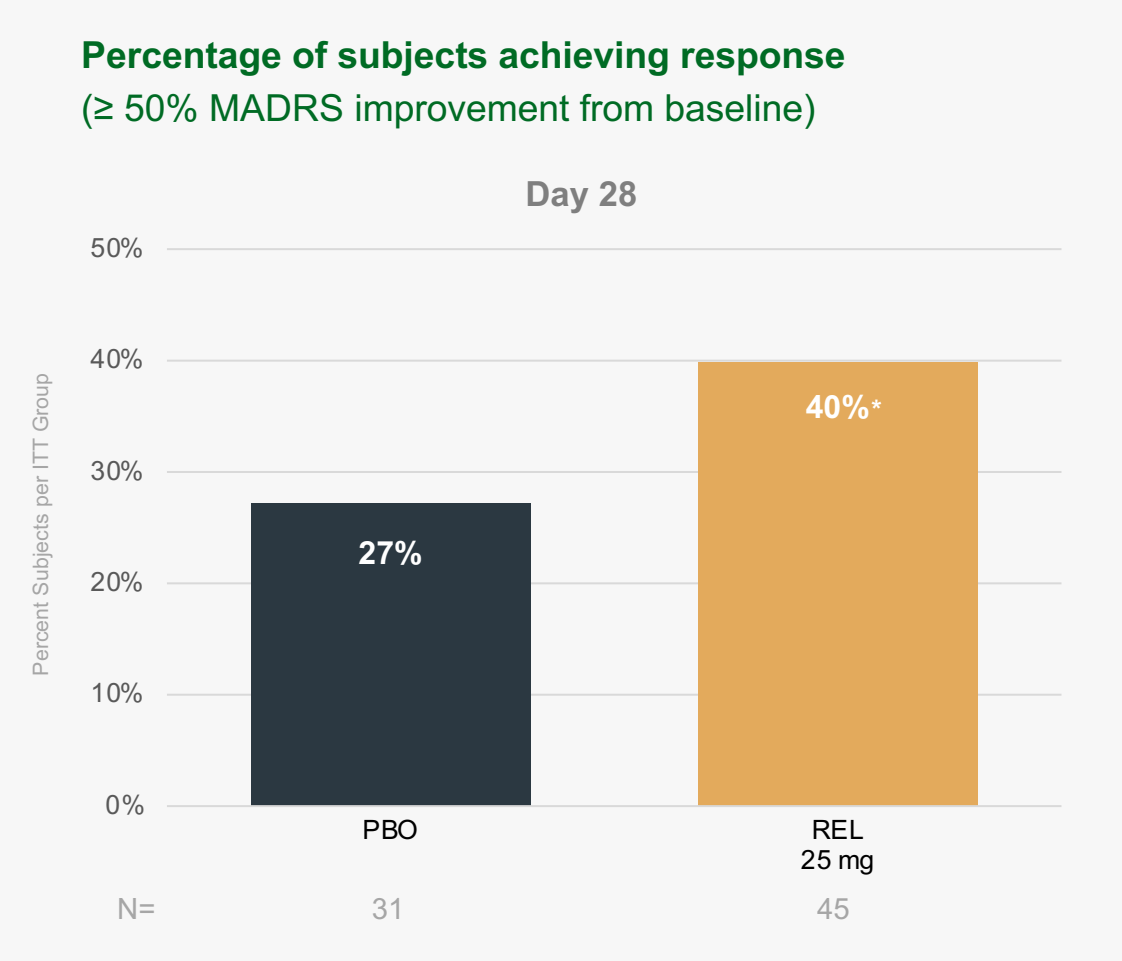
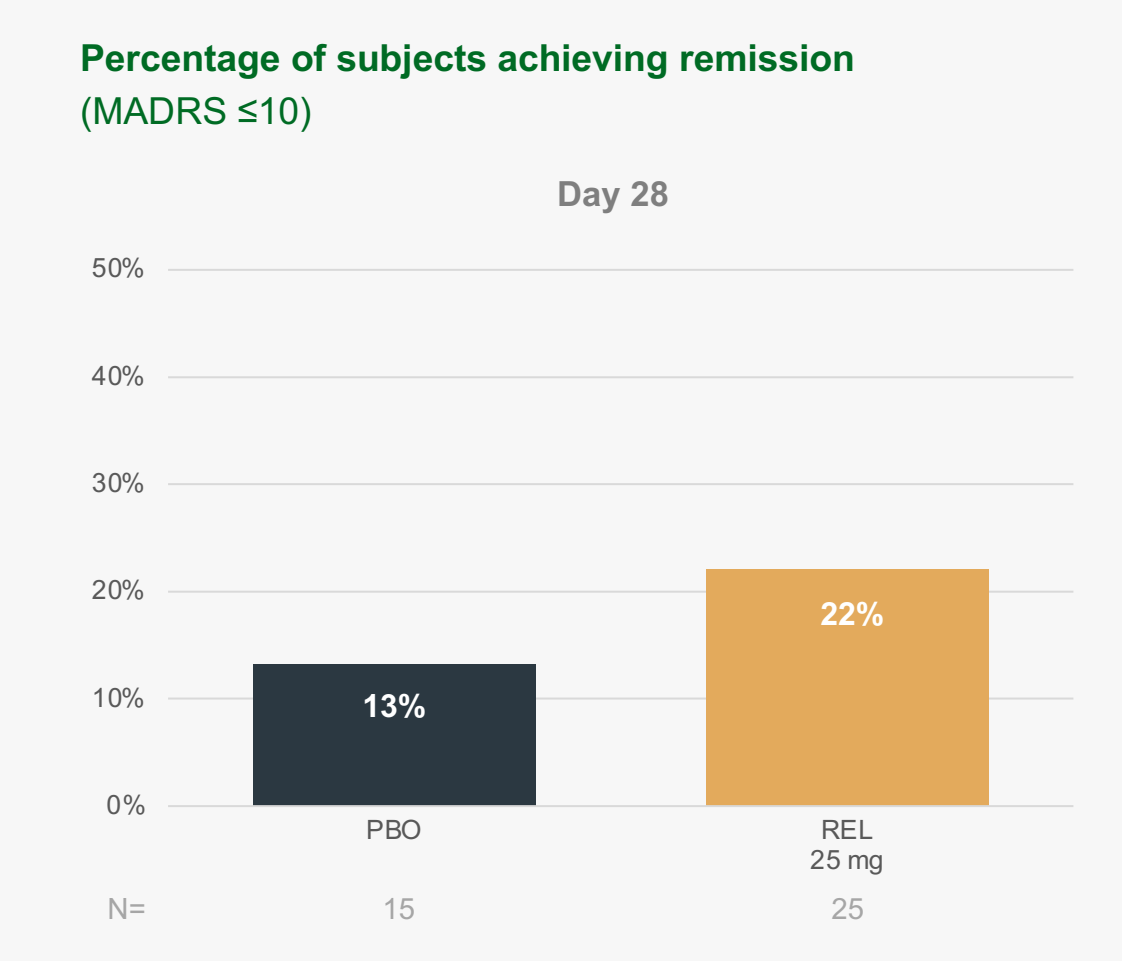
Reliance I achieved a statistically significant response rate of 40% (p=0.044), and achieved remission rate of 22% (p=0.076) at Day 28 in the full analysis set





