GABA Modulators as a novel molecular target in PPD
Update on the status of clinical data

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Maternal Mental Health Markedly Worse During the Pandemic

New mothers' untreated mental health issues cost billions

Mental health issues not only weigh down new mothers but also often go untreated, leading to $14.2 billion in economic costs.

Great Need for New, Effective, Rapidly-Acting Therapies for PPD

- The postpartum is a critical period for maternal infant bonding and attachment.
- Lasting negative effects for mother and offspring with untreated or poorly treated PPD.[1,2]
- Clear unmet need for improved treatment options.[3,4]
- Effective and rapidly-acting medications could:[5]
  - Reduce potential for significant morbidity and mortality.
  - Potentially allow more positive interactions with mother and baby.

PPD: Homogenous Form of Major Depression

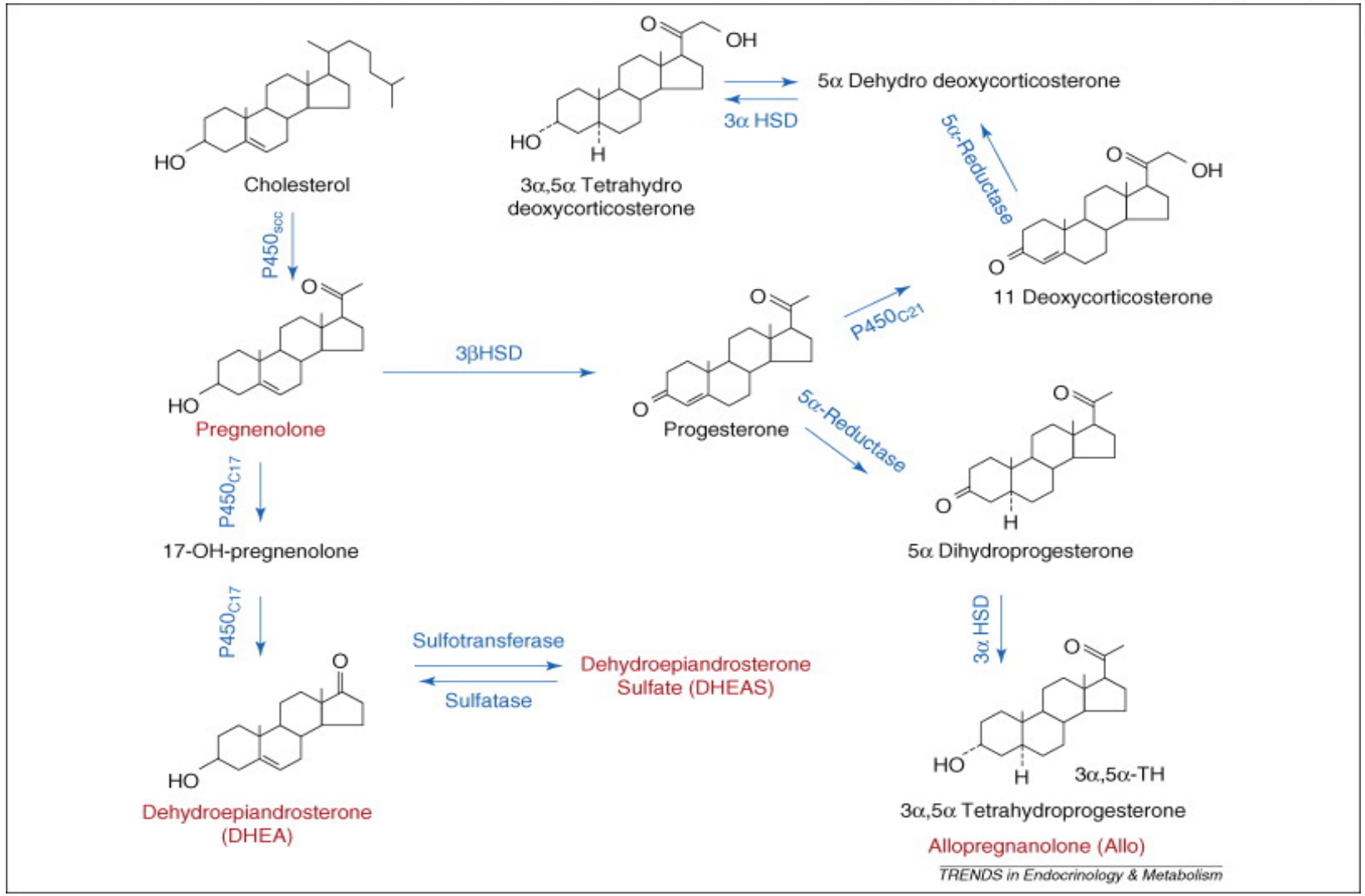
- Prevalence is at least 10-15% in general population. Occurs in reproductive-aged women during pregnancy or after childbirth.[1]

