Stanford
MEDICINE

Novel Agents in the Treatment of Depression

Charles DeBattista, MD
Professor of Psychiatry and Behavioral Sciences
Stanford University School of Medicine

Disclosures

- Research Support: Biolite, Compass, Jannsen, PCORI, NIMH, Relmada, Sage
- Consultant: Sage,Alkermes, Corcept, AbbVie Genentech

Stanford MEDICINE

Limitations of Current Antidepressants

- Many patients fail to respond adequately
- Side effects of currently available antidepressants: wt gain, sexual side effects, etc…
- Take 1-2 months to work

Stanford MEDICINE

Novel Agents in Late Stage Development

- Brexanolone/ Zuranolone
- Desmethadone
- Axsome-05

Stanford MEDICINE

Brexanalone

- Allopregnanalone: Progesterone derived neurosteroid
- Approved in Post Partum Depression
- Given by IV over 60 hours (in-home nurse or infusion center
- 14-20 point drop in HamD at 60 hours

Stanford MEDICINE

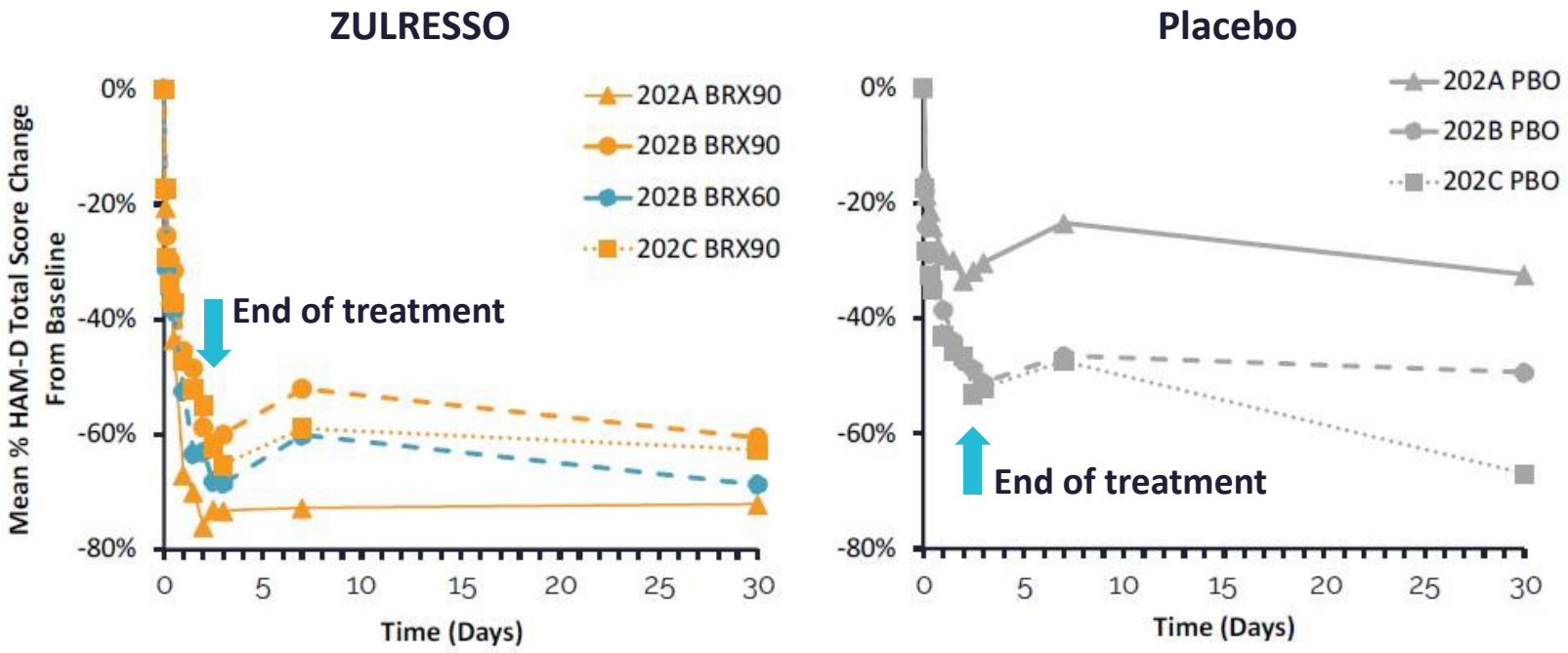
Phase III Brexanalone Studes in PPD

- 2 RCTs N=138 / N=108
- End pt at 60 hours on HamD
- Brx60> Plb p=0.0013 Brx90>Plb p=0.016
- 50% remission and 74-81% response rate
- Most responses sustained at day 30
- AES; HA, dizziness, somnolence

