UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the
Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **February 23, 2022**

RELMADA THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Nevada	**001-39082**	**45-5401931**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

2222 Ponce de Leon Blvd., Floor 3 **Coral Gables, FL**	**33134**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code **+1-786-629-1376**

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of exchange on which registered
Common stock, $0.001 par value per share	**RLMD**	**The NASDAQ Stock Market LLC**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On February 23, 2022, Relmada Therapeutics, Inc. (the "Company"), issued a press release regarding top-line results of its human abuse potential (HAP) study with REL-1017, a novel NMDA receptor (NMDAR) channel blocker and the Company's lead candidate in Phase 3 development for the treatment of major depressive disorder (MDD). The Company also announced that it would conduct a conference call and webcast on February 23, 2022, at 8:30 AM Eastern Time, to discuss the study results. A copy of the press release, including information on accessing the conference call and webcast, is furnished herewith as Exhibit 99.1 and is incorporated herein by reference, and a copy of slides to be presented on the webcast is furnished herewith as Exhibit 99.2 and is incorporated herein by reference.

Item 8.01 Other Events.

On February 23, 2022, the Company updated its corporate presentation, a copy of which is filed herewith as Exhibit 99.3 and is incorporated herein by reference.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	**Description**
99.1	Press Release dated February 23, 2022
99.2	Slide Presentation: Human Abuse Potential (HAP) Study of REL-1017 vs. Ketamine
99.3	Corporate Presentation dated February 23, 2022
104	Cover Page Interactive Data File (formatted as Inline XBRL)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: February 23, 2022

RELMADA THERAPEUTICS, INC.

By: */s/ Sergio Traversa*
Name: Sergio Traversa
Title: Chief Executive Officer

Exhibit 99.1

Relmada Therapeutics Announces Top-Line Results of Study Evaluating REL-1017 vs Ketamine for Abuse Potential

- All doses of REL-1017, including the maximum tolerated dose, demonstrated a statistically significant difference in abuse potential vs. ketamine (p-values <0.05)

- All doses of REL-1017, including the maximum tolerated dose, were statistically equivalent to placebo (p-values <0.05)

- Company to host conference call at 8:30 AM Eastern Time today, February 23, 2022

CORAL GABLES, Fla., February 23, 2022 /PRNewswire/ -- Relmada Therapeutics, Inc. (NASDAQ: RLMD), a late-stage biotechnology company addressing diseases of the central nervous system (CNS), today announced top-line results of the human abuse potential (HAP) study with REL-1017, a novel NMDA receptor (NMDAR) channel blocker and the company's lead candidate in Phase 3 development for the treatment major depressive disorder (MDD).

Top-line results showed that all three doses of REL-1017 (25 mg, 75 mg, and 150 mg, the therapeutic, supratherapeutic and maximum tolerated doses, respectively) tested in recreational drug users, demonstrated a substantial (30 points) and statistically significant difference vs. the active control drug, intravenous ketamine 0.5 mg/kg over 40 minutes, and were statistically equivalent to placebo. The study's primary endpoint was a measure of "likability" with the subjects rating the maximum effect (or Emax) for Drug Liking "at this moment", using a 1-100 bipolar rating scale (known as a visual analog scale or VAS), with 100 as the highest likability, 50 as neutral (placebo-like), and 0 the highest dislike. Consistent results are seen for the secondary endpoints. Results of the primary endpoint are summarized in the table below.

	Placebo	REL-1017 25 mg	REL-1017 75 mg	REL-1017 150 mg	Ketamine 0.5 mg/kg
Mean Emax for Drug Liking	50.9	51.4	54.9	59.2	90.0
P-value for REL-1017 Difference vs ketamine 0.5 mg/Kg over 40 minutes	<0.05	<0.05	<0.05	<0.05	-
P-value for REL-1017 Difference vs. placebo	-	<0.05	<0.05	<0.05	<0.05

"These results demonstrate that REL-1017 strongly differentiates from ketamine and is comparable to placebo for the maximum effect for Drug Liking 'at this moment," said Sergio Traversa, CEO of Relmada Therapeutics. "Importantly, these data are consistent with previously generated results of the REL-1017 vs. oxycodone HAP study, which showed no meaningful abuse potential on the opioid domain. With the ketamine comparative study, we completed the extensive abuse potential testing program in line with the FDA 2017 published guidance. These collective results confirm the previously published data and the DEA statement that esmethadone does not have meaningful abuse potential.

Paolo Manfredi, M.D., Chief Scientific Officer of Relmada said, "We are very satisfied with the results of our second confirmatory HAP study, designed following FDA guidance, as part of the planned New Drug Application for REL-1017 for the treatment of MDD. These data are consistent with our prior oxycodone HAP study and confirm the large body of literature indicating the lack of meaningful abuse potential of REL-1017. There is a significant need for new treatment options for patients suffering from depression, and we continue to believe that REL-1017 has the potential to be a very safe, well tolerated and effective rapid acting antidepressant."

Jack Henningfield, Ph.D., Vice President, Research, Health Policy, and Abuse Liability at Pinney Associates and former Chief of the Clinical Pharmacology Research Branch and the Abuse Potential and Biology of Dependence Assessment Section of the National Institute on Drug Abuse (NIDA), added, "These data show no evidence of meaningful abuse potential of REL-1017 compared to ketamine, including at the maximum tolerated dose with a likability profile comparable to placebo. These ketamine data and the previously released oxycodone data are consistent with HAP study results of other approved products that are unscheduled or in Schedule V."

Conference Call and Webcast Information

Relmada will host a conference call and webcast presentation today, February 23, 2022, at 8:30 AM Eastern Time to discuss the study results, which can be accessed with the information below:

Wednesday, February 23 at 8:30 AM ET

Domestic: 1-866-409-1555
International: 1-313-209-4906
Conference ID: 1751730
Webcast: https://viavid.webcasts.com/starthere.jsp?ei=1532206&tp_key=c85c506a7e

The subsequent archived recording will be available on the Investors section of the Relmada website at www.relmada.com.