Day 28: last efficacy assessment
Total N=227; * p= <0.05
MADRS=Montgomery-Asberg Depression Rating Scale; Source: Relmada Data on File

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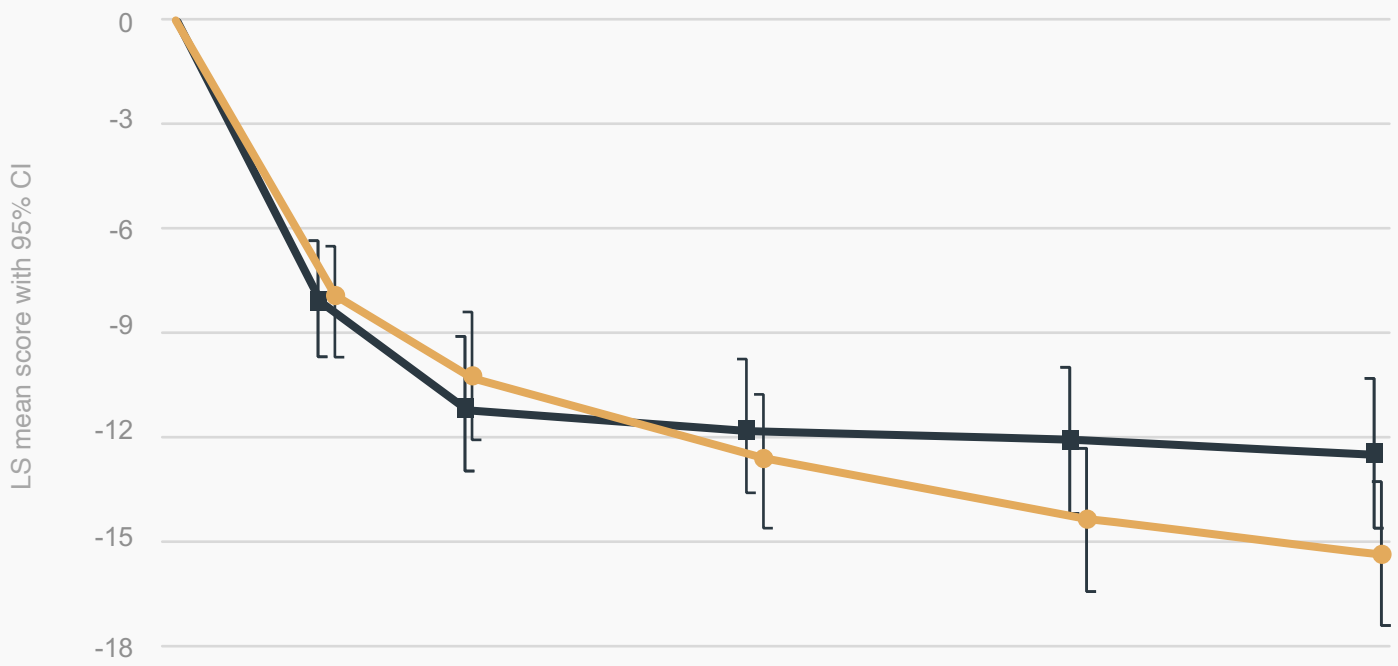
Reliance I: REL-1017 showed a clinically meaningful -3.1 MADRS point difference vs. placebo at Day 28 in the Reliance I per protocol set* (p=0.051)