Stanford MEDICINE

ZULRESSO™ (brexanolone injection) in PPD

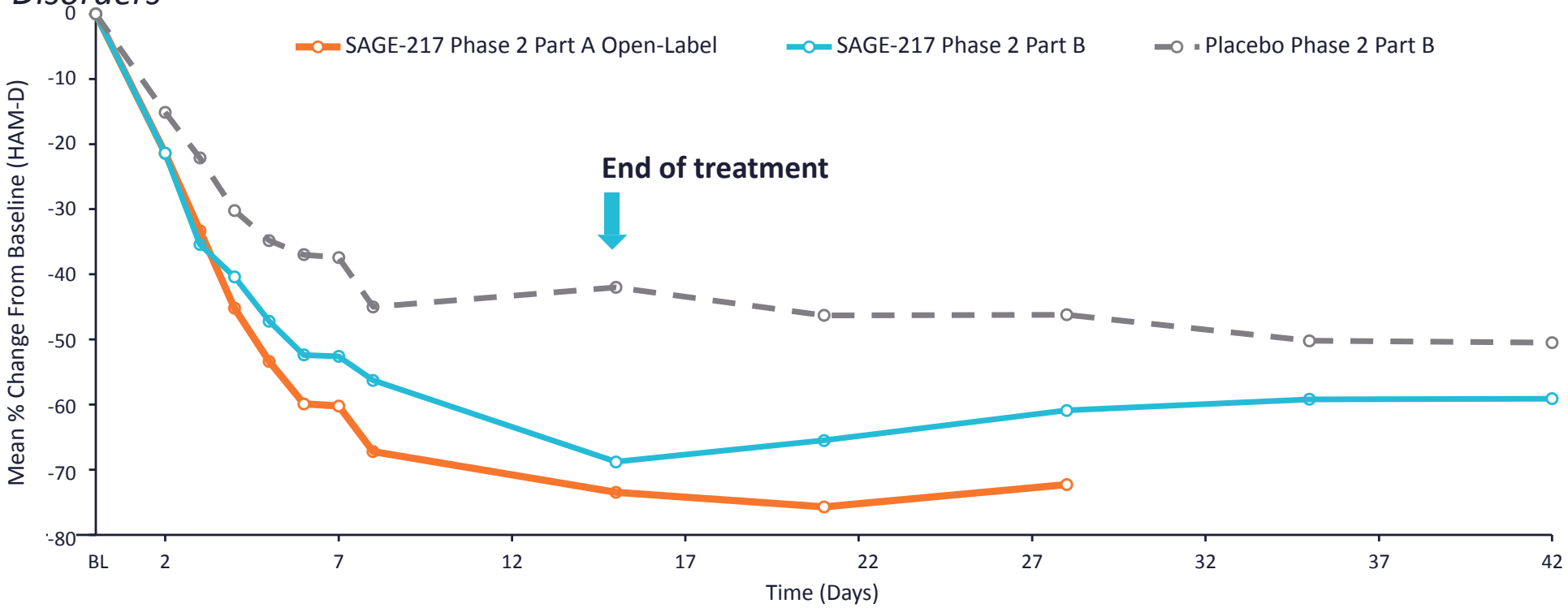
Consistent Rapid Antidepressant Effect in Three Placebo-Controlled Trials



ZULRESSO™ was generally well tolerated in all three studies. The most common AEs were headache, somnolence/sedation and dizziness/vertigo. The most common adverse events leading to dose reduction or interruption were related to sedation or the infusion site.

