Relmada THERAPEUTICS

Targeting Major Advances in the Treatment of CNS Disorders

March 2024

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Investment highlights

Lead program, REL-1017 is a novel NMDAR antagonist in Phase 3 trials as adjunctive treatment for MDD

Phase 1, 2 and 3 results support the continued development of REL-1017 as adjunctive treatment of MDD

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

Expanding therapeutic portfolio with innovative approaches to treatments for large unmet needs

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

MDD = major depressive disorder; NMDAR = N-methyl-D-aspartate receptor; NDA = new drug application

Our development programs are focused on innovative science-driven treatment options for patients

Adjunctive treatment for MDD in advanced clinical development

Esmethadone (REL-1017), our lead program, is a novel NMDA receptor antagonist that has the potential to be the first in class oral once daily antidepressant approved as adjunctive treatment of major depressive disorder. The program is underway with two ongoing Phase 3 clinical trials in the US.

Metabolic program

We are developing a novel modified release psilocybin formulation that has shown promising pre-clinical activity for the treatment of obesity and other metabolic diseases. A Phase 1 SAD study will commence in 2024.

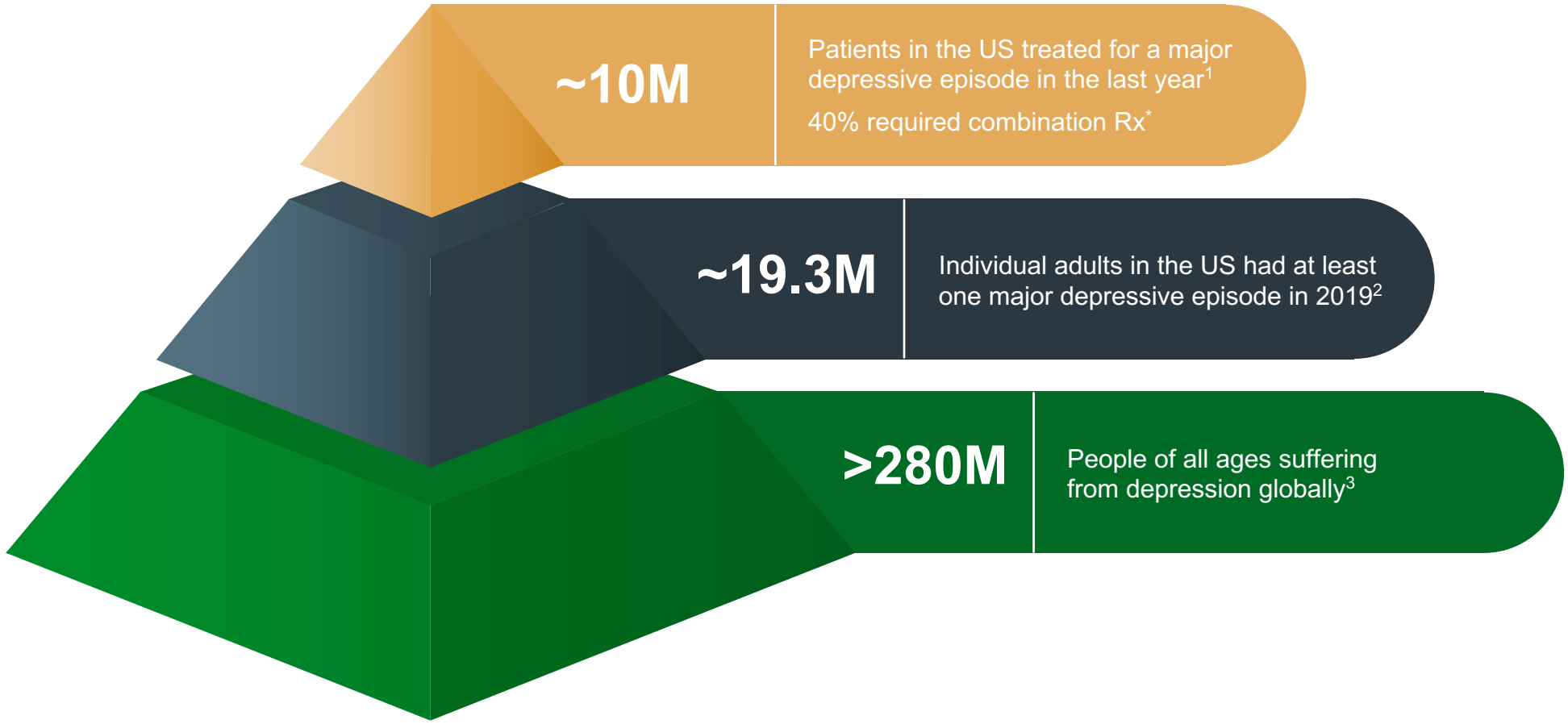
Neuroplastogen™ program

We have synthesized a series of novel esmethadone and psilocybin derivatives. We are in the process of selecting the most promising candidates for clinical development.

MDD = major depressive disorder; SAD = single ascending dose; NMDA = N-methyl-D-aspartate

The unique profile of esmethadone (REL-1017) addresses the limitations of current treatment options for MDD

The 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

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

The unique profile of esmethadone (REL-1017) addresses limitations of current treatments

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

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 [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

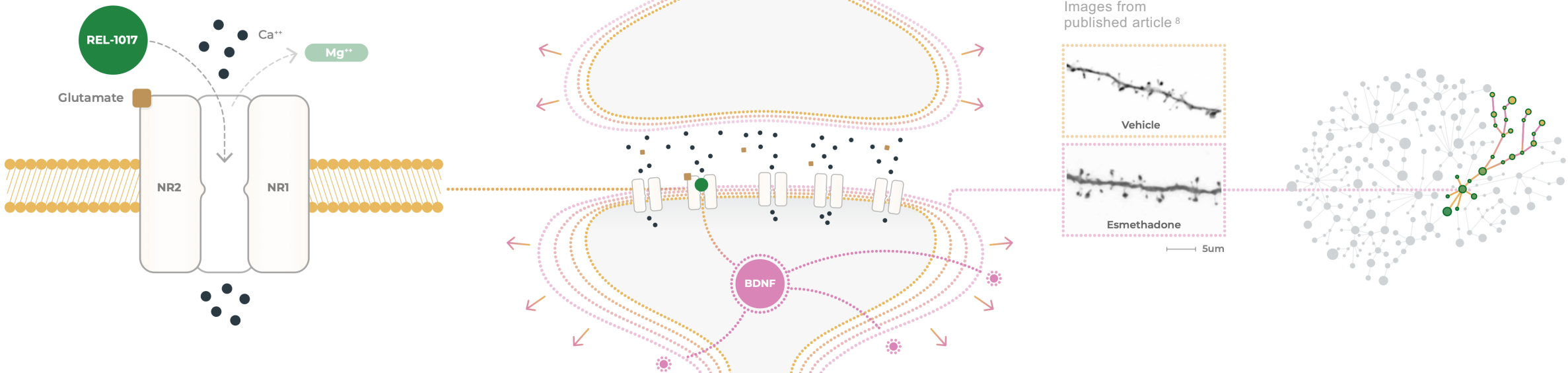
MDD = major depressive disorder; NMDAR = N-methyl-D-aspartate receptor

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

Esmethadone [1] (REL-1017) is a novel NMDA receptor antagonist

NMDA: N-methyl-D-aspartate
GluN2D: Glutamate NMDA receptor with 2D subunits
BDNF: brain-derived neurotrophic factor
MDD: major depressive disorder

Receptor, synapses and brain images are artistic renditions



Esmethadone preferentially blocks tonically hyperactive GluN2D receptor subtypes [2], potentially increasing BDNF [3], decreasing neuroinflammation [4] and restoring physiological neuroplasticity [5,6,7].

Synaptic spines increase in size within 24 hours of administration [8]. Esmethadone is devoid of dissociative effects [9], has no meaningful abuse potential [10] and is administered orally once-daily.