Placebo

REL-1017 25mg

ΔMADRS (N=198) Placebo N=97, 25 mg N=101	Day 4	Day 7	Day 14	Day 21	Day 28 End of Treatment
Placebo Mean (SD)	-9.0 (7.4)	-11.2 (9.7)	-11.8 (10.2)	-12.5 (10.8)	**-12.5** (9.9)
25 mg Mean (SD)	-8.3 (8.7)	-10.4 (9.5)	-12.6 (9.5)	-15.0 (10.5)	**-15.6** (11.2)
Placebo LSMean (SE), MMRM	-8.2 (0.9)	-11.2 (1.0)	-11.9 (1.0)	-12.3 (1.1)	-12.7 (1.1)
25 mg LSMean (SE), MMRM	-8.3 (0.8)	-10.4 (1.0)	-12.9 (1.0)	-14.6 (1.1)	-15.6 (1.1)
REL-1017 vs Placebo LSMean Diff (SE); p-value, MMRM	-0.8 (1.2); 0.95	0.8 (1.4); 0.56	-1.0 (1.4); 0.50	-2.3 (1.5); 0.12	-2.94 (1.5); 0.057

-3.1 diff.
REL-1017
vs. placebo
p= 0.051
ES=-0.29

*Per-Protocol Set: Valid completer, ie, participants who complete the 28-day treatment and do not have any major protocol deviations impacting the efficacy assessments. This set will be analyzed according to the treatment actually received.
Day 28: End of treatment and primary efficacy endpoint
MADRS=Montgomery-Asberg Depression Rating Scale; Source: Relmada Data on File