Background

REL-1017 (which is also known as esmethadone, dextromethadone, or d-methadone), is the opioid-inactive, dextro- or right-side isomer of racemic methadone. Prior preclinical and clinical findings have indicated that the dextro-isomer, REL-1017, lacks the addiction liability and respiratory depressant effects of its parent molecule. In contrast, levomethadone, the left-side isomer, is an opioid agonist and is entirely responsible for the analgesic activity of the parent molecule.[1]

HAP studies are conducted to evaluate the likelihood that a medicine affecting the central nervous system may be abused by patients or the general public. The study comparing REL-1017 to ketamine is the second of two clinical trials to assess abuse potential per FDA guidance as part of the planned REL-1017 NDA for the treatment of MDD.

The scheduling of a drug depends on the analysis of several parameters (receptor studies, animal studies, human studies, history of abuse). These parameters are generally referred to as the "eight factor analysis". All tested parameters suggest a lack of any meaningful abuse potential for REL-1017 and are fully aligned with the 2019 DEA statement on methadone.[1]

About The Human Abuse Potential Study for REL-1017 vs. Ketamine

The study was a single-dose, Phase 1, randomized, double-blind, double-dummy, active- and placebo-controlled, six-way crossover study to assess the abuse potential of REL-1017 relative to ketamine and placebo in healthy experienced recreational drug users. Ketamine, the active control, was administered intravenously at the dose of 0.5 mg/kg, a standard dose in HAP studies. A total of 51 subjects were enrolled and fulfilled criteria for the predefined statistical analysis.

Once available, the full data set and detailed results will be submitted to the FDA and for presentation at future scientific conferences and publication in peer-reviewed journals.

About REL-1017

REL-1017, a new chemical entity (NCE) and novel NMDA receptor (NMDAR) channel blocker that preferentially targets hyperactive channels while maintaining physiological glutamatergic neurotransmission, is currently in late-stage development for the treatment of MDD in adjunctive and monotherapy Phase 3 studies. The ongoing RELIANCE Phase 3 Clinical Research Program is designed to evaluate the potential for REL-1017 as a rapid-acting, oral, once-daily antidepressant treatment. In a Phase 2 trial, REL-1017 demonstrated rapid, robust, and sustained antidepressant effects with statistically significant improvements compared to placebo in tested measures of depression. The Phase 2 study also showed a favorable safety, tolerability, and pharmacokinetics profile of REL-1017, consistent with observed in previously completed Phase 1 studies.

About Relmada Therapeutics, Inc.

Relmada Therapeutics is a late-stage biotechnology company addressing diseases of the central nervous system (CNS), with a focus on major depressive disorder (MDD). Relmada's experienced and dedicated team is committed to making a difference in the lives of patients and their families. Relmada's lead program, REL-1017, is a new chemical entity (NCE) and novel NMDA receptor (NMDAR) channel blocker that preferentially targets hyperactive channels while maintaining physiological glutamatergic neurotransmission. REL-1017 has entered late-stage development as an adjunctive treatment and monotherapy treatment for MDD in adults. In addition, Relmada is advancing a clinical-stage program in neurodegenerative diseases based on psilocybin and select derivative molecules. Learn more at www.relmada.com.

Forward-Looking Statements

The Private Securities Litigation Reform Act of 1995 provides a safe harbor for forward-looking statements made by us or on our behalf. This press release contains statements which constitute "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, including but not limited to statements regarding the effectiveness of REL-1017, or its potential approval by the FDA, for treatment of MDD or any other indication, or of the safety, tolerability, effectiveness or potential for approval of psilocybin or derivative molecules for any indication. Any statement that is not historical in nature is a forward-looking statement. These may, but will not always, be identified by the use of words and phrases such as "expects," "anticipates," "believes," "will," "will likely result," "will continue," "plans to," "potential," "promising," and similar expressions. These statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and assumptions that could cause actual results to differ materially from those described in the forward-looking statements, including the risk factors described under the heading "Risk Factors" set forth in the Company's reports filed with the SEC from time to time. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Relmada undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Readers are cautioned that it is not possible to predict or identify all the risks, uncertainties and other factors that may affect future results and that the risks described herein should not be a complete list.