1. Esmethadone is a promising non-dissociative NMDAR antagonist antidepressant (Fava 2023)
2. Esmethadone preferentially targets tonically hyperactive GluN2D receptors (Bettini 20222A)
3. Esmethadone increases BDNF release (Fogaca 2019; De Martin 2021)
4. Esmethadone reduces calcium influx induced by quinolinic acid (Bettini 2022B)
5. Esmethadone restores impaired neuroplasticity (Fogaca 2019; Stahl 2022)
6. Impaired neuroplasticity and neuroinflammation may be central to the pathophysiology of MDD (Cooper 2023)
7. Esmethadone is a promising neuroplastogen® that could transform the current treatment of MDD (Cooper 2023)
8. A single dose of esmethadone increases synaptic spines (Fogaca 2019)
9. Esmethadone does not cause dissociative effects (Shram 2023)
10. Esmethadone differs pharmacologically from levomethadone because it is devoid of clinically relevant opioid activity. Esmethadone has no meaningful abuse potential in healthy subjects (Bernstein 2019), patients with MDD (Fava 2022) and recreational substance users (Shram 2023)

The clinical development of esmethadone (REL-1017) is steadily progressing as Adjunctive Treatment for MDD

Esmethadone (REL-1017) clinical development status

All non-clinical studies have been successfully completed

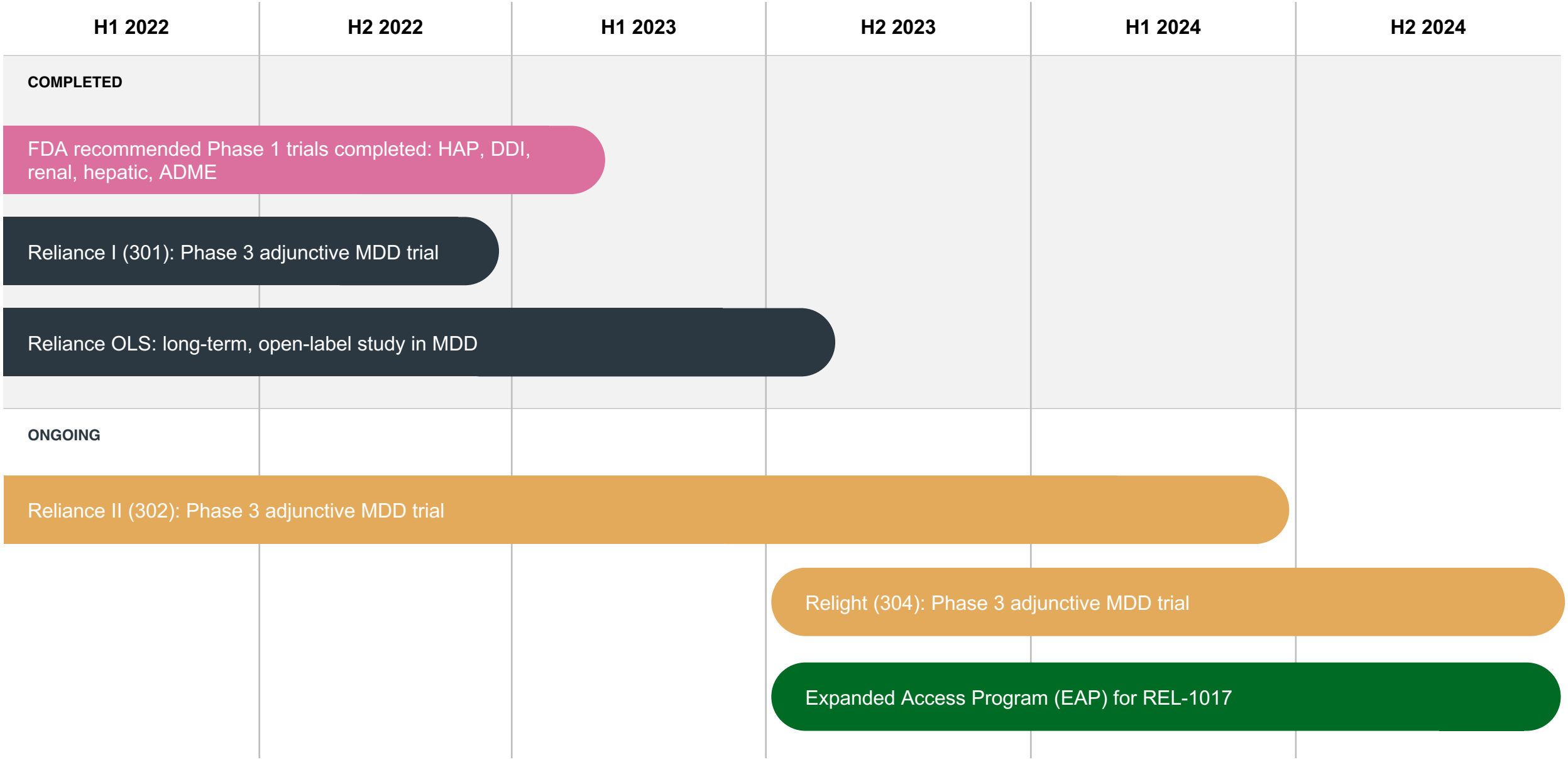
All Phase 1 studies and Human Abuse Potential studies (HAPs) have been successfully completed

The open-label 12-month study has been successfully completed

The Phase 3 development program is ongoing; Reliance I (study 301) has been completed, Reliance II (study 302) and Relight (study 304) are currently in progress

Stability testing of primary packaging has been completed, and production at scale has been validated

REL-1017 clinical program for adjunctive treatment for MDD



MDD = major depressive disorder; HAP = human abuse potential; DDI = drug-drug interaction; ADME = absorption, distribution, metabolism, excretion

Data from the Phase 1, 2 and 3 indicate favorable safety and tolerability of esmethadone (REL-1017)

All Phase 1 studies have been successfully completed

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

The Human Abuse Potential studies have been successfully completed and indicate no abuse potential of REL-1017

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 [2] indicate no meaningful abuse potential and support the DEA statement below:

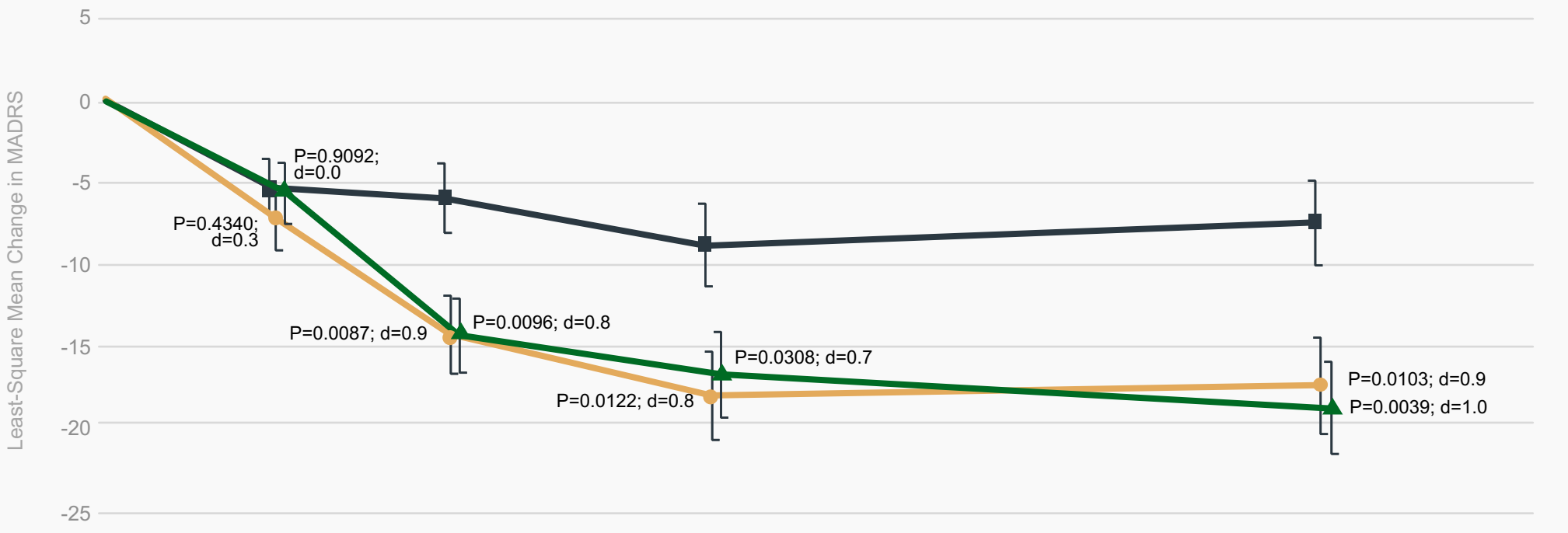
"The *d*-isomer lacks significant respiratory depressant action and addiction liability..."