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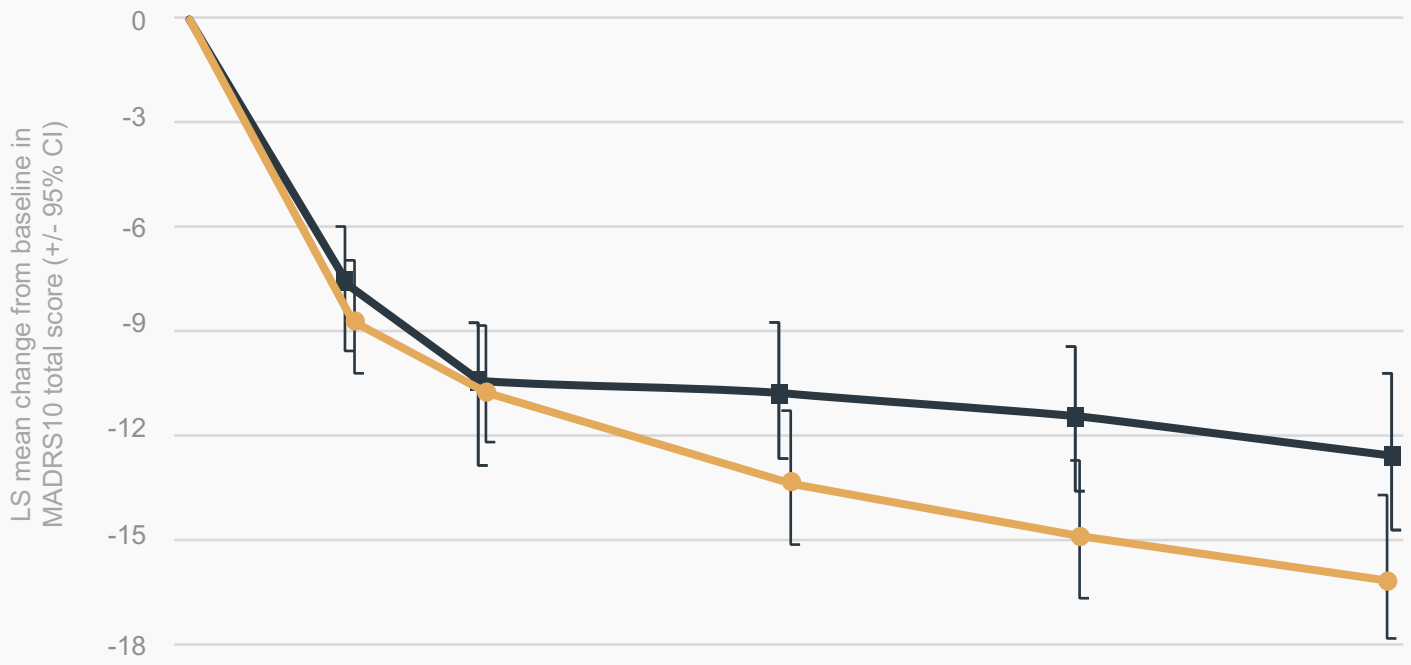
Reliance I: REL-1017 vs placebo with post-hoc removal of two sites with paradoxical results

Modified analysis of 41 of 43 centers and 185 of 227 subjects*



Placebo

REL-1017 25mg

ΔMADRS (N=185) Placebo N=88, 25 mg N=97, 41 sites	Day 4	Day 7	Day 14	Day 21	Day 28 End of Treatment
Placebo Mean (SD)	-8.5 (7.0)	-11.0 (9.6)	-11.0 (10.8)	-11.8 (10.5)	**-12.6** (9.8)
25 mg Mean (SD)	-8.8 (9.1)	-10.7 (9.6)	-13.4 (9.1)	-15.3 (10.1)	**-16.7** (11.1)
REL-1017 vs Placebo LSMean Diff (SE); p-value, MMRM	-1.0 (1.3); 0.45	0.1 (1.4); 0.95	-2.6 (1.5); 0.08	-3.3 (1.6); **0.03**	-3.7 (1.6); **0.02**

-4.1 diff. REL-1017 vs. placebo

*These same two centers produced non-plausible results in Reliance III
Day 28: last efficacy assessment
Total N=185; * p= <0.05
MADRS=Montgomery-Asberg Depression Rating Scale; Source: Relmada Data on File

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Patient sources: verifiable vs. unverifiable

Verifiable sources

- Past patients at site*
- Current patient*
- Site database**
- HCP referral

**For past/current patients at site, they are not necessary patients who were treated by the site. For sites that are Research-only (no psychiatric practice), these patients have worked with the sites for Research purposes, but not for ongoing care*

***Patients from site database are patients that sites have contacted in the past*

Unverifiable sources

- Radio/TV AD
- Banner/Pop AD
- Social media
- Internet search
- Friend
- Recruitment company
- Referral from other patients