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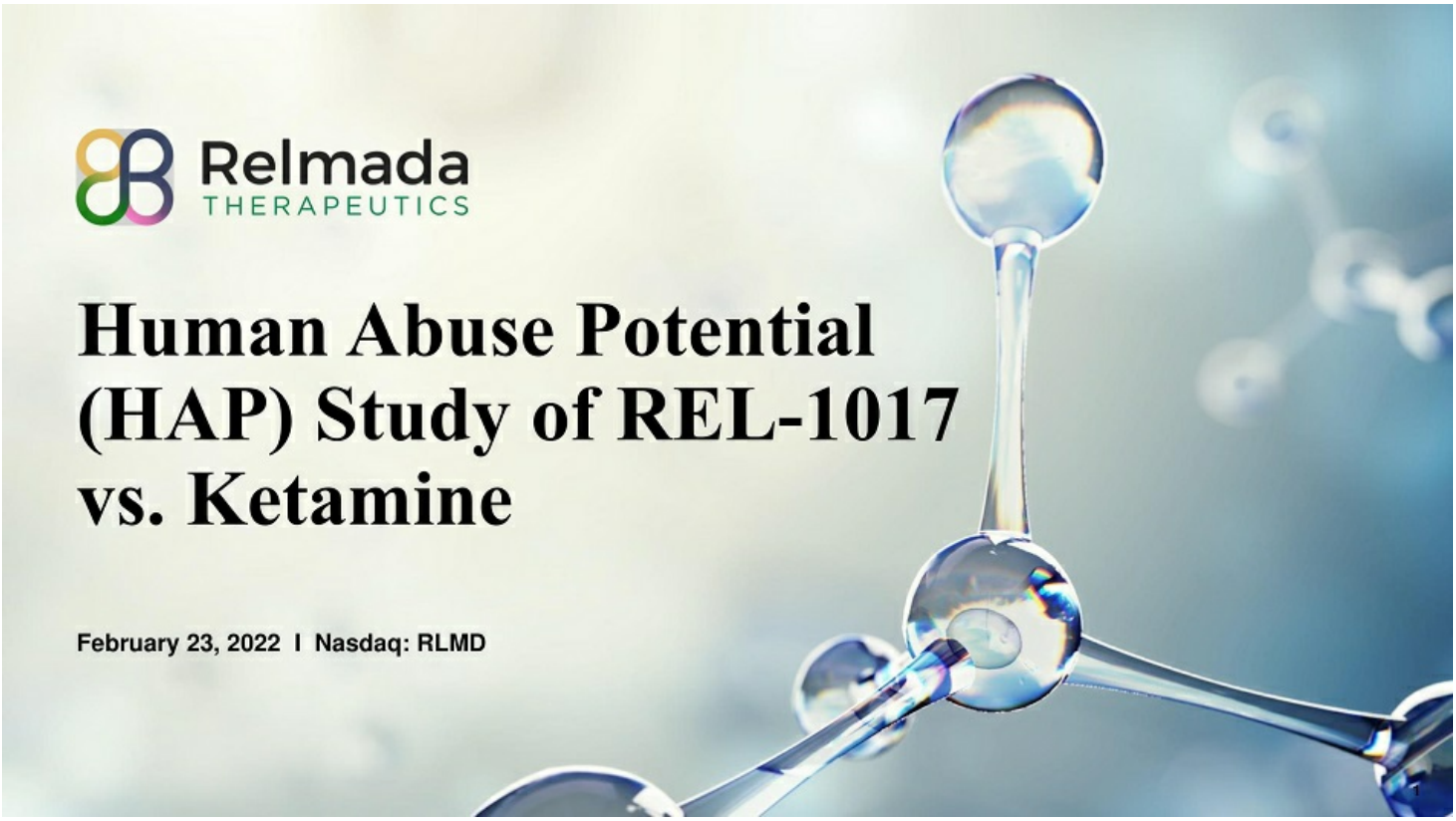
1. DEA: Diversion Control Division. December 2019. Accessed May 2020.https://www.deadiversion.usdoj.gov/drug_chem_info/methadone/methadone.pdf



Disclosures

Certain statements contained in this presentation or in other documents of Relmada Therapeutics, Inc. (the "Company"), along with certain statements that may be made by management of the Company orally in presenting this material, may contain "forward-looking statements." These statements can be identified by the fact that they do not relate strictly to historic or current facts. They use words such as "estimate," "expect," "intend," "believe," "plan," "anticipate," "projected" and other words and terms of similar meaning in connection with any discussion of future operating or financial performance or condition. These statements are based upon the current beliefs and expectations of the Company's management and are subject to significant risks and uncertainties. Statements regarding future action, future performance and/or future results, those relating to the timing for completion, and results of, scheduled or additional clinical trials and the FDA's or other regulatory review and/or approval and commercial launch and sales results (if any) of the Company's formulations and products and regulatory filings related to the same may differ from those set forth in the forward-looking statements.

Because actual results are affected by these and other potential risks, contingencies and uncertainties, the Company cautions investors that actual results may differ materially from those expressed or implied in any forward-looking statement. It is not possible to predict or identify all such risks, contingencies and uncertainties. The Company identifies some of these factors in its Securities and Exchange Commission ("SEC") filings on Forms 10-K, 10-Q and 8-K, and investors are advised to consult the Company's filings for a more complete listing of risk factors, contingencies and uncertainties affecting the Company and its business and financial performance.

The Company assumes no obligation to update forward-looking statements as circumstances change. Investors are advised to consult further disclosures that the Company makes or has made on related subjects in the Company's Form 10-K, 10-Q and 8-K reports.

Human Abuse Potential (HAP) Study of REL-1017 vs Ketamine

Top-Line Results – Conference Call & Webcast Agenda

Introduction	**Sergio Traversa,** Chief Executive Officer of Relmada
Study Design & Top-Line Results	**Jack Henningfield, Ph.D.,** Vice President, Research, Health Policy, and Abuse Liability at Pinney Associates; former Chief of the Clinical Pharmacology Research Branch, and the Abuse Potential and Biology of Dependence Assessment Section of the National Institute on Drug Abuse (NIDA); four decades experience in HAP assessment beginning at Johns Hopkins School of Medicine and NIDA

Human Abuse Potential (HAP) Study of REL-1017 vs. IV Ketamine Summary

Primary endpoint, Drug Liking (Emax) Completer Population

- All REL-1017 doses, including 150 mg (6x therapeutic dose and MTD), were statistically different from IV ketamine 0.5 mg/Kg ($p<0.05$)
- All REL-1017 doses including, 150 mg (6x therapeutic dose and MTD), were statistically equivalent to placebo ($p<0.05$)
- Key secondary endpoint results were consistent with primary endpoint

MTD = Maximum tolerated dose; IV = Intravenous.
Source: Relmada data on file.

Primary Endpoint – "Drug Liking at This Moment" [Emax] REL-1017 vs. IV Ketamine, Completer Population

Summary of Drug Liking (at this moment) VAS[1]

Statistic Parameter	Placebo	REL-1017 25 mg	REL-1017 75 mg	REL-1017 150 mg	Ketamine 0.5 mg/Kg
n	51	51	51	51	51
Mean	**50.9**	**51.4**	**54.9**	**59.2**	**90**
Median	**50**	**50**	**50**	**51**	**100**

All REL-1017 doses are statistically different from IV ketamine. All REL-1017 doses are statistically equivalent to placebo (p<0.05) . Consistent results are seen for the secondary endpoints.

VAS = Visual Analogue Scale; IV = Intravenous
1.) The primary endpoint for the study was the subject's rating of the maximum effect (or Emax) for Drug Liking ("at the moment"), using a 1=100 rating scale (known as a visual analog scale or VAS), where a score of 0 represents 'strong disliking,' a score of 100 represents 'strong liking,' and a score of 50 represents 'neither like nor dislike' (neutral point). The question text is 'At this moment, my liking for this drug is.'
Source: Relmada data on file.