- The underlying cause of PPD is unknown and is likely multifactorial.[2-10]
  - PPD has been linked to history of depression, inflammatory signaling, fluctuations in perinatal hormones, dysregulation of stress pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis, and GABA signaling dysfunction, including altered GABA receptor regulation.

- More heritable than non-perinatal depression[11]
  - 44 to 54% in perinatal vs 32% in non-perinatal depression

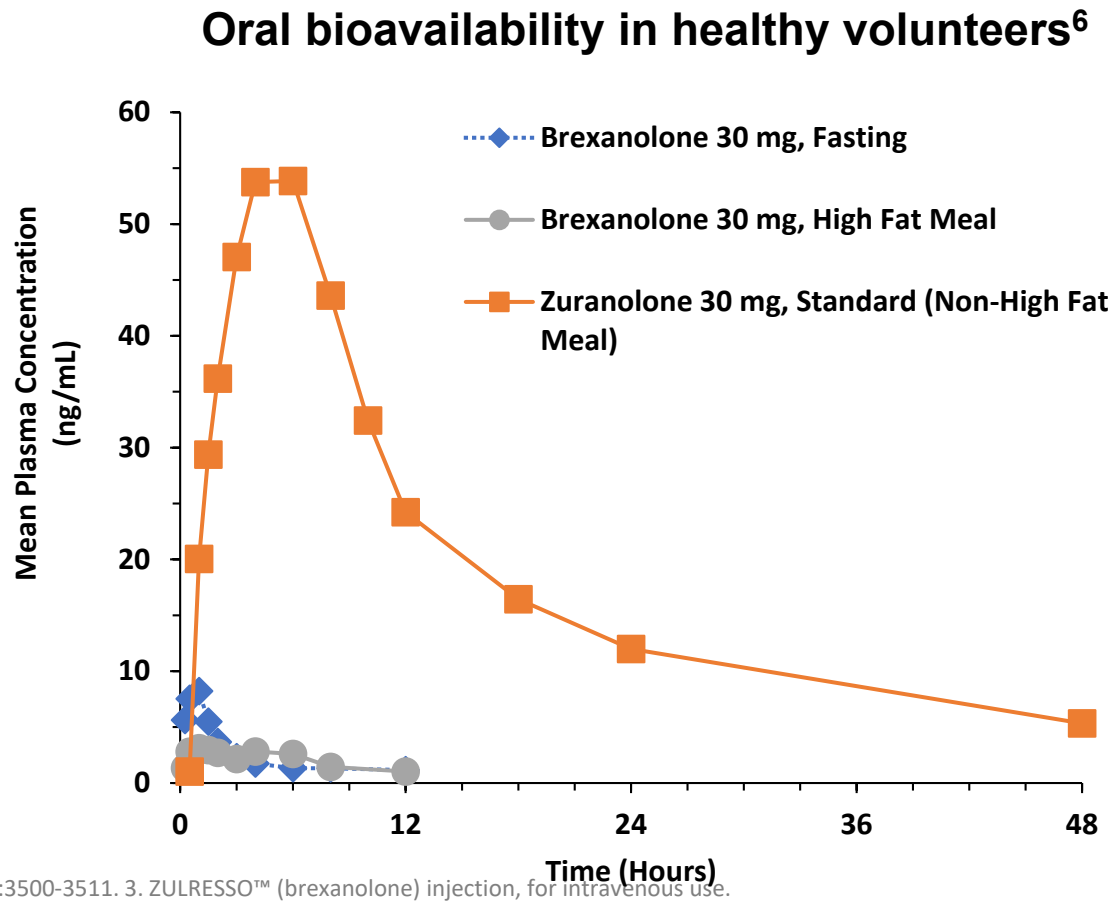
1. American Psychiatric Association, *Diagnostic and statistical manual of mental disorders: DSM*-5. 2013; 2. Osborne LM, et al. *Psychoneuroendocrinology*. 2017; 79: 116-21; 3. Roberston E at al. *Gen Hosp Psychiatry*. 2004;26:289-295; 4. Silverman ME et al. *Depress Anxiety*. 2017;34:178-187; 5. Osborne LM and Monk C. *Psychoneuroendocrinol*. 2013;38:1929-1952; 6. Luisi S, et al. *J Clin Endocrinol Metab*. 2000; 85(7): 2429-2433; 7. Guintivano J et al. Psychological Med 2017; 48(7): 1190-2000; 8. Melon LC, et al. Psychoneuroendocrinology. 2018; 90:182-193; 9. Maguire J and Mody I. *Neuron*. 2008; 59(2): 207-13; 10. Mody I and Maguire J. *Front Cell Neurosci*. 2011; 6:4; 11. Viktorin, A. *et al. Am J Psychiatry*. 2016;173:58-65.