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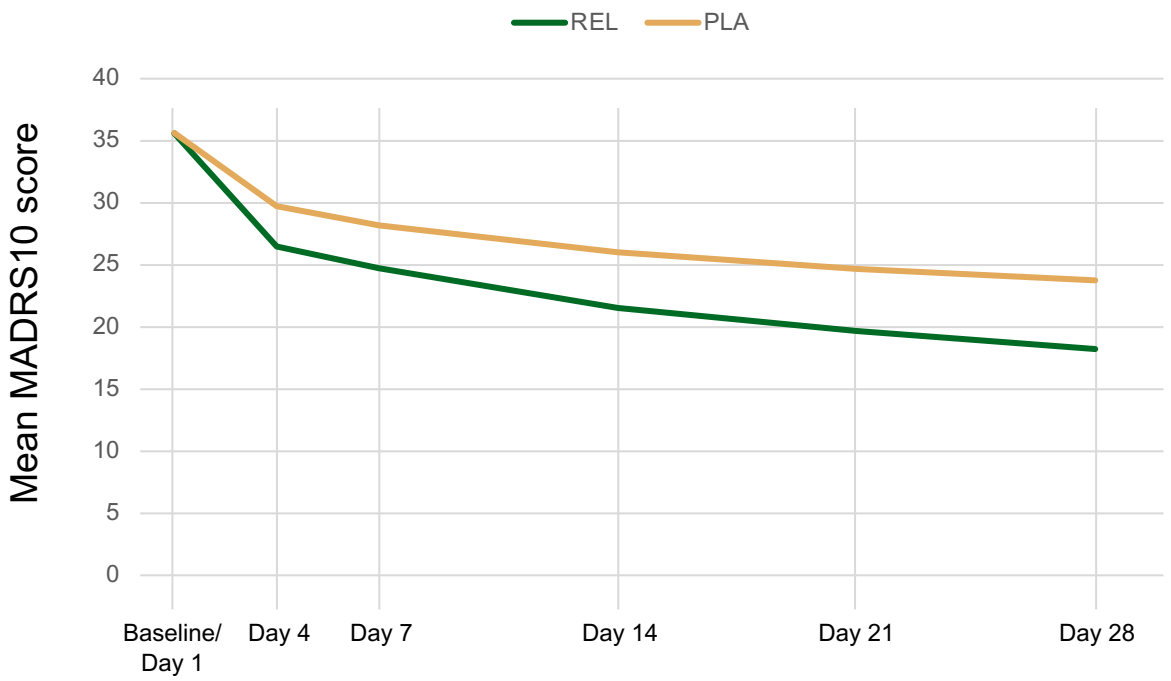
Reliance I: MADRS10 results for patients from verifiable sources vs unverifiable sources

Patients from verifiable sources

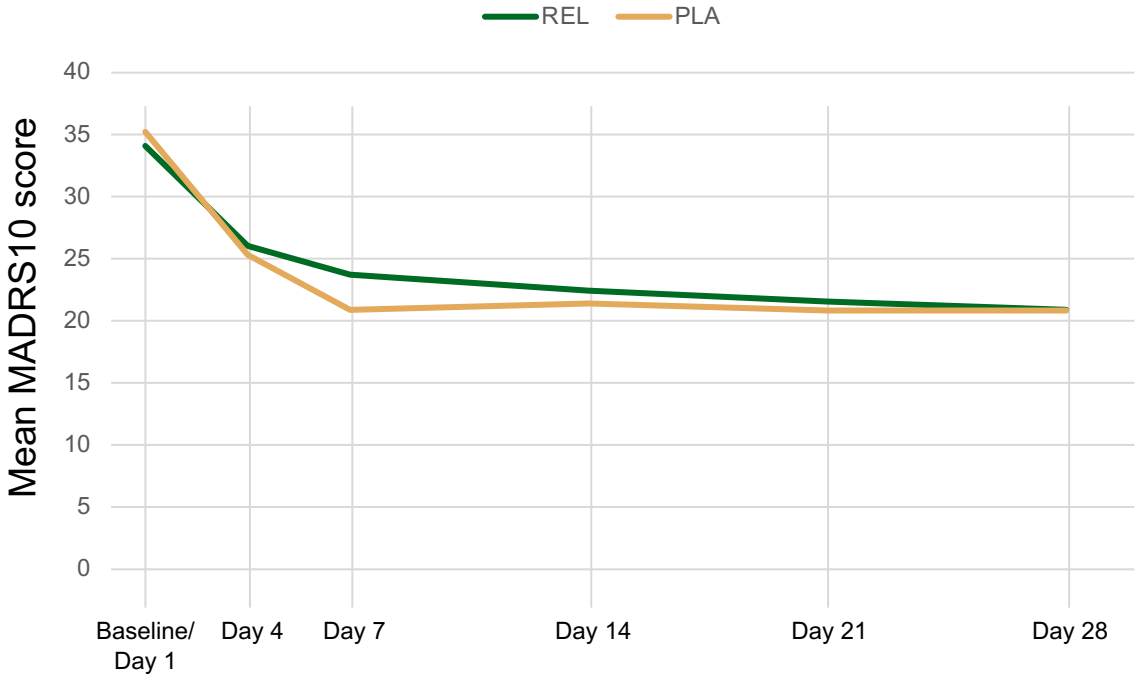


REL	52	50	50	50	49	49
PLA	40	39	39	39	37	37

Average change from baseline on Day 28	REL-1017	-17.22	p = 0.01614
	PLACEBO	-11.76	

-5.5 diff. REL-1017 vs. placebo

Patients from unverifiable sources



REL	61	61	60	60	59	60
PLA	74	70	70	66	65	70

Average change from baseline on Day 28	REL-1017	-13.22	p = 0.58911
	PLACEBO	-14.31	

p values is calculated using Student's Two-sample equal variance t-Test, with a two-tailed distribution
*Enrollment date is the date of Baseline/Day 1 visit