Primary Endpoint – "Maximum Drug Liking at This Moment" [Emax] REL-1017 vs. IV Ketamine, Completer Population

Statistical Analysis

REL-1017 vs. Ketamine

Treatment 1	Treatment 2	P-value
Ketamine 0.5 mg/ Kg	Placebo	**<0.05**
Ketamine 0.5 mg/ Kg	REL-1017 25 mg	**<0.05**
Ketamine 0.5 mg/ Kg	REL-1017 75 mg	**<0.05**
Ketamine 0.5 mg/ Kg	REL-1017 150 mg	**<0.05**

REL-1017 vs. Placebo

Treatment 1	Treatment 2	P-value
REL-1017 25 mg	Placebo	**<0.05**
REL-1017 75 mg	Placebo	**<0.05**
REL-1017 150 mg	Placebo	**<0.05**

All REL-1017 doses are statistically different from IV ketamine. All REL-1017 doses are statistically equivalent to placebo (p<0.05) . Consistent results are seen for the secondary endpoints.

SD = Standard deviation; SE = Standard error; IV = Intravenous
Source: Relmada data on file.

US DEA July 2019 Statement on esmethadone

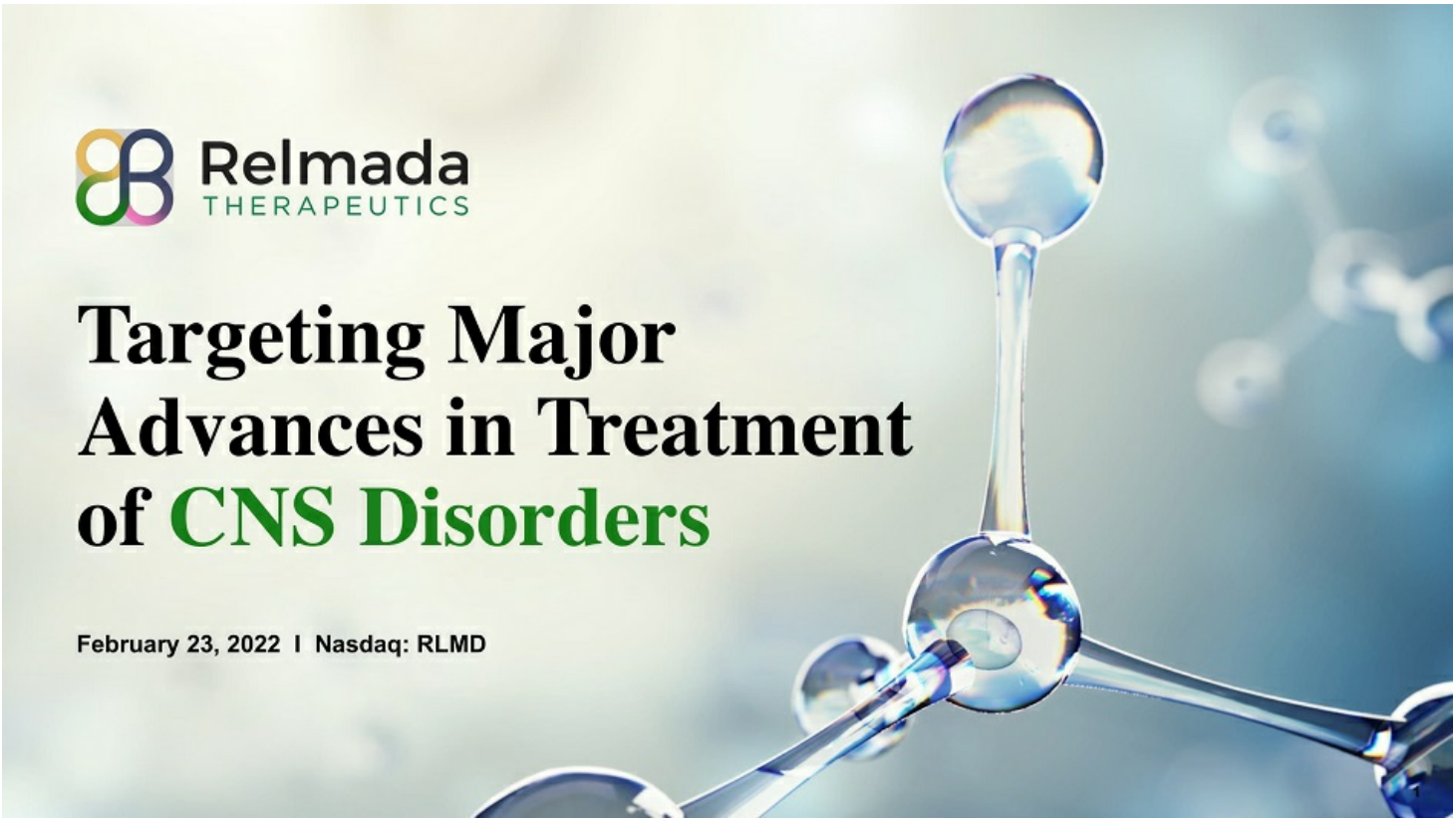
"The ***d*-isomer lacks significant respiratory depressant action and addiction liability..."**

- DEA Statement July 2019[1]

1.US DEA Statement on Methadone 2019 https://www.deadiversion.usdoj.gov/drug_chem_info/methadone/methadone.pdf#search=methadone

Q&A


Relmada
THERAPEUTICS
Thank You



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Because actual results are affected by these and other potential risks, contingencies and uncertainties, the Company cautions investors that actual results may differ materially from those expressed or implied in any forward-looking statement. It is not possible to predict or identify all such risks, contingencies and uncertainties. The Company identifies some of these factors in its Securities and Exchange Commission ("SEC") filings on Forms 10-K, 10-Q and 8-K, and investors are advised to consult the Company's filings for a more complete listing of risk factors, contingencies and uncertainties affecting the Company and its business and financial performance.