SAGE-217: Potential 1st Line Treatment for MDD

Positive Placebo-Controlled Results Demonstrate Potential in Depressive Disorders



SAGE-217 was generally well-tolerated in both studies. The most common adverse events in both trials included headache, dizziness, nausea and somnolence, and in Part A, also included myalgia.

Zuranolone LS Mean Change from Baseline in HAMD-17 Oral Administration

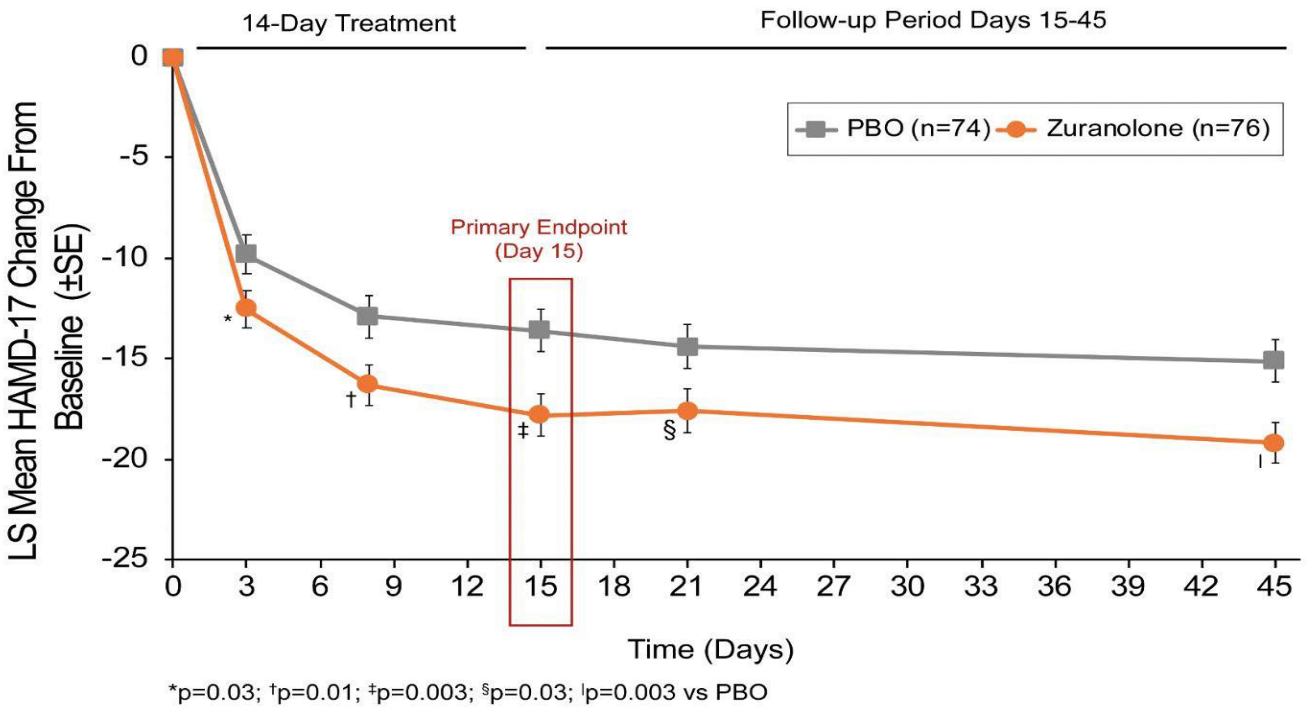


Figure 2 Legend: Treatment with zuranolone achieved the primary endpoint of a significant change from baseline HAMD-17 total score at Day 15 compared with PBO. HAMD-17 total score at timepoints other than Day 15 were secondary endpoints, for which the zuranolone group also showed significant improvements compared with the PBO group.

Abbreviations: HAMD-17, the 17-item Hamilton Rating Scale for Depression; PBO, placebo.