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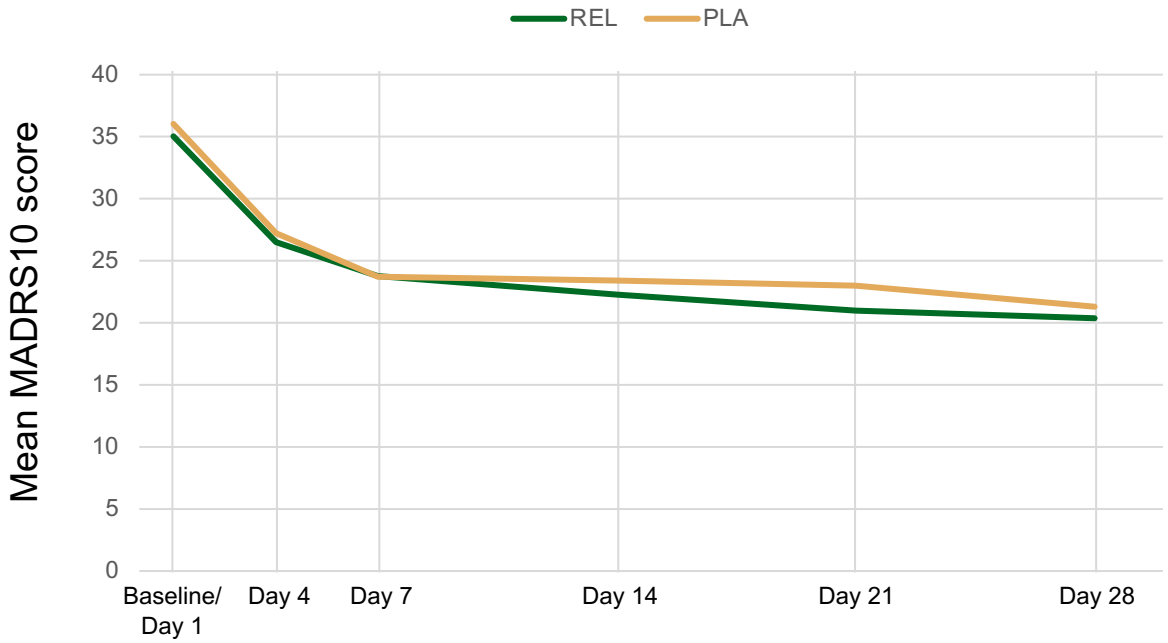
Potential impact of the COVID-19 pandemic on Reliance I: MADRS10 results for patients enrolled* before vs. after April 1st, 2022

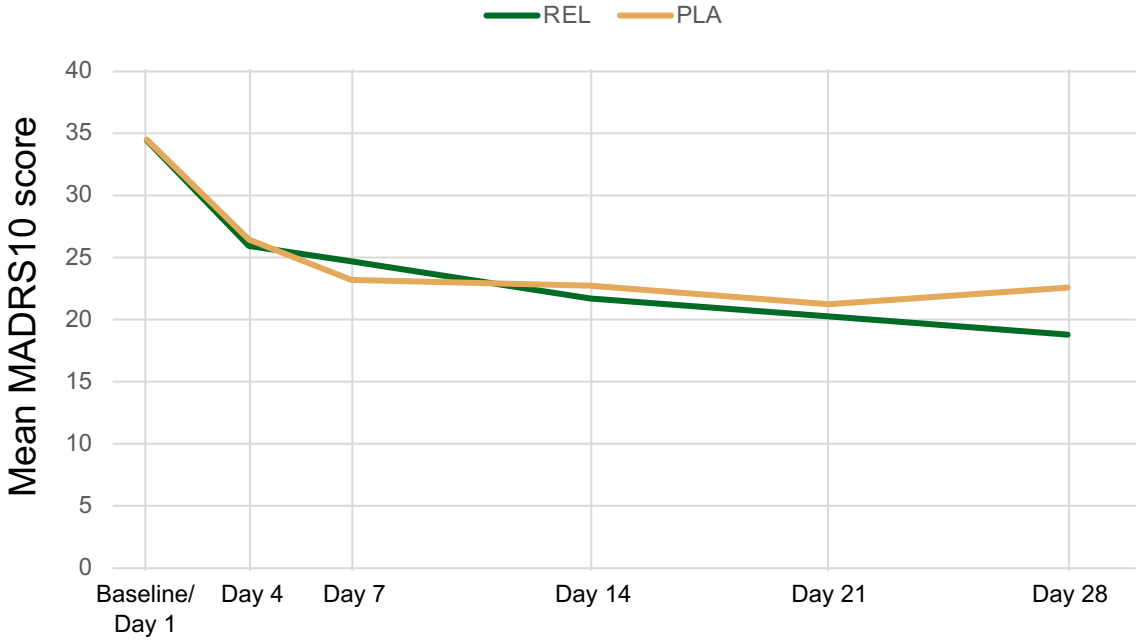
Patients enrolled before April 1st, 2022