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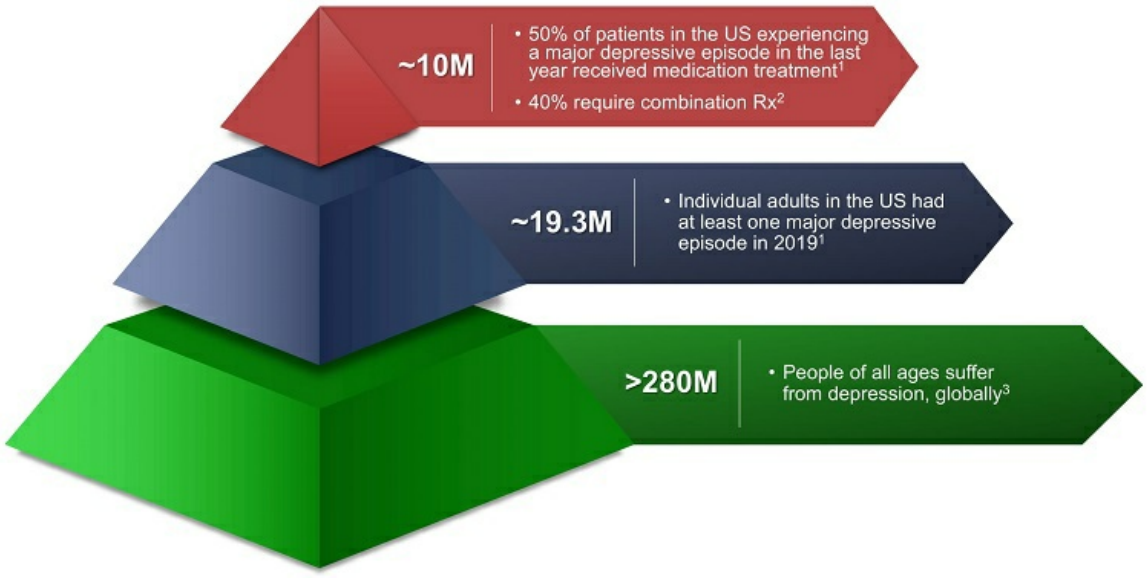
Investment Highlights

- CNS Focus with Lead Program in Major Depressive Disorder (MDD)
- Highly Compelling Opportunity in REL-1017
- Multiple Catalysts Expected Over Next 18 Months

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

Major Depressive Disorder & REL-1017

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[1]

Safety & Tolerability Challenges

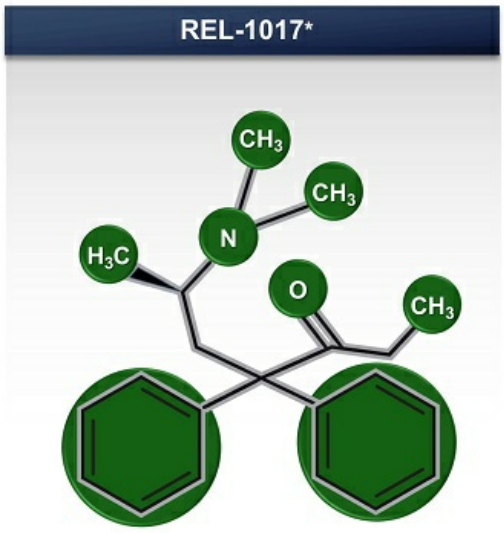
Side effects of atypical antipsychotics approved as adjunctive treatments for MDD include tardive dyskinesia, metabolic syndrome, cognitive impairment and stroke[2]

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; 2. US Prescribing Information, brexpiprazole, quetiapine, aripiprazole

Unique Profile of REL-1017

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]
- Available clinical data demonstrated:
  - Robust, rapid, and sustained statistically significant antidepressant effects on all tested scales[2]
  - Rapid onset: significant efficacy effects by Day 4[2]
  - Favorable safety and tolerability profile consistent across Phases 1 & 2 studies: no opioid and no psychotomimetic adverse events[2,3] and no metabolic side effects
  - Orally administered, once-daily tablet



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. Esmethadone (REL-1017) Reduces Glutamate-Induced Currents in NMDA Receptors With the GluN2D Subunit. Biological Psychiatry, 89(9), S198-S199. 2. 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. Poster presented at: American Psychiatric Association Annual Meeting. 3. Bernstein, et al. *2019 Journal of Clinical Psychopharmacology;*

REL-1017 Ph 1 & 2 Efficacy & Safety Data

Phase 1 SAD & MAD Studies for REL-1017, Data Published 2019

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 clinically significant opioid or NMDA AESI signal

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

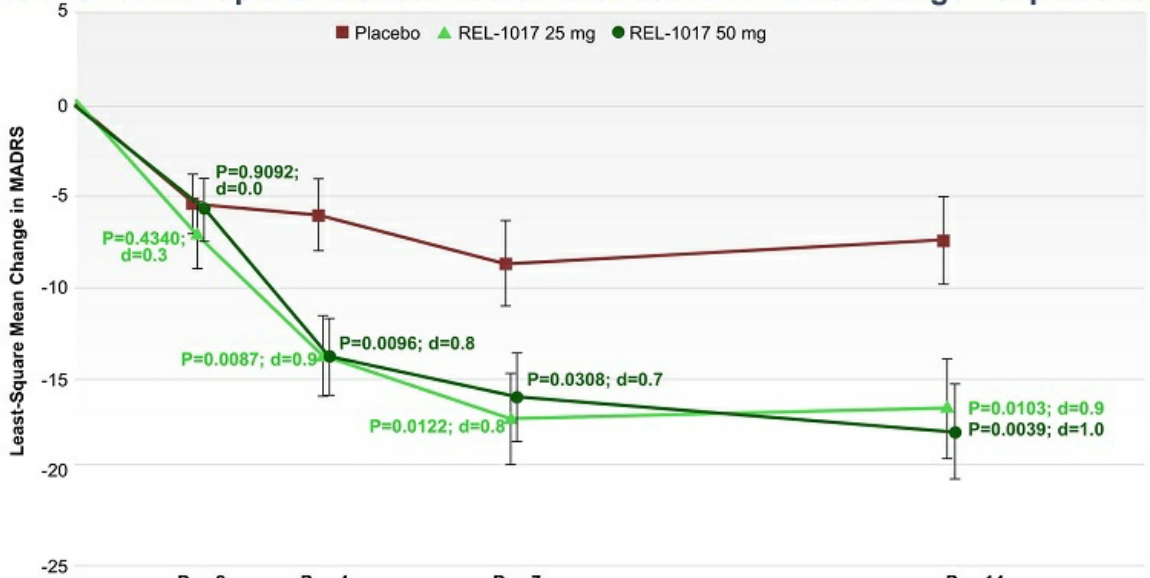
- The highest dose studied, 75mg daily, was well tolerated
- Favorable safety and tolerability profile
- No clinically significant opioid or NMDA AESI signal