***Data from Sage Therapeutics Manuscript under review** Deligiannidis K et al

Stanford MEDICINE

Opiate like Agents

- Alkermes 5461 (Suboxone+samidorphan)
- Buprenorphine+ Mu opiod receptor (MOR) antagonist
- Decreases risk of addiction, Kappa antagonism decreases dynorphin level, increases DA
- Phase two trials of add on to SNRI or SSRI showed 5-8 point MADRS drops
- 2/3 Phase III have failed

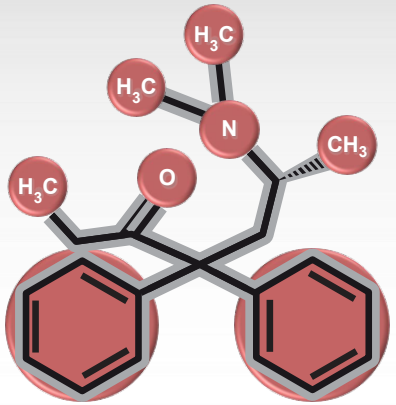
Stanford MEDICINE

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

Not FDA approved.

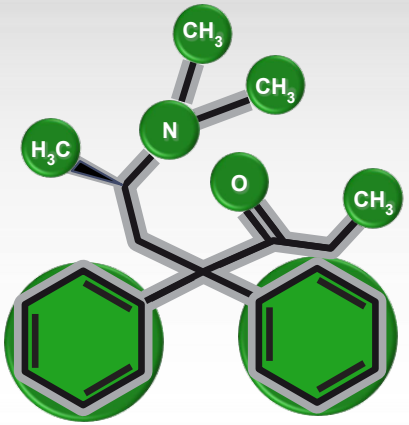
REL-1017 (esmethadone), the opioid-inactive isomer of methadone, is a novel NMDAR channel blocker

Levomethadone
(levo-isomer)



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

REL-1017 (esmethadone)
(dextro-isomer)



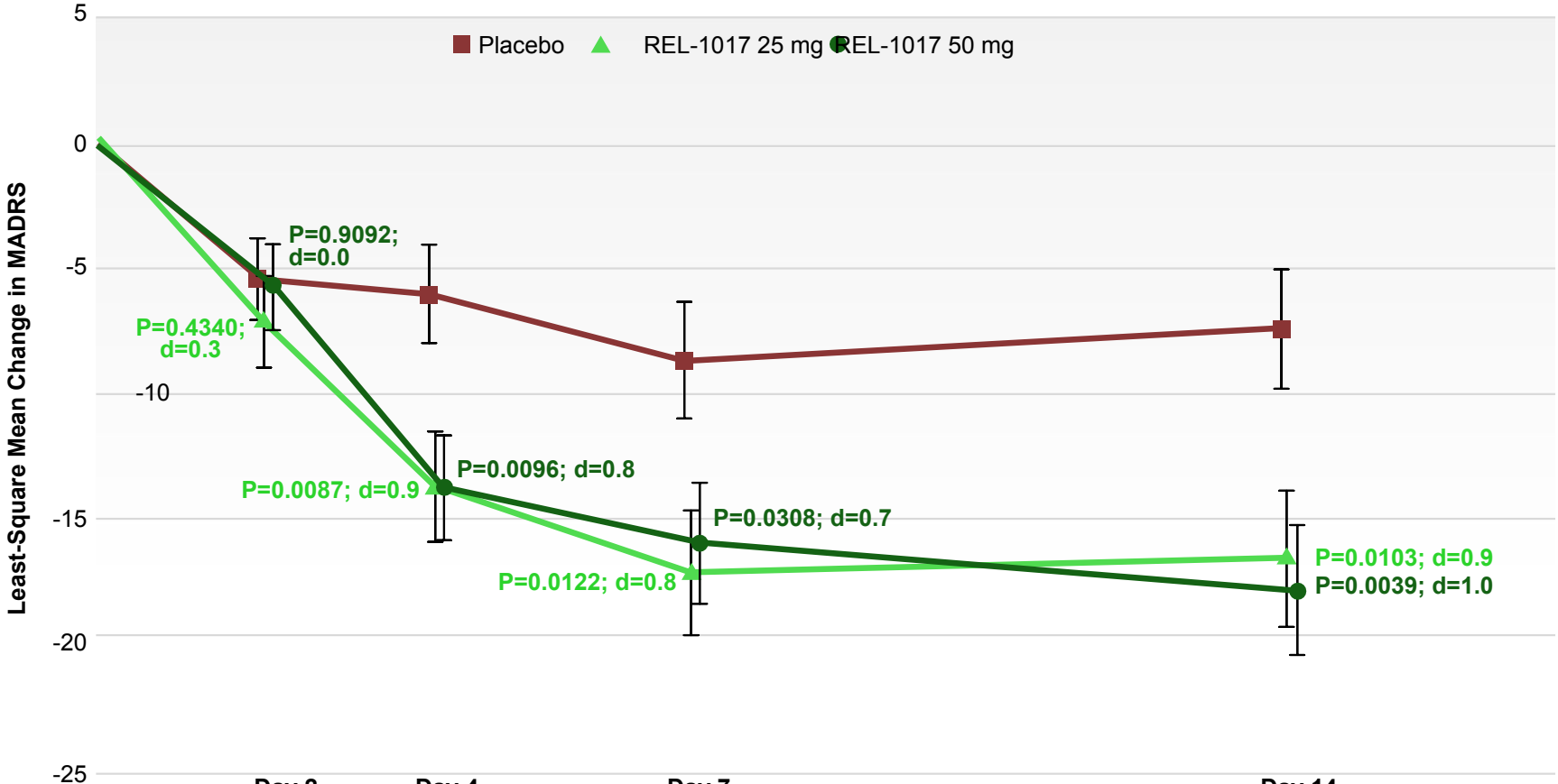
- A novel uncompetitive NMDAR channel blocker[4,5]
- Free from clinically relevant opioid activity at all tested doses: no euphoric, dissociative and respiratory depressant effects and no known addiction liability[2,3,6]