Progesterone to Allopregnanolone Pathway



Development of NAS PAMs in Depressive Disorders: Brexanolone and Zuranolone by Sage Therapeutics

- Positive allosteric modulators (PAMs) of synaptic and extrasynaptic $GABA_A$ receptors.[1]
- Brexanolone is chemically identical to endogenous allopregnanolone, with low oral bioavailability.[2]
    - Brexanolone IV (BRX), an intravenous formulation of brexanolone, was recently approved for the treatment of adults with PPD by the US Food and Drug Administration (FDA) and is not approved for use outside the US.[3]
- Zuranolone (SAGE-217) is an investigational oral NAS $GABA_A$ receptor PAM.[4]
    - Zuranolone is in clinical development for both PPD[4] and MDD.[5]



1. Martinez Botella et al. *J Med Chem* 2017; 60(18): 7810-7819. 2. Martinez Botella G et al. *J Med Chem*. 2015;58(8):3500-3511. 3. ZULRESSO™ (brexanolone) injection, for intravenous use. Sage Therapeutics, Inc., Cambridge, MA. Revised: 06/2019. 4. Deligiannidis KM, et al. ASCP Scottsdale, AZ May 28-31, 2019. Poster T74. 5. Gunduz-Bruce H, et al. *N Engl J Med.* 2019;381(10):903-911. 6. Data on File Sage Therapeutics Inc. 2019.

Rationale for Development of Brexanolone: No Pharmacologic Therapies Approved to Treat PPD

Standard of Care	Limitations
SSRI antidepressant medications	▪ Approved for major depressive disorder ▪ May take weeks to months for initial effect ▪ Many women do not achieve adequate response or symptom remission[1]

Patients and physicians need novel pharmacologic options

1. Molyneaux E et al. *Cochrane Database Syst Rev*. 2014;9:CD002018.

Brexanolone injection in postpartum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

Samantha Meltzer-Brody, Helen Colquhoun, Robert Riesenberg, C Neill Epperson, Kristina M Deligiannidis, David R Rubinow, Haihong Li, Abdul J Sankoh, Christine Clemson, Amy Schacterle, Jeffrey Jonas, Stephen Kanes