US Drug Enforcement Administration
December 2019 [3]

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 MJ, et al. The novel uncompetitive NMDA receptor antagonist esmethadone (REL-1017) has no meaningful abuse potential in recreational drug users. Transl Psychiatry. 2023 Jun 7;13(1); 3. US DEA Statement on Methadone, December 2019 February 2022:

Phase 2 study results: 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



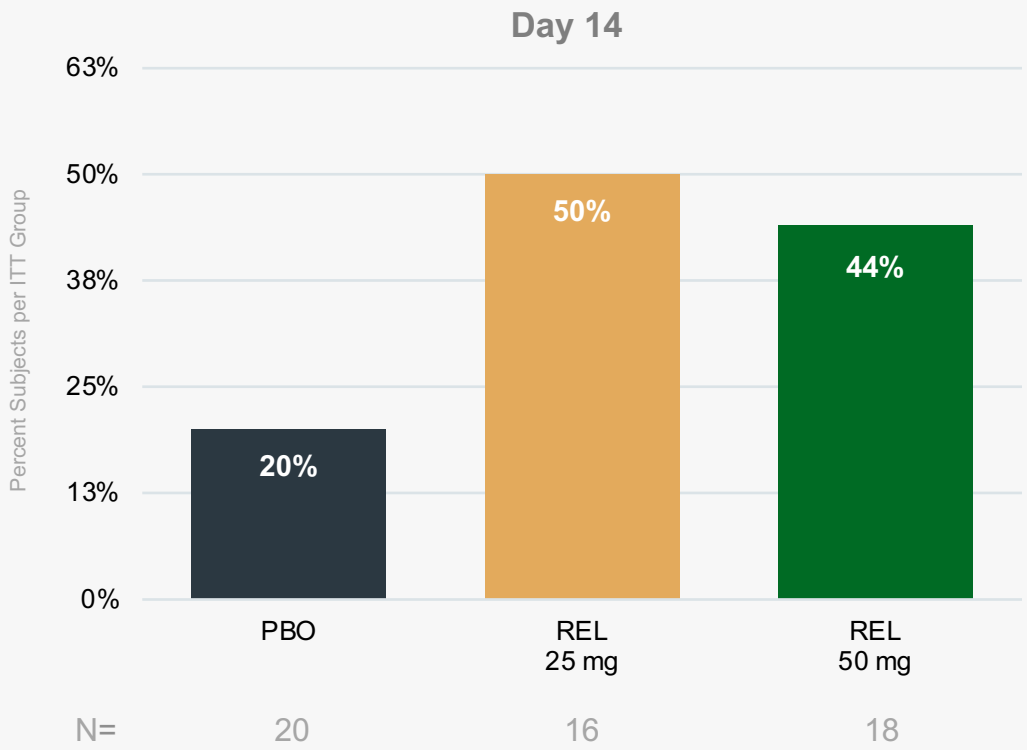
Mean drug-placebo difference

MADRS	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*

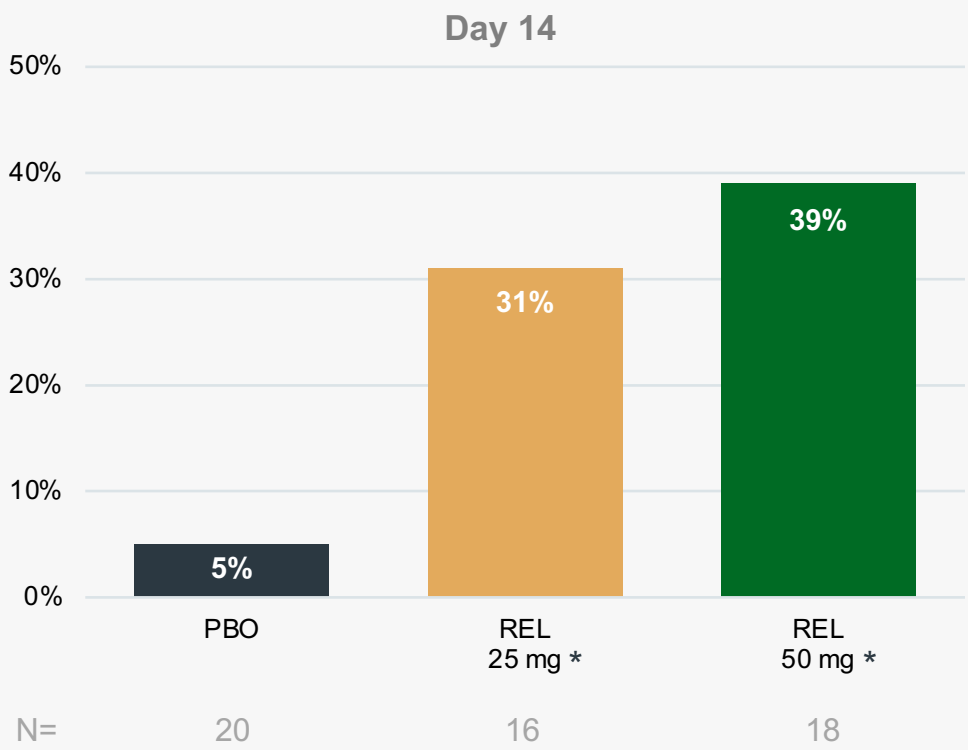
*P-value <.05
MADRS=Montgomery-Asberg Depression Rating Scale

Phase 2 study efficacy results: response & remission

Percentage of subjects achieving response
(≥ 50% MADRS improvement from baseline)



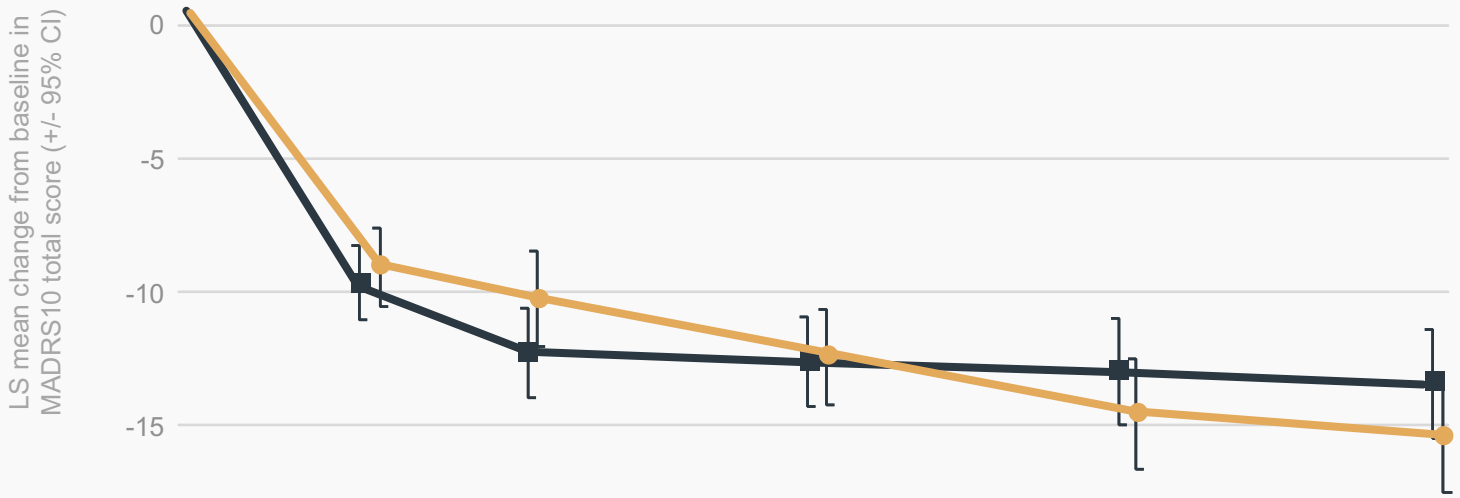
Percentage of subjects achieving remission
(MADRS ≤10)