NMDAR=N-methyl-D-aspartate receptor; CH3=Methyl Group; O=Oxygen; N=Nitrogen

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

Phase 2 Study REL-1017: Primary Efficacy Endpoint

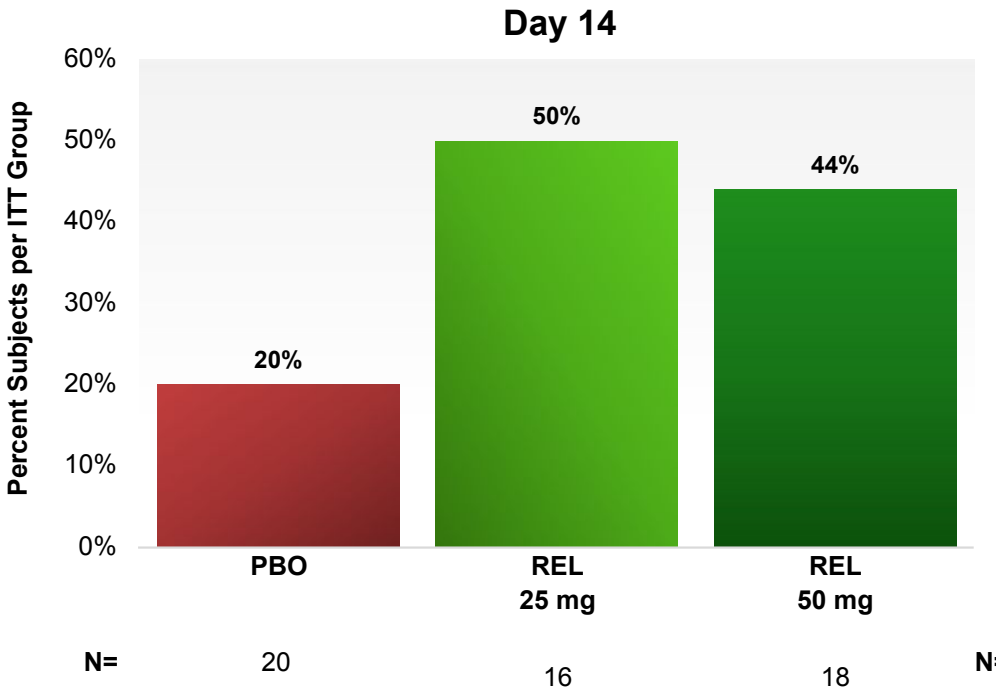
REL-1017 showed rapid, robust, and sustained differences in MADRS change vs. placebo