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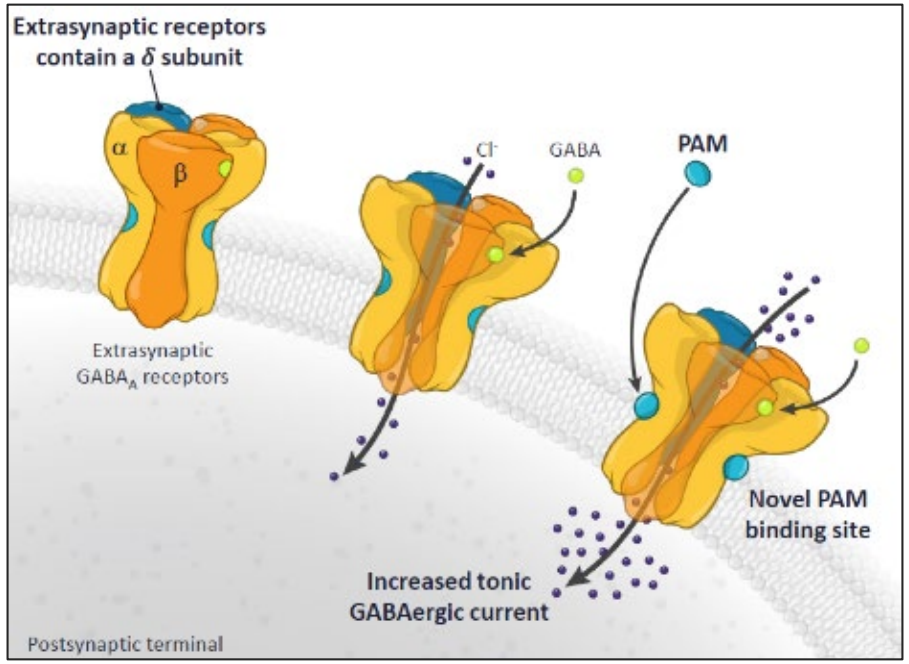
THE LANCET

Rationale: Brexanolone Injection is Hypothesized to Work in PPD by Increasing GABA Function

Brexanolone injection

- Proprietary iv formulation of allopregnanolone
- Positive allosteric modulator of $GABA_A$ receptors