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

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

Phase 2 Study REL-1017: Primary Efficacy Endpoint

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

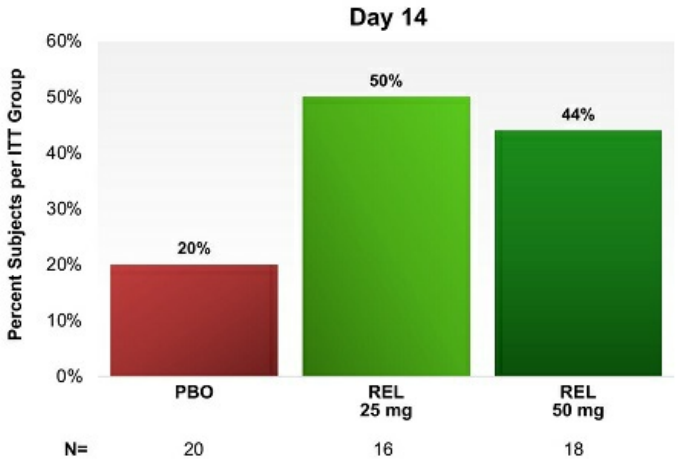


		Day 2	Day 4	Day 7	Day 14
Δ MADRS vs Placebo	25 mg	7.9	8.7		9.4
	50 mg	7.6	7.2		10.4

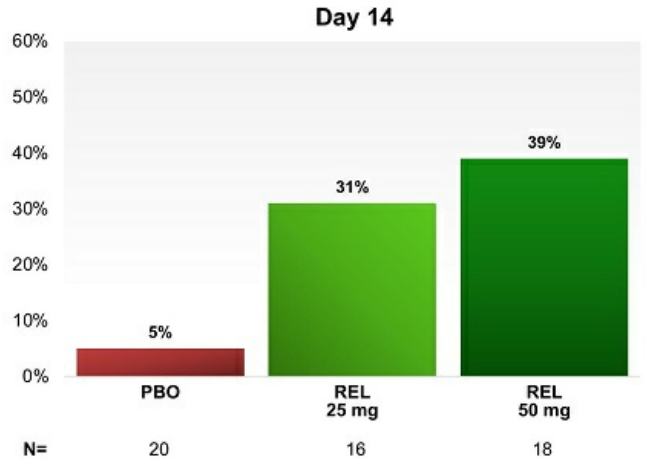
MADRS = Montgomery-Asberg Depression Rating Scale

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
MADRS=Montgomery-Asberg Depression Rating Scale
Source: Relmada Data on File

Safety & Tolerability Findings from Phase 2

Safety & Tolerability Comparable to Placebo

- Only Mild and Moderate transient AEs – no SAEs
- No increased prevalence of specifically relevant organ group AEs in treatment groups vs placebo
- No evidence of opiate effects or withdrawal symptoms in treatment groups vs placebo
- No evidence of treatment-induced dissociative or psychotomimetic symptoms in the treatment groups vs placebo

AE = adverse event; SAE = serious adverse event
Source: 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. Poster presented at: American Psychiatric Association Annual Meeting

REL-1017 Phase 2 Study Safety: Treatment Emergent Adverse Events

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

Variable	Placebo (N = 23)		REL-1017 25 mg (N=19)		REL-1017 50 mg (N=21)		All Patients (N = 62)	
	N	%	N	%	N	%	N	%
Patients with a serious adverse event	0	0.0	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	0	0.0
Patients with at least one adverse event	12	54.5	9	47.4	15	71.4	36	58.1
Treatment-emergent adverse events occurring in three or more patients								
Constipation	3	13.6	1	5.3	3	14.3	7	11.3
Nausea	2	9.1	1	5.3	2	9.5	5	8.1
Diarrhea	3	13.6	0	0.0	0	0.0	3	4.8
Headache	3	13.6	2	10.5	3	14.3	8	12.9
Somnolence	2	9.1	1	5.3	1	4.8	4	6.5
Dizziness	1	4.5	1	5.3	1	4.8	3	4.8
Back Pain	0	0.0	1	5.3	2	9.5	3	4.8

Source: Fava et al. 2021 *American Journal of Psychiatry*
*Treatment-emergent adverse event was defined as an adverse event that started or worsened after treatment with the trial drug

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Human Abuse Potential (HAP) Studies:

REL-1017 vs. Oxycodone
REL-1017 vs. Ketamine

Human Abuse Potential (HAP) Studies of REL-1017

HAP Studies, per FDA's *Guidance for Industry*[1]:

- Typically required for CNS-active drugs
- Should be conducted in experienced recreational drug users
- Should use standardized questionnaires at specific timepoints
- Positive controls should be FDA-approved controlled substances pharmacologically similar to the test drug
- HAP studies are included in the New Drug Application (NDA) and used in determination of drug scheduling

The HAP Program for REL-1017 includes two studies:

- Mu Opioid Agonist HAP
  - Oxycodone as active control
  - **Completed in July 2021**
- NMDA Receptor Antagonist HAP
  - Ketamine as active control
  - **Completed in February 2022**

1 Assessment of Abuse Potential of Drugs Guidance for Industry 2017 https://www.fda.gov/media/116739/download

Human Abuse Potential (HAP) Studies of REL-1017 vs. Oxycodone Primary endpoint, Drug Liking (Emax) Completer Population*

- All REL-1017 doses including 150 mg (6x therapeutic dose and MTD) were statistically different from oxycodone 40 mg ($p<0.05$)
- All REL-1017 doses including 150 mg (6x therapeutic dose and MTD) were statistically equivalent to placebo in both studies ($p<0.05$)
- Key secondary endpoint results were consistent with primary endpoint

*Statistical analysis were performed on the Completer Population which includes all patients who completed all treatments. Previously reported results for the oxycodone REL-1017-124 study analyzed the Modified Completer Population (44 subjects) instead of the Completer Population (47 patients).