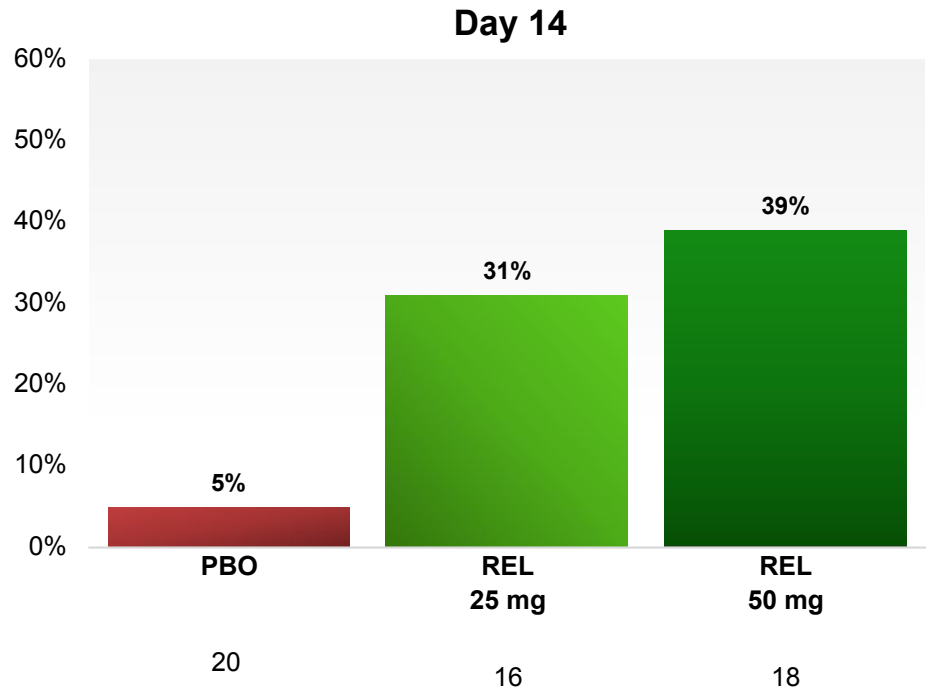
		Day 2	Day 4	Day 7	Day 14
DMADRS	25 mg	7.9	8.7		9.4
vs	50 mg	7.6	7.2		10.4

REL-1017 Phase 2 Study Efficacy: Response & Remission

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



% of Subjects Achieving Remission
(MADRS ≤10)



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

REL-1017 Phase 2 Safety Findings

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

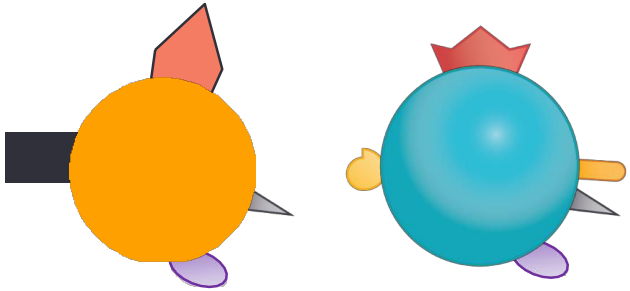
- Across all groups, there were no Serious Adverse Events (SAEs) or Adverse Events of Special Interest (AESIs)
- Also, no signs of euphoric, dissociative or opioid like effects

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

Stanford MEDICINE

What Is AXS-05?

- Two Drugs
  - Bupropion
  - Dextromethorphan



- Seven Mechanisms
  - Dopamine reuptake blockade (bupropion)
  - Serotonin reuptake blockade (dextromethorphan)
  - Norepinephrine reuptake blockade (both)
  - Alpha 4 beta 2 nicotinic antagonist (both)
  - CYP450 2D6 inhibitor (bupropion)
  - NMDA receptor antagonist (dextromethorphan)
  - Sigma 1 agonist (dextromethorphan)