REL	65	63	62	62	62	62
PLA	64	63	62	60	59	61

Average change from baseline on Day 28	REL-1017	-14.52	p = 0.89048
	PLACEBO	-14.79	

Patients enrolled after April 1st, 2022



REL	48	48	48	48	46	47
PLA	50	46	47	45	43	46

Average change from baseline on Day 28	REL-1017	-15.68	p = 0.08898
	PLACEBO	-11.63	

-4.1 diff.
REL-1017
vs. placebo

p values is calculated using Student's Two-sample equal variance t-Test, with a two-tailed distribution
*Enrollment date is the date of Baseline/Day 1 visit

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REL-1017 displays a robust safety profile and confirms no evidence for abuse potential or dissociative effects across studies

Cardiac safety

No AE related to QTcF prolongation

Suicidality

No evidence of increased suicidal ideation/behavior measured with C-SSRS[1] scales

Dissociative effects and withdrawal symptoms

No evidence of drug-induced dissociation based on CADDS[2]

No evidence of withdrawal symptoms based on the SOWS[3], COWS[4] and PWC-20[5] scales

Abuse potential MADDERS® reports[6]

No signal of abuse potential as assessed in the **MADDERS®** reports[6]

These results are consistent with safety and tolerability findings from the Phase 2 study

1.) C-SSRS: Columbia Suicide Severity Rating Scale; 2.) CADDS: Clinician-Administered Dissociative States Scale; 3.) SOWS: Subjective Opioid Withdrawal Scale; 4.) COWS: Clinical Opiate Withdrawal Scale; 5.) PWC-20: Physician Withdrawal Checklist; 6.) MADDERS®: Misuse, Abuse, and Diversion Drug Event Reporting System

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In Reliance I no serious treatment related treatment-emergent adverse event (TEAE) and no opioid like effects were observed

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

Variable	Placebo (N=114)		REL-1017 25 mg (N=113)		All patients (N=227)	
	N	%	N	%	N	%
Patients with at least one TEAE	61	53.5	55	48.7	116	51.1
Patients with at least one treatment related TEAE	28	24.6	30	26.5	58	25.6
Patients with at least one serious treatment related TEAE	0	0.0	0	0.0	0	0.0
Treatment-emergent adverse events* occurring in 5% or more patients per treatment arm						
Headache	9	7.9	13	11.5	22	9.7
COVID19	10	8.8	6	5.3	16	7.0
Upper respiratory tract infection	6	5.3	8	7.1	14	6.2
Nausea	5	4.4	8	7.1	13	5.7
Diarrhea	7	6.1	5	4.4	12	5.3
Constipation	7	6.1	3	2.7	10	4.4
Dizziness	2	1.8	7	6.2	9	4.0

*Treatment-emergent adverse event was defined as an adverse event that started or worsened after treatment with the trial drug

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Key learnings from stakeholders following Reliance I and Reliance III results

- Study site visits were too long and entailed too many assessments
- High enrolling sites with high placebo rates were over-represented in the final dataset
- Study screening eligibility adjudication needed improvement
- COVID-19 impacted our trial due to the large number of patients experiencing situational depression related to isolation and other pandemic related issues

External stakeholders include KOLs, principal investigators, and study coordinators

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Changes to improve subject quality and better manage placebo response for ongoing and new studies

- Requirement of medical records to verify depression diagnoses and ADT history to ensure enrollment of patients with true clinical depression
- Increased clinical trial oversight and management to improve screening eligibility adjudication
- Careful site selection based on the wealth of data gathered from recent trial experiences
- Limiting the number of patients enrolled per site to ensure there is not a disproportionate effect on study outcomes
- Protocol simplification to reduce the duration of site visits and assessments, enhance recruitment, and minimize placebo response

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Significant progress on the path to NDA

- ✓ All non-clinical & phase 1 studies completed
- ✓ All Human Abuse Potential studies (HAPs) completed
- ✓ Stability testing of primary packaging completed and engineering production batch at scale completed
- ✓ Considerable safety data collected from two phase 3 studies and open-label extension