MTD = Maximum tolerated dose; IV = Intravenous.
Source: Relmada data on file.

Primary Endpoint – "Drug Liking at This Moment" [Emax] REL-1017 vs. Oxycodone, Completer Population*

Statistic Parameter	Placebo	REL-1017 25 mg	REL-1017 75 mg	REL-1017 150 mg	Oxycodone 40 mg
n	47	47	47	47	47
Mean	**52.7**	**54.2**	**58.7**	**64.9**	**83.2**
Median	**50**	**50**	**50**	**58**	**85**
SD	6.52	10.35	15.82	16.58	16.57
SE	0.95	1.51	2.31	2.42	2.42

Statistical Analysis

Treatment 1	Treatment 2	P-value
Oxycodone 40 mg	Placebo	**<0.001**
Oxycodone 40 mg	REL-1017 25 mg	**<0.001**
Oxycodone 40 mg	REL-1017 75 mg	**<0.001**
Oxycodone 40 mg	REL-1017 150 mg	**<0.001**

All REL-1017 doses are statistically different from oxycodone. All REL-1017 doses are statistically equivalent to placebo (p<0.05). Consistent results were seen for the secondary endpoints.

* Previously reported results for the oxycodone REL-1017-124 study analyzed the Modified Completer Population (44 subjects) instead of the Completer Population (47 patients).

SD = Standard Deviation; SE = Standard Error
Source: Relmada data on file.

Human Abuse Potential (HAP) Studies of REL-1017 vs. IV Ketamine, Primary endpoint, Drug Liking (Emax) Completer Population*

- All REL-1017 doses including 150 mg (6x therapeutic dose and MTD) were statistically different from IV ketamine 0.5 mg/Kg (p<0.05)
- All REL-1017 doses including 150 mg (6x therapeutic dose and MTD) were statistically equivalent to placebo in both studies (p<0.05)
- Key secondary endpoint results were consistent with primary endpoint

*Statistical analysis was performed on the Completer Population which includes all patients who completed all treatments.

MTD = Maximum tolerated dose; IV = Intravenous,
Source: Relmada data on file.

Primary Endpoint – "Drug Liking at This Moment" [Emax] REL-1017 vs. IV Ketamine, Completer Population

Statistic Parameter	Placebo	REL-1017 25 mg	REL-1017 75 mg	REL-1017 150 mg	Ketamine 0.5mg/Kg
n	51	51	51	51	51
Mean	**50.9**	**51.4**	**54.9**	**59.2**	**90**
Median	**50**	**50**	**50**	**51**	**100**
SD	2.23	3.28	9.58	14.38	14.52
SE	0.31	0.46	1.34	2.01	2.03

Statistical Analysis

Treatment 1	Treatment 2	P-value
Ketamine 0.5 mg/ Kg	Placebo	**<0.001**
Ketamine 0.5 mg/ Kg	REL-1017 25 mg	**<0.001**
Ketamine 0.5 mg/ Kg	REL-1017 75 mg	**<0.001**
Ketamine 0.5 mg/ Kg	REL-1017 150 mg	**<0.001**

All REL-1017 doses are statistically different from ketamine. All REL-1017 doses are statistically equivalent to placebo ($p<0.05$). Consistent results were seen for the secondary endpoints.

SD = Standard Deviation; SE = Standard Error; IV = intravenous
Source: Relmada data on file.

These results support the DEA conclusion that REL-1017 has no meaningful abuse liability

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

US Drug Enforcement Administration
December 2019[1]

1.US DEA Statement on Methadone, December 2019 https://www.deadiversion.usdoj.gov/drug_chem_info/methadone/methadone.pdf#search=methadone last access February 2022

RELIANCE: The Phase 3 Program for REL-1017

REL-1017 Phase 3 Program for the Treatment of MDD

Reliance I
Reliance II
	Two sister two-arm, placebo-controlled pivotal studies as adjunctive treatment for MDD:
	• In MDD patients with inadequate response to 1-3 ADT (n= ~364 per study)
	• 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	**Two-arm, placebo-controlled pivotal study as a monotherapy treatment for MDD:**
	• In MDD patients with ≤ 1 prior use of ADT for current MDE (n=~364)
	• Primary Endpoint: Change from baseline 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