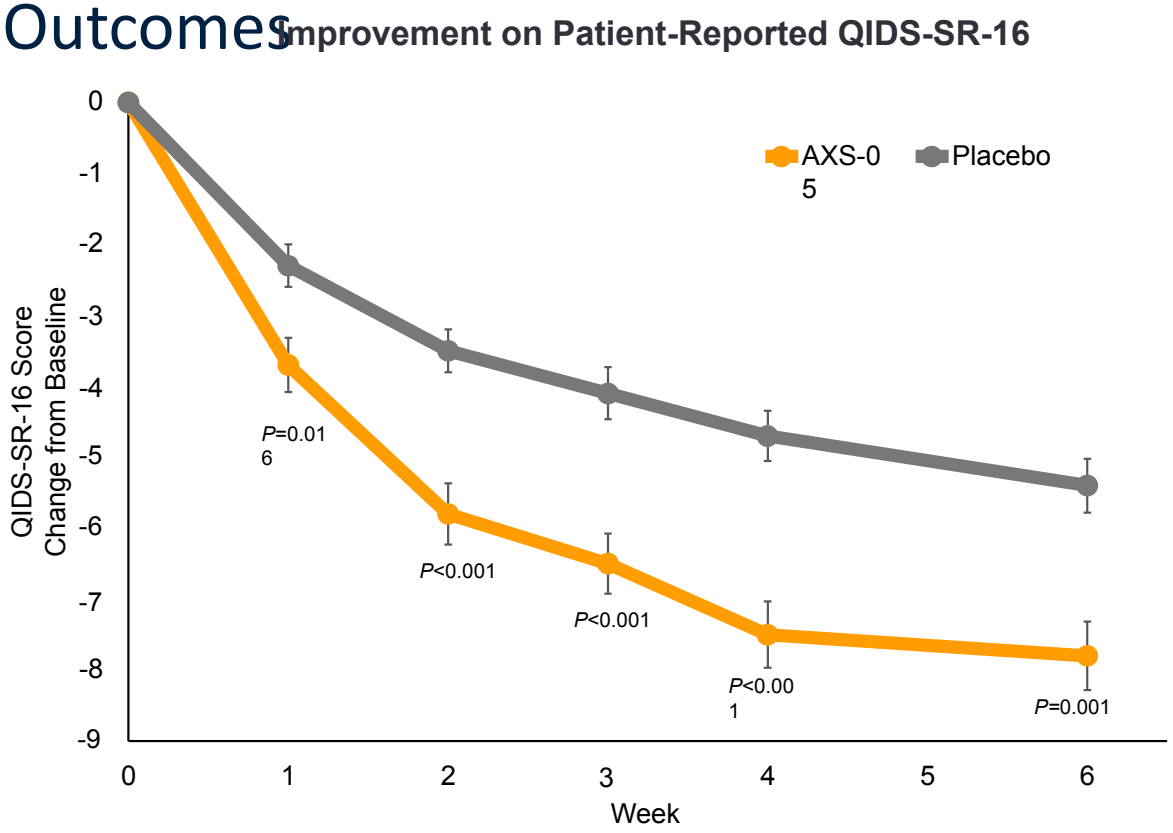
Abbreviations: CYP 450 2D6 = Cytochrome P450 2D6; NMDA = N-methyl-D-aspartate

[1]Figure adapted from: Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications.* Cambridge University Press; 2013.

What Is AXS-05?

- Five approved therapeutic targets
  - Major depressive disorder
  - Obesity (with naltrexone)
  - Pseudobulbar affect (with quinidine)
  - Cough suppressant
  - Smoking cessation
- Three potential therapeutic targets where there is unmet need
  - Treatment-resistant depression
  - Agitation in Alzheimer's disease
  - Smoking cessation

Results: Effects of AXS-05 on Patient-Reported Depression Outcomes



- Treatment with AXS-05 resulted in a rapid, substantial, and significant reduction in patient reported depressive symptoms as measured by the QIDS-SR-16
- Statistically significant treatment effects were observed at Week 1, the earliest time point assessed, and were sustained through Week 6

Stanford MEDICINE

Other Rapidly Acting Novel Treatments in Development

- Psilocybin (fastracked by the FDA)
- DMT
- Accelerated TBS TMS

Stanford MEDICINE

Conclusions

- Several antidepresssants with novel mechanisms are poised for possible approval
- These drugs appear faster acting and offer a different side effect profile than currently available agents
- Some patient unresponsive to current medications may benefit from drugs that work differently

Stanford MEDICINE


Stanford
MEDICINE