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

The Phase 3 program as Adjunctive Treatment for MDD is currently ongoing

Reliance I primary efficacy endpoint ITT: REL-1017 showed a clinically meaningful -2.3 MADRS point difference vs. placebo at Day 28

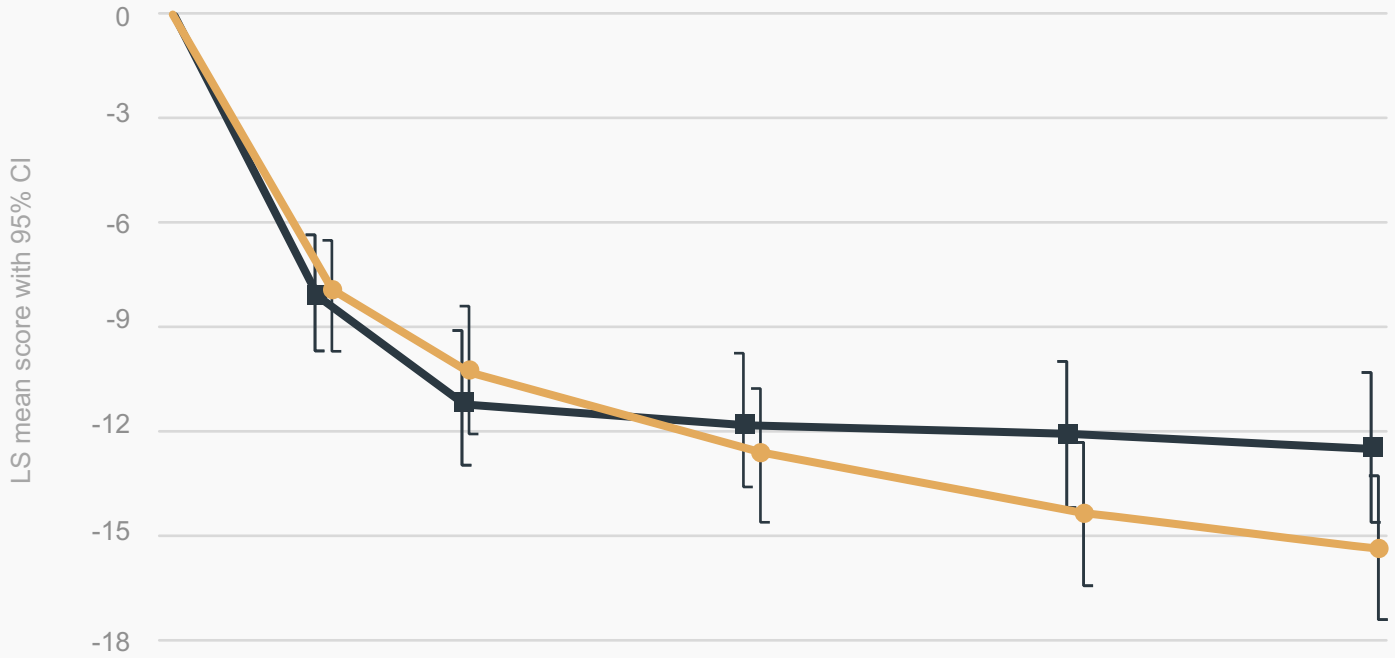


ΔMADRS (N=227) **Placebo N=114, 25 mg N=113, 43 sites**	**Day 4**	**Day 7**	**Day 14**	**Day 21**	**Day 28** **End of treatment**
Placebo Mean (SD)	-9.3 (7.3)	-11.8 (9.9)	-12.2 (10.9)	-13.0 (11.2)	**-12.9** (10.4)
25 mg Mean (SD)	-8.3 (8.9)	-10.2 (9.5)	-12.4 (9.4)	-14.4 (10.4)	**-15.1** (11.3)
Placebo 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**;
MADRS=Montgomery-Asberg Depression Rating Scale; ITT = intent-to-treat; SD = standard deviation; SE= standard error; MMRM = mixed models for repeated measures
Source: Relmada Data on File

Reliance I primary efficacy endpoint PP*: REL-1017 showed a clinically meaningful -3.1 MADRS point difference vs. placebo at Day 28 (p=0.051)



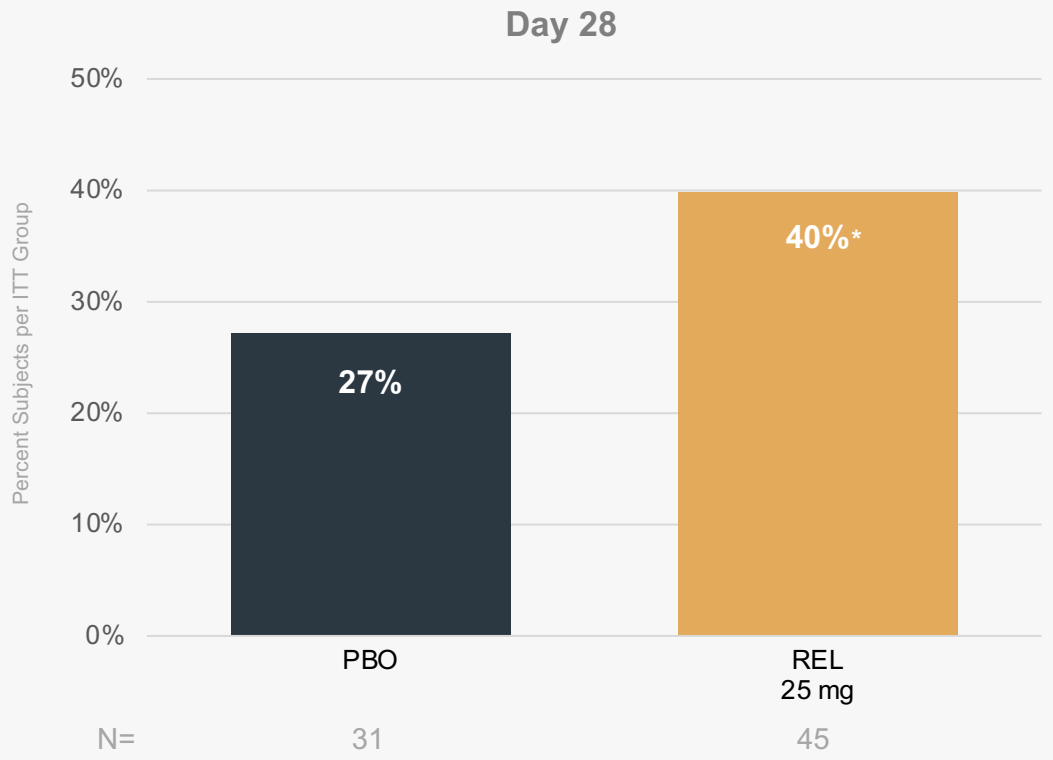
ΔMADRS (N=198) Placebo N=97, 25 mg N=101	Day 4	Day 7	Day 14	Day 21	Day 28 End of treatment
Placebo Mean (SD)	-9.0 (7.4)	-11.2 (9.7)	-11.8 (10.2)	-12.5 (10.8)	**-12.5** (9.9)
25 mg Mean (SD)	-8.3 (8.7)	-10.4 (9.5)	-12.6 (9.5)	-15.0 (10.5)	**-15.6** (11.2)
Placebo LSMean (SE), MMRM	-8.2 (0.9)	-11.2 (1.0)	-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	-2.9 (1.5); 0.057