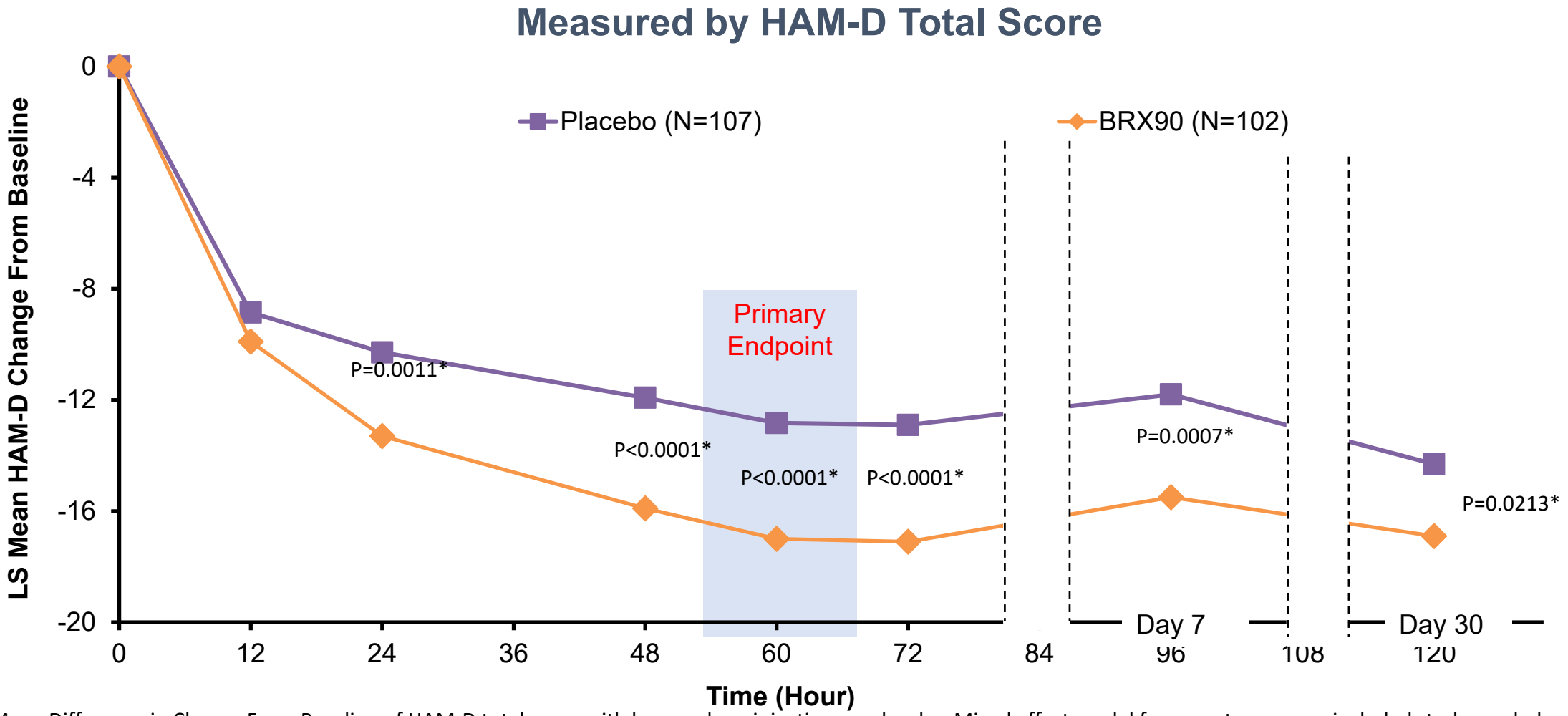


Therapeutic Rationale for Use of Brexanolone injection

- GABAergic hypofunction has been associated with PPD[1,2,3]
- Brexanolone injection is a positive allosteric modulator of $GABA_A$ receptors[4,5]
- Therefore, brexanolone injection may have therapeutic potential in PPD by increasing GABAergic function

1. Luscher B, et al. Molecular Psychiatry 2011; 16(4): 383-406; 2. Deligiannidis KM, et al. Psychoneuroendocrinology. 2016;70:98-107.; 3. Epperson CN et al Psychopharmacology 2006; 186(3): 425-433; 4. Maguire J and Mody I. Psychoneuroendocrinology 2009 Dec;34 Suppl 1:S84-90; 5. Bialer M, et al. Epilepsy Res 2015; 11:85-141.

Brexanolone Injection Anti-depressant Effects vs Placebo Intravenous administration



*LS Mean Difference in Change From Baseline of HAM-D total score with brexanolone injection vs. placebo. Mixed effect model for repeat measures included study, pooled center, treatment, baseline antidepressant use, visit time point, and treatment-by-visit time point interaction terms as fixed effects and baseline total score as a covariate.

Meltzer-Brody S et al. *Lancet*. 2018;392(10152)1058-1070.