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Corporate Information

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Financial overview

$132.4 million

Cash, cash equivalents & short-term investments

As of 03/31/2023

~3.0 million

Warrants outstanding

As of 03/31/2023, weighted average exercise price, $17.02

$16.5 million

Operating cash burn

1Q23

~30.1 Million

Common shares outstanding*

As of 03/31/2023

*As converted share count of 45.6 MM share as of 03/31/2023

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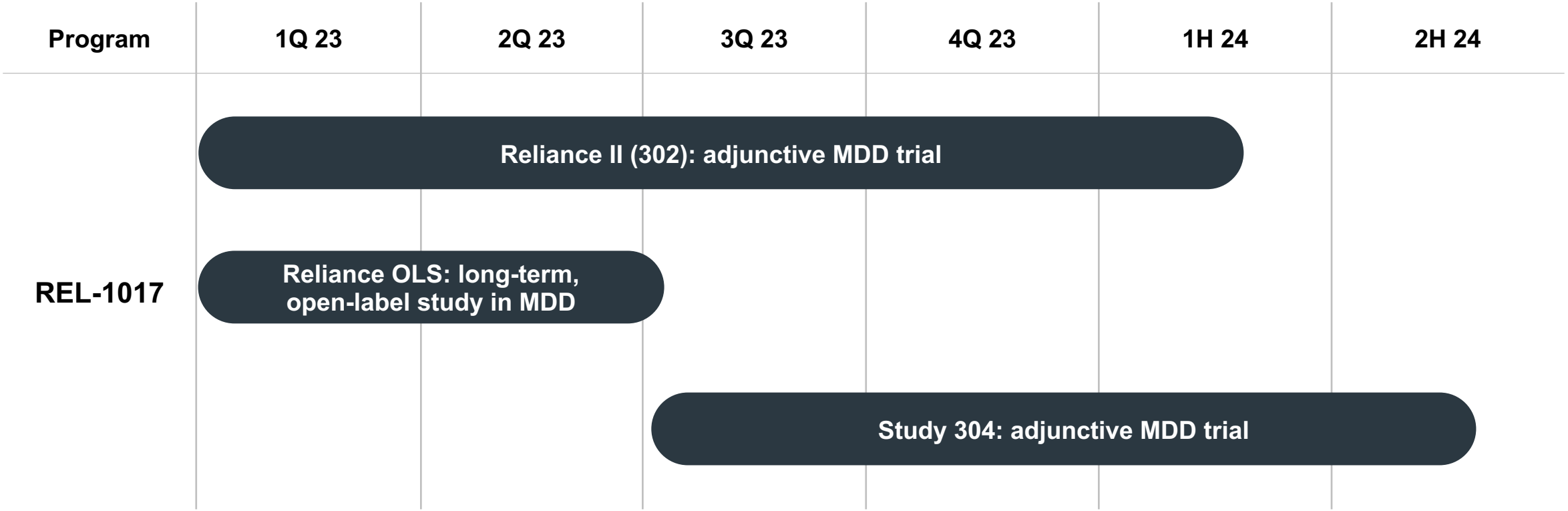
Relmada development program & timeline



Upcoming events

- Concluded Reliance-OLS with data coming in 2023
- Complete ongoing Reliance II 1H 2024
- Initiating additional phase 3 adjunctive MDD trial mid-2023 with completion anticipated 2H 2024

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Investment summary

Focus on CNS diseases and lead program in major depressive disorder

- REL-1017 is in Phase 3 for depression, a primary cause of disability worldwide[1]
- REL-1017 potentially addresses the limitations of current MDD treatments where 50%–66% of patients do not fully recover on an antidepressant medication[2], take 2-8 weeks to work, and have significant side effects
- Highly experienced clinical team with CNS focused backgrounds and a successful track record advancing programs through NDA approval

Highly compelling opportunity in REL-1017

- **Phase 3 program underway** with positive efficacy signals and safety data consistent with phase 1 and 2 studies
- Novel MOA with successful Phase 2 trial in adjunctive MDD that showed statistically significant, robust, rapid, and sustained antidepressant effects with favorable safety and tolerability profile[3]
- Strong intellectual property position around REL-1017 with expirations through the mid/late-2030s

Lessons learned provide strong confidence in the path to NDA

- Improved clinical trial management
- Quality patient selection
- Careful site selection
- Protocol simplification

CNS= Central Nervous System; MDD = major depressive disorder; MOA = mechanism of action\
**Our fiscal year end is December 31. The periods referred to in this slide are calendar years and quarters.
1.) WHO Depression Fact Sheet; 2.) Al-Harbi K.S. 2012 *Patient Preference and Adherence*; 3.) Fava et al. Rapid and Sustained Antidepressant Effects of REL-1017 (dextromethadone) as an Adjunctive Treatment for Major Depressive Disorder: A Phase 2 Trial. 2021

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Thank you