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

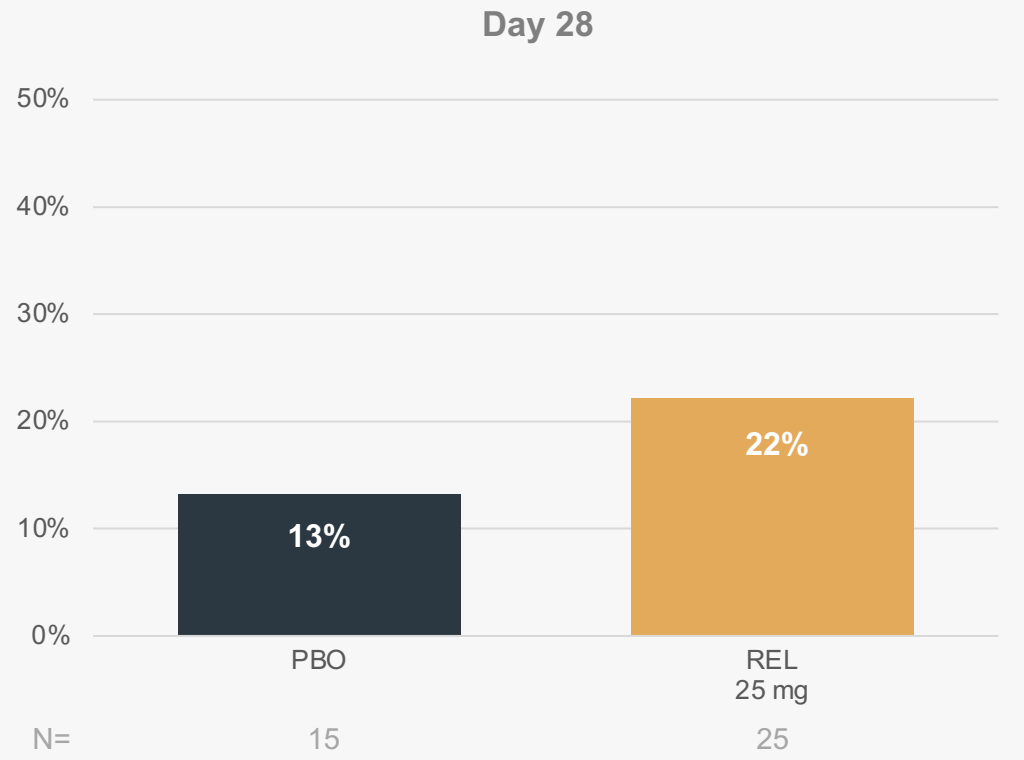
*Per-Protocol Set: Valid completer, i.e, participants who completed the 28-day treatment and did not have any major protocol deviations impacting the efficacy assessments. This set was analyzed according to the treatment actually received.
Day 28: End of treatment and primary efficacy endpoint
MADRS=Montgomery-Asberg Depression Rating Scale; ITT = intent-to-treat; SD = standard deviation; SE= standard error; MMRM = mixed models for repeated measures
Source: Relmada Data on File

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

Percentage of subjects achieving response
(≥ 50% MADRS improvement from baseline)



Percentage of subjects achieving remission
(MADRS ≤10)



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

Patient sources: verifiable vs. unverifiable

Verifiable sources

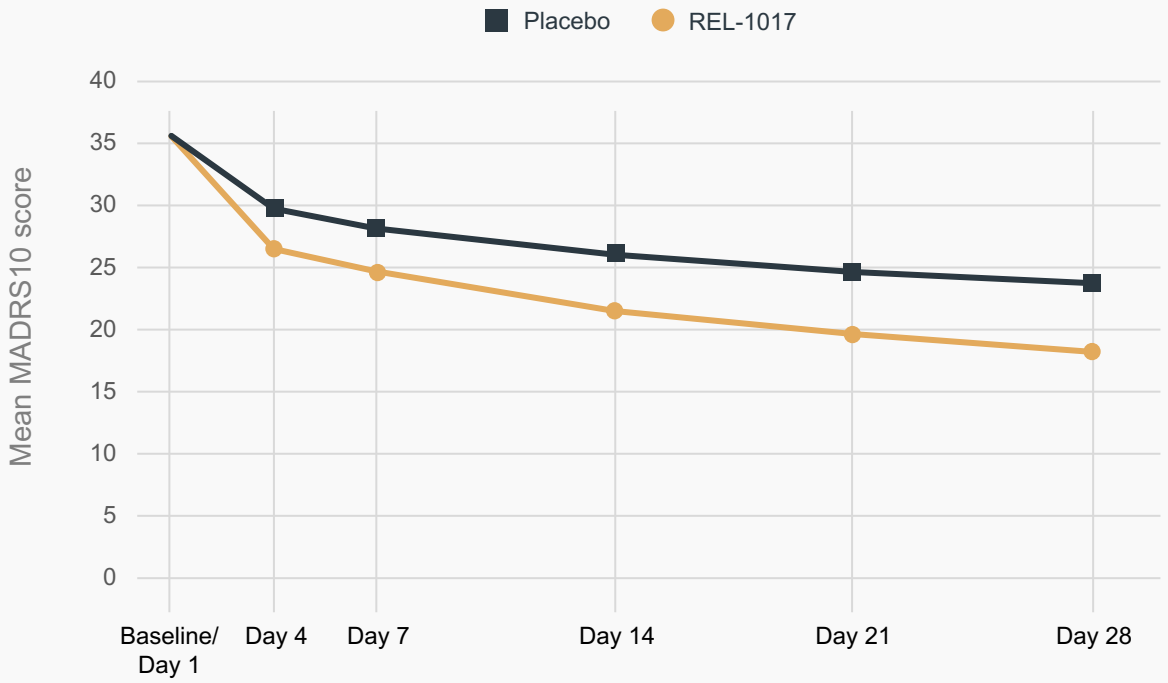
- Past patient at site
- Current patient
- Site database
- HCP referral