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

Pivotal Phase 3 Trial Design for Adjunctive Therapy

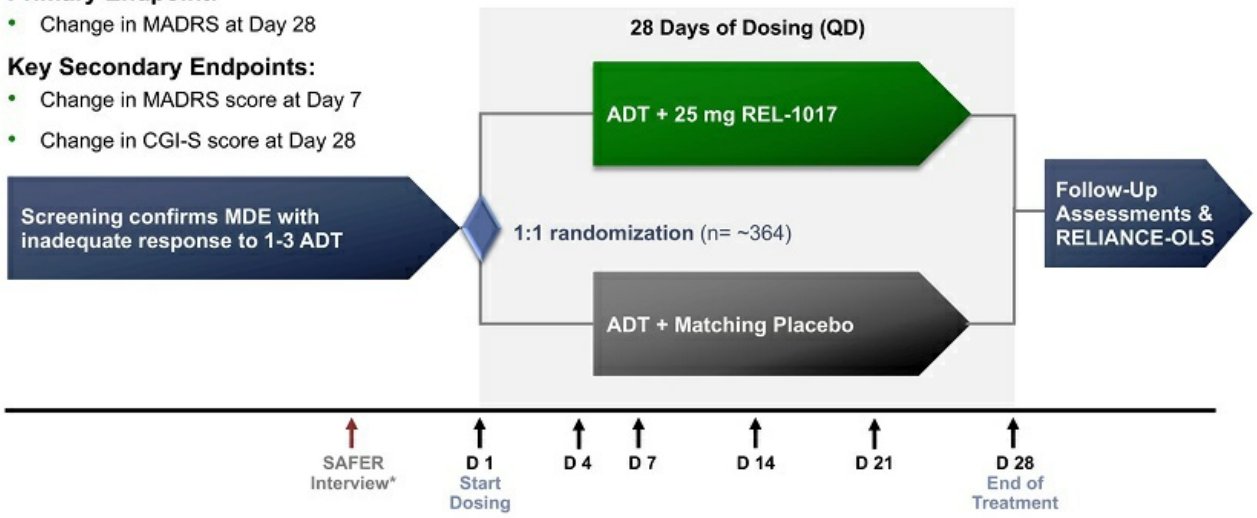
Reliance I
Reliance II

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.

Pivotal Phase 3 Trial Design for Monotherapy

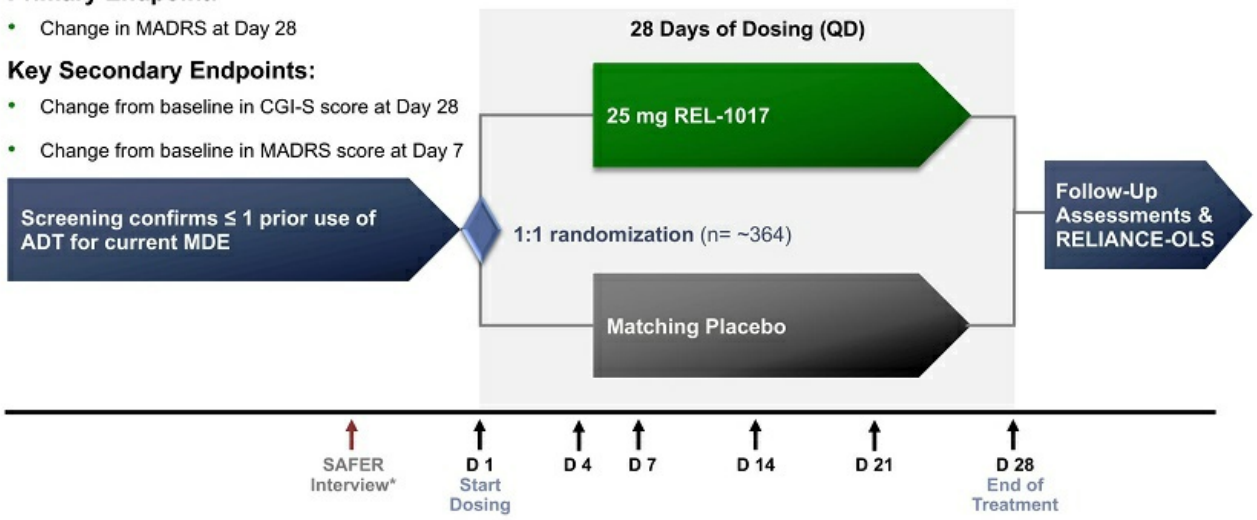
Reliance III

Primary Endpoint:

- Change in MADRS at Day 28

Key Secondary Endpoints:

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



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.

Relmada Development Programs & Timeline*

Program	4Q 21	1Q 22	2Q 22	3Q 22	4Q 22
REL-1017	Human Abuse Potential vs. Ketamine				
	RELIANCE-III: MDD Monotherapy				
	RELIANCE I: 1st Pivotal Adjunctive MDD trial				
	RELIANCE II: 2nd Pivotal Adjunctive MDD trial				
	RELIANCE-OLS: Long-Term, Open-Label Study in MDD				

MDD = Major Depressive Disorder; OLS = Open Label Study
*Subject to FDA feedback **Our fiscal year end is December 31. The periods referred to in this slide are calendar years and quarters

Neuroplastogen™ Program

We have a pipeline of molecules with neural plasticity modulating activity for the treatment of CNS disorders

Novel esmethadone derivatives

We have synthesized a series of novel esmethadone derivatives with NMDAR regulating activity. We are in the process of selecting the most promising candidates for advancing their development in the treatment of CNS disorders

Novel psilocybin formulation and novel psilocybin derivatives

We are developing a novel psilocybin formulation and we are synthetizing psilocybin derivatives with promising activity for the treatment of CNS disorders

CNS = Central Nervous System; NMDAR = N-methyl-D-aspartate receptor

Corporate Information

Financial Overview

* Does not include $162.2 million net proceeds from an equity offering which closed on 12/14/2021
**As converted share count of 25.8 MM share as of 9/30/2021 and does not include 10.1 million shares from an equity offering which closed on 12/14/2021

Investment Highlights

Focus on CNS diseases and Lead Program in Major Depressive Disorder (MDD)

- REL-1017, lead candidate, is in Phase 3 for depression, a leading cause of disability worldwide[1]
- CNS focus, with expertise in developing novel therapeutics that show potential for neuroplasticity
- 50%–66% of patients with depression do not fully recover on an antidepressant medication[2]
- Standard anti-depressants can take 2-8 weeks to work and have significant side-effects

Highly Compelling Lead Product Opportunity in REL-1017

- Novel MOA with successful Phase 2 trial in adjunctive MDD that showed statistically significant, robust, rapid, and sustained anti-depressant effects with favorable safety and tolerability profile[3]
- **Phase 3 program underway** following successful end of Phase 2 Meeting with the FDA
- Fast track designation from FDA
- Strong intellectual property position around REL-1017 with expirations through the mid/late-2030s

Key Catalysts Expected Over Next 3-18 Months

- 2Q22 – Completion of the monotherapy MDD trial
- 2H22 – Completion of RELIANCE I and RELIANCE II adjunctive MDD trials
- 2H22 – Completion of RELIANCE – OLS (Long-term, Open-label study in MDD)

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. Poster presented at: American Psychiatric Association Annual Meeting