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

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

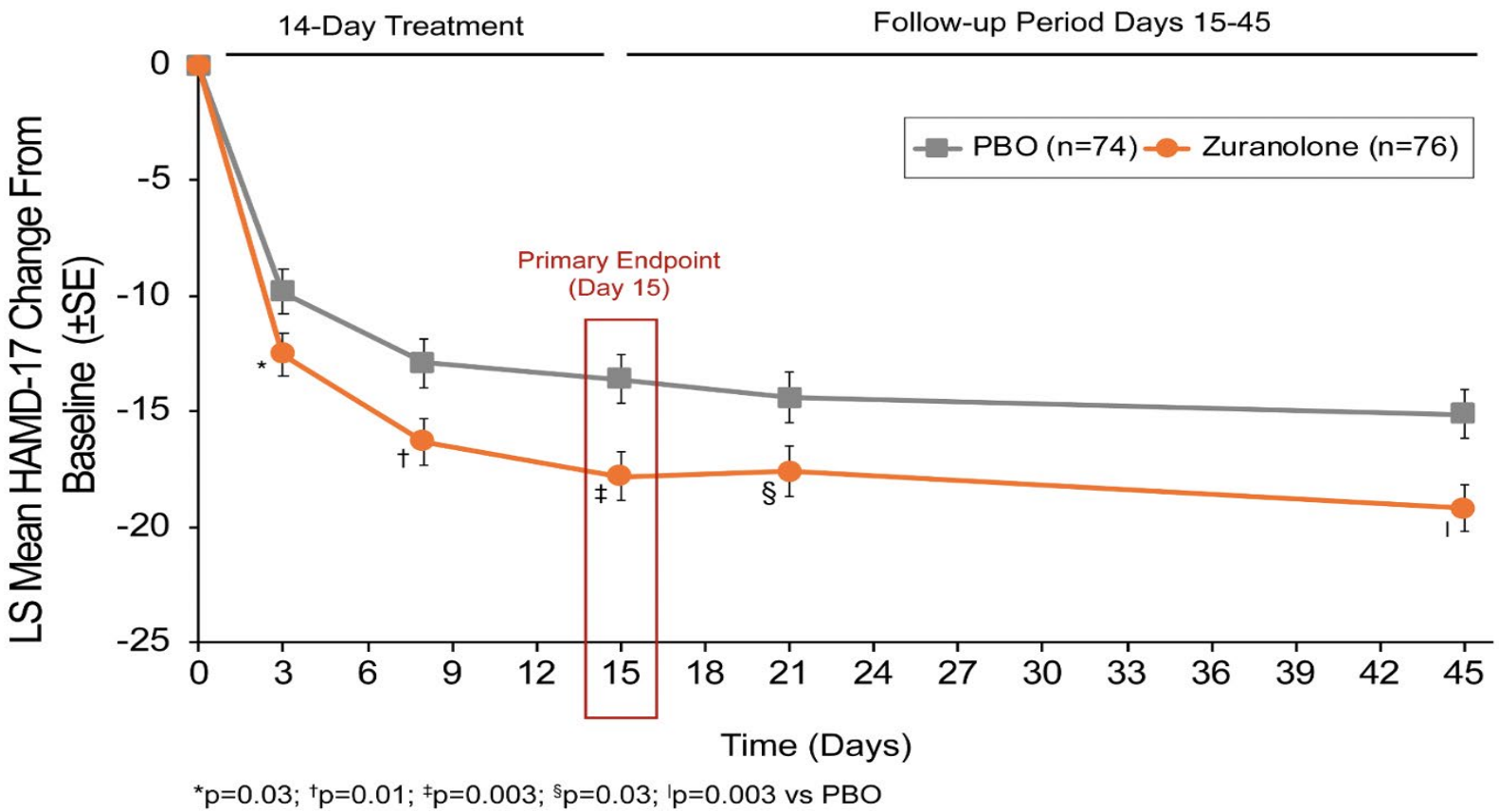


Figure 2 Legend: Treatment with zuranolone achieved the primary endpoint of a significant change from baseline HAMD-17 total score at Day 15 compared with PBO. HAMD-17 total score at timepoints other than Day 15 were secondary endpoints, for which the zuranolone group also showed significant improvements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

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

Overall Conclusions

- Great Need for New, Effective, Rapidly-Acting Therapies for PPD.
- The rapid antidepressant effects of brexanolone and zuranolone support the development of neuroactive steroid $GABA_AR$ positive allosteric modulators as PPD therapies and potential fast-acting antidepressants.
- Brexanolone is an example of using underlying hypotheses of pathophysiology to develop a novel treatment– first approved drug for PPD.
- Brexanolone showed rapid onset by 24 hours (of 60 hour infusion) and sustained through day 30 in the clinical trials.
- Zuranolone showed rapid (by Day 3), sustained (all measured timepoints through Day 45), and clinically meaningful improvements in depressive symptoms, anxiety, and global and maternal functioning, and was generally well tolerated.

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UNC Center for Women's Mood Disorders

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