Unverifiable sources

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

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

Patients from verifiable sources

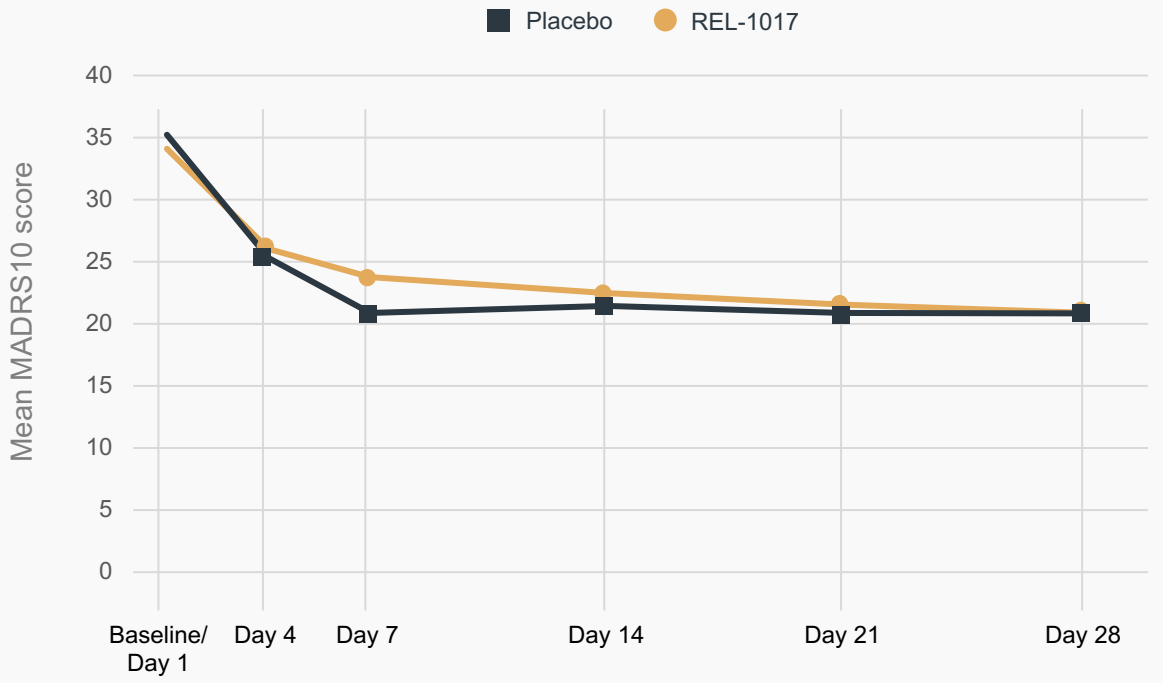


REL	52	50	50	50	49	49
PLA	40	39	39	39	37	37

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 are calculated using Student's Two-sample equal variance t-Test, with a two-tailed distribution
MADRS=Montgomery-Asberg Depression Rating Scale

In Reliance I no serious treatment-related adverse events (AE)* and no opioid like effects were observed

Treatment-related 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 AE	61	53.5	55	48.7	116	51.1
Patients with at least one treatment-related AE	28	24.6	30	26.5	58	25.6
Patients with at least one serious treatment-related AE	0	0.0	0	0.0	0	0.0
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

MDD = major depressive disorder; AE = adverse event

REL-1017 displays a favorable safety & tolerability profile and confirms no evidence for meaningful abuse potential across studies

Cardiac safety

No AE related to QTcF prolongation

No increase in suicidality

No signal of drug induced suicidal ideation/behavior measured with C-SSRS[1]

No dissociative effects

No signal of drug-induced dissociation measured with CADDS[2]

No abuse potential

No "drug liking" VAS differences from placebo

No signal of withdrawal measured with SOWS[3], COWS[4] and PWC-20[5]

No MADDERS® reports of concern[6]

These Phase 3 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

Change from baseline by visit in MADRS10 total score and response and remission rates—de novo & FAS data set

De novo population	**Baseline MADRS (N=202)** **Total Mean (SD): 33.8 (4.5)**	**Month 3 (N=168)**	**Month 6 (N=134)**	**Month 9 (N=93)**	**Month 12 (N=57)**
	ΔMADRS Total Mean (SD)	-19.9 (10.0)	-19.9 (10.4)	-20.1 (10.2)	-22.5 (9.7)
	Response Rate n (%)	102 (60.7%)	85 (63.4%)	56 (60.2%)	44 (77.2%)
	Remission Rate n (%)	74 (44.0%)	64 (47.8%)	43 (46.2%)	31 (54.4%)
Total FAS population	**Baseline MADRS (N=582)** **Total Mean (SD): 34.5 (4.7)**	**Month 3 (N=542)**	**Month 6 (N=435)**	**Month 9 (N=323)**	**Month 12 (N=200)**
	ΔMADRS Total Mean (SD)	-20.1 (10.7)	-21.0 (10.8)	-21.6 (10.7)	-21.7 (10.3)
	Response Rate n (%)	347 (64.0%)	289 (66.4%)	212 (65.6%)	139 (69.5%)
	Remission Rate n (%)	242 (44.6%)	203 (46.7%)	168 (52.0%)	98 (49.0%)

Note: Total FAS Data set includes De Novo and Rollover patients (REL-1017-301, REL-1017-302, and REL-1017-303); Rollover baseline score is the last non-missing value prior to the first double-blind dose; De Novo baseline score is the last non-missing value prior to the first open-label dose; Month 12 are patients that completed Month 12 visit; CFB=Change from Baseline; MADRS=Montgomery-Asberg Depression Rating Scale; FAS = Full Analysis Set; MADRS=Montgomery-Asberg Depression Rating Scale; SD = standard deviation; Source: Relmada Data on File

In Reliance-OLS no serious treatment-related adverse event was observed for all patients (de novo and rollover)

There was no significant safety signal for weight gain, sexual dysfunction, cardiovascular issues, dissociative effects, withdrawal phenomena or abuse liability

Variable	All patients (N=618)	
	N	%
Patients with at least one AE	347	56.1
Patients with at least one treatment-related AE	168	27.2
Patients with at least one serious treatment-related AE	0	0.0
Adverse events occurring in 5% or more patients		
COVID-19	60	9.7
Headache	60	9.7
Upper respiratory tract infection	53	8.6
Nausea	31	5.0
The most common treatment-related adverse events		
Headache	27	4.4
Nausea	25	4.0
Dizziness	15	2.4

OLS = Open label study; AE = adverse events

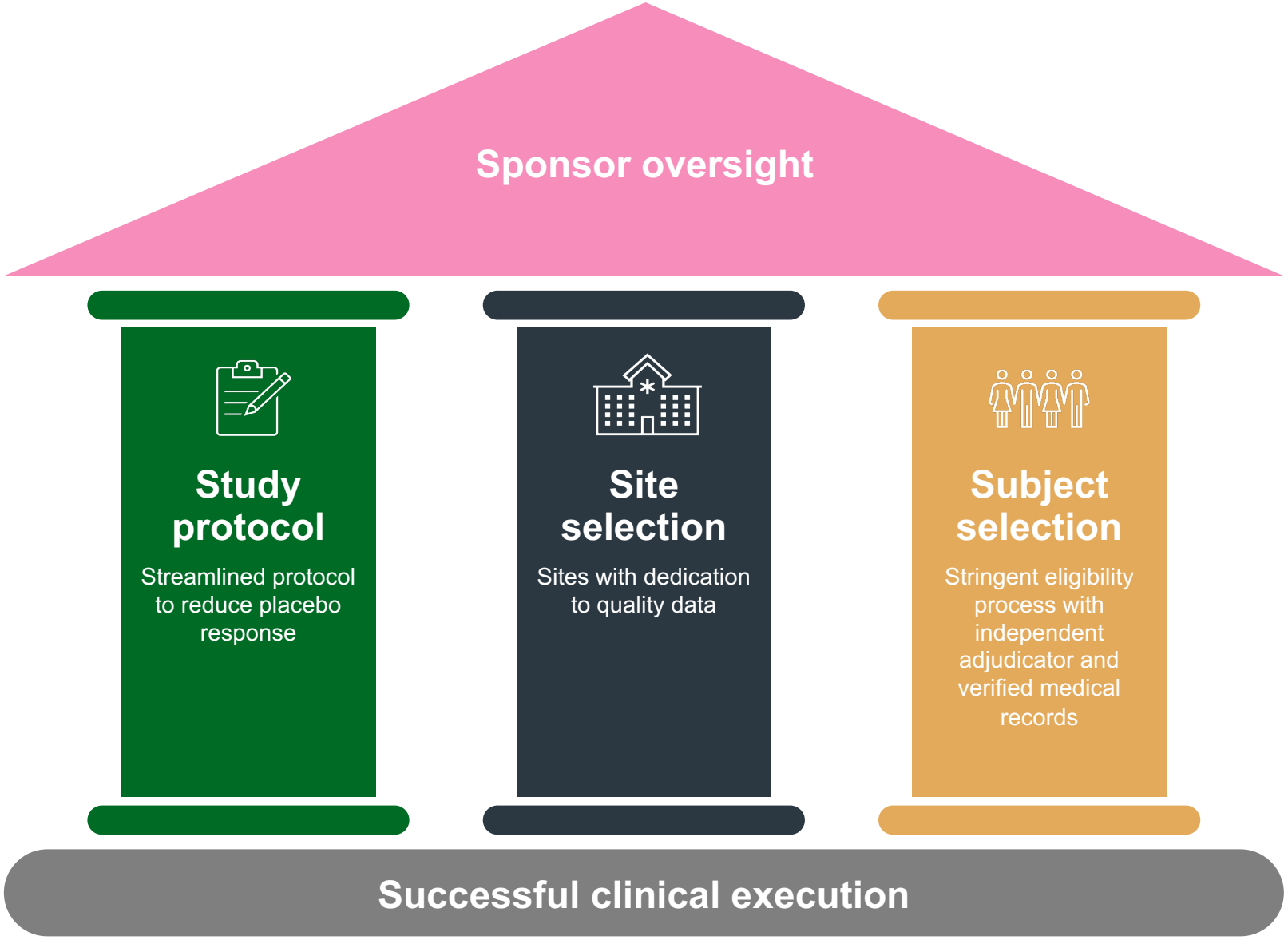
Relmada is conducting two Phase 3 trials

Reliance II

Relight

Phase 3 studies, currently ongoing in the United States, to evaluate the efficacy and safety of REL-1017 as an adjunctive treatment for MDD

Three pillars for successful clinical execution



Reliance II (study 302) trial design for Adjunctive Treatment of MDD

Reliance II

ADJUNCTIVE THERAPY

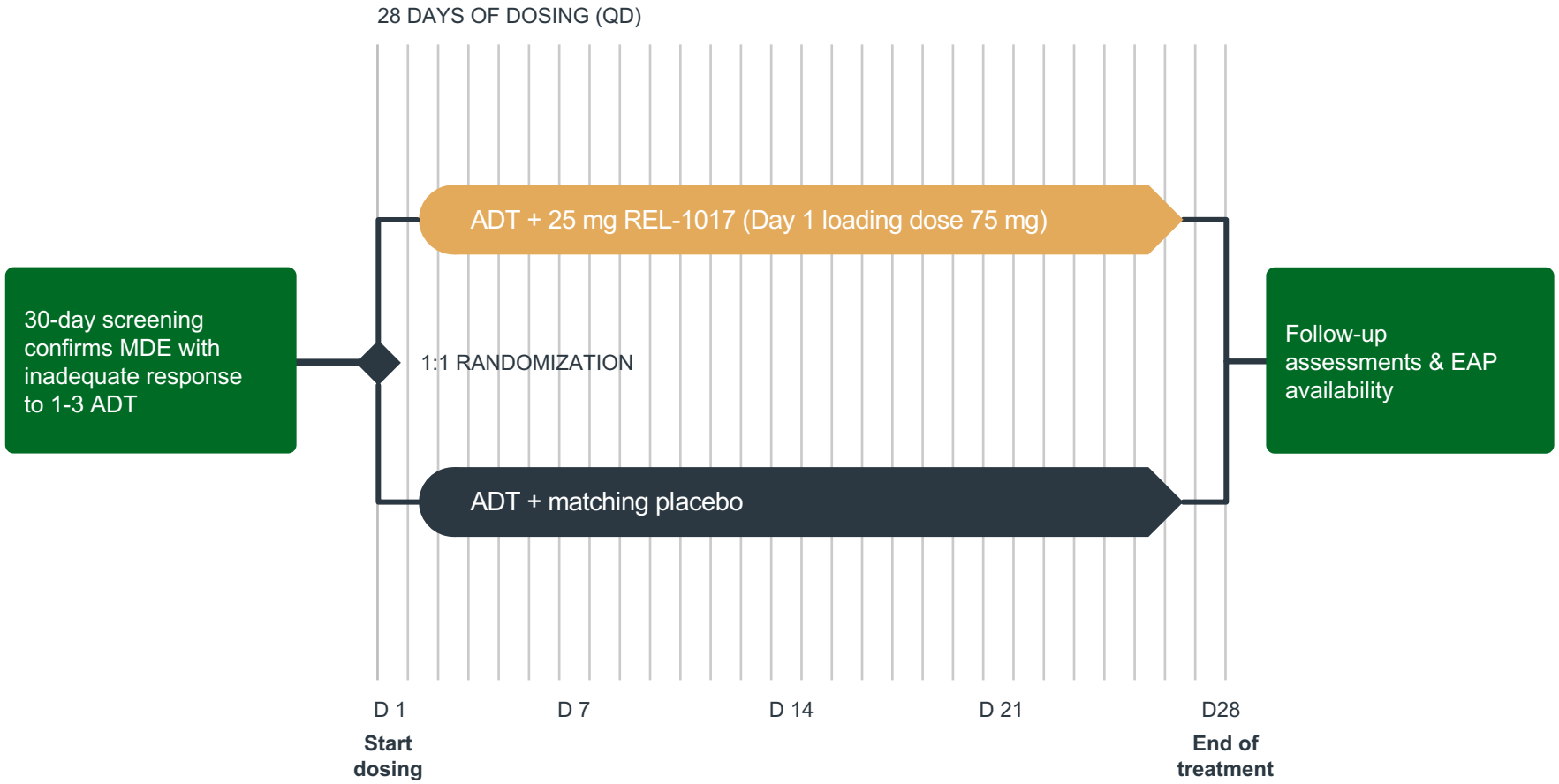
Primary endpoint:

- Change in MADRS at Day 28

Secondary endpoints:

- Change in MADRS score at Day 7
- Change in CGI-S score at Day 28
- Response Rate at Day 28
- Remission Rate at Day 28

Safety and tolerability assessments



MDD = major depressive disorder; MADRS = Montgomery-Asberg Depression Rating Scale; ADT = antidepressant; CGI-S = clinical global impression – severity scale; EAP = expanded access program; MDE = major depressive episode; QD = once daily

Relight (study 304) trial design for Adjunctive Treatment of MDD

Relight

ADJUNCTIVE THERAPY

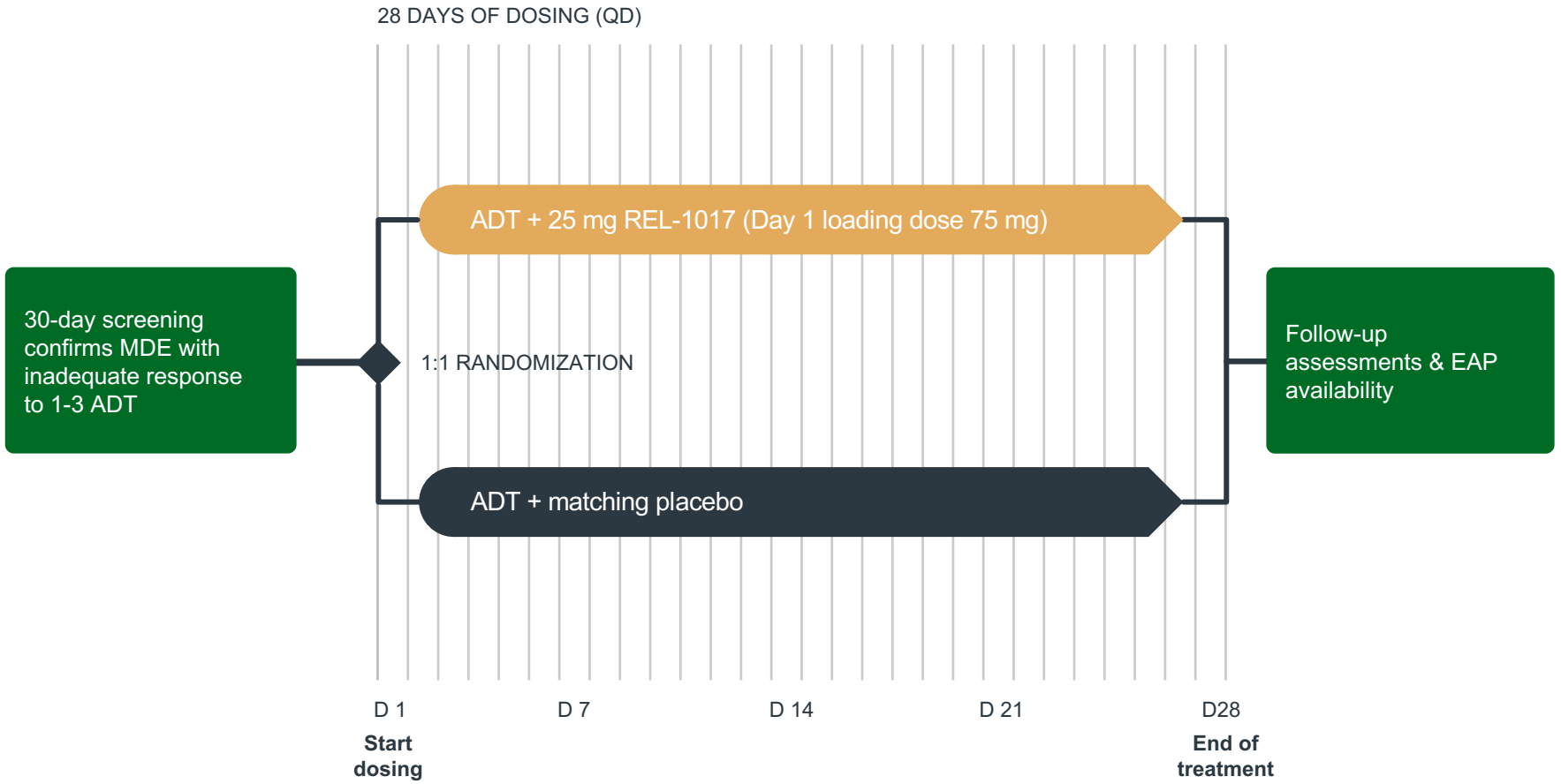
Primary endpoint:

- Change in MADRS at Day 28

Secondary endpoints:

- Change in MADRS score at Day 7
- Change in CGI-S score at Day 28
- Response Rate at Day 28
- Remission Rate at Day 28

Safety and tolerability assessments



MDD = major depressive disorder; MADRS = Montgomery-Asberg Depression Rating Scale; ADT = antidepressant; CGI-S = clinical global impression – severity scale; EAP = expanded access program; MDE = major depressive episode; QD = once daily

Data generated for esmethadone (REL-1017) support efficacy, safety, and tolerability for adjunctive treatment of depression

- Phase 2 trial reached significance p= 0.0122 (25 mg) for the primary endpoint in the intent-to-treat (ITT) analysis
- Reliance I, the first adjunctive Phase 3 trial, showed a 40% response rate (p = 0.044) in the ITT analysis and 3.1 MADRS-points CFB difference compared with placebo (p = 0.0510) in the Per Protocol (PP) analysis
- All studies to date have shown a consistent favorable safety and tolerability profile with no evidence of abuse potential or withdrawal

MADRS = Montgomery-Asberg Depression Rating Scale; CFB = change from baseline

Promising pre-clinical data support advancing MR psilocybin to a clinical program for the treatment for metabolic disorders

MR psilocybin: modified release psilocybin

Promising pre-clinical data support advancing MR psilocybin to a clinical program for the treatment for metabolic disorders

Phase 1 clinical trials to begin in 1H 2024

Reduces liver steatosis and triglycerides in HFHF rodent models

Preliminary data suggest **synergistic effects with semaglutide** in cellular models

Reduces increase in body weight without changing food intake in HFHF models

No psychedelic-like effects at tested dose

Improves glucose tolerance and reduces fasting glucose in HFHF mouse model

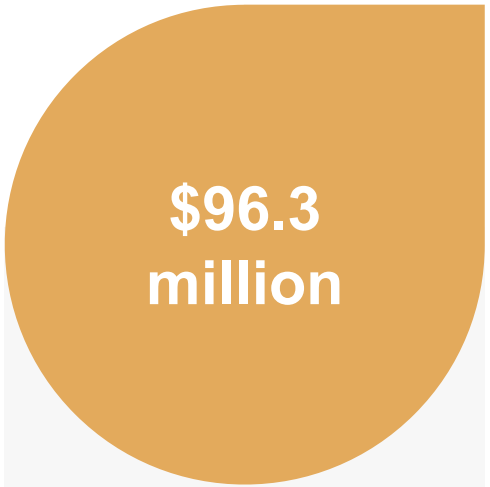
Preserves muscle mass and may reduce sarcopenia in HFHF mouse model

Relmada has a **robust IP portfolio for MR psilocybin**

MR = modified release; HFHF = high-fat high-fructose; IP = intellectual property; CNS: central nervous system

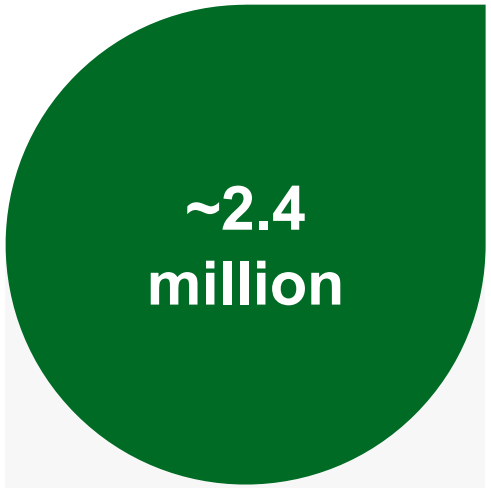
Corporate information

Financial overview



Cash, cash equivalents & short-term investments

As of 12/31/2023

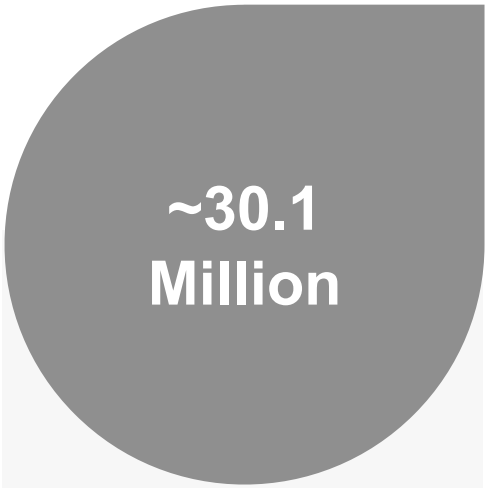


Warrants outstanding

As of 12/31/2023, weighted average exercise price, $20.02

Operating cash burn

Fourth-quarter 2023 (4Q23)



Common shares outstanding*

As of 12/31/2024

*As converted share count of 49.9 MM share as of 12/31/2023

Summary

Lead program focused on CNS diseases and Major Depressive Disorder

- REL-1017 is in Phase 3 trials for major depressive disorder, 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 4-8 weeks to work, and have significant side effects
- Highly experienced clinical team with CNS focused backgrounds and successful track record of advancing programs through NDA approval

Highly compelling opportunity with esmethadone (REL-1017)

- **Phase 3 program underway** with positive efficacy signals and safety data
- 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 estate around REL-1017 with expirations through the mid/late-2030s
- Ongoing Phase 3 trials are operationally improved

Expanding therapeutic profile

- Novel modified release Psilocybin program offers a distinct mechanism of action with compelling pre-clinical data for the potential to treat metabolic diseases
- Phase1 SAD clinical study to commence in 2024
- Robust portfolio of patent applications

CNS= Central Nervous System; MDD = major depressive disorder; MOA = mechanism of action; SAD – single ascending dose

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

Thank you