SKYLARK Study: Pivotal Clinical Evidence in Postpartum Depression

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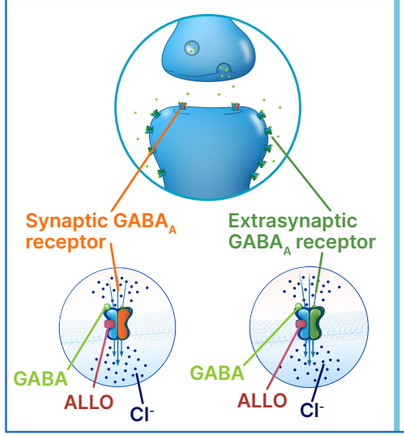
Mechanism of Action of Zuranolone

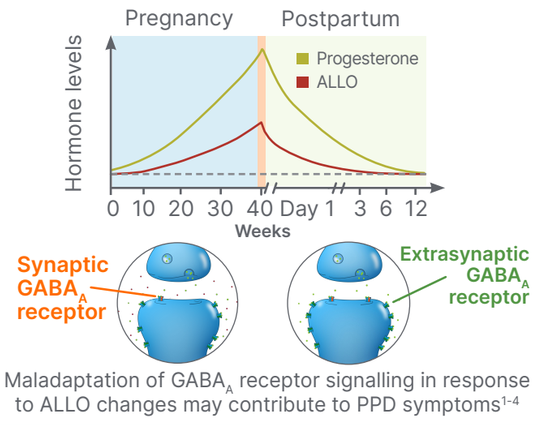
Several mechanisms underlying the pathogenesis of PPD have been proposed.[1] One proposed mechanism involves ALLO, a NAS metabolite of progesterone that rises during pregnancy and falls following birth.[1]

ALLO is a NAS metabolite of progesterone that acts as a PAM of $GABA_A$ receptors, enhancing inhibitory signalling in the brain[1-3]

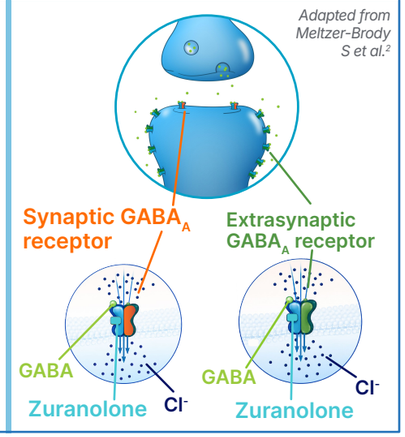
$GABA_A$ receptor expression is hypothesised to adapt to fluctuations in ALLO in the perinatal period[2]

Based on preclinical data, zuranolone is hypothesised to enhance synaptic and extrasynaptic $GABA_A$ receptor signalling and expression, which may help restore reduced $GABA_A$ receptor signalling associated with PPD[1,2,5,6]



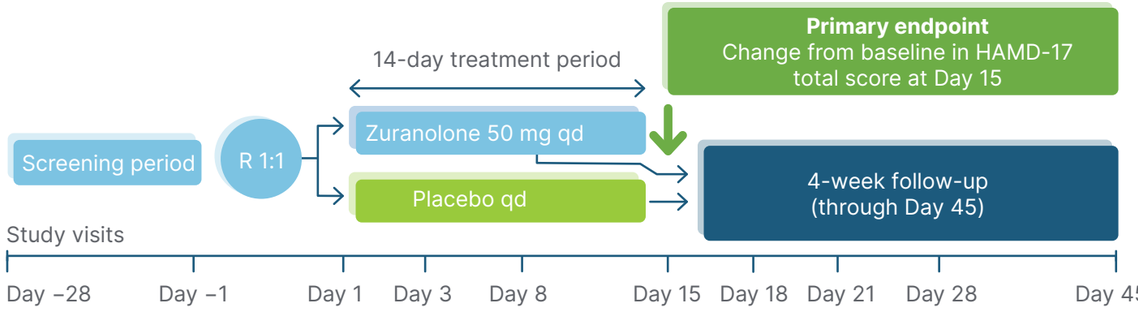


Maladaptation of $GABA_A$ receptor signalling in response to ALLO changes may contribute to PPD symptoms[1-4]



Study Design of the SKYLARK Study[7]

SKYLARK was a randomised, double-blind, placebo-controlled, parallel-group Phase III study evaluating the efficacy and safety of zuranolone at 50 mg/day compared with placebo in women with PPD.[7,a]



Participants could not provide breastmilk to their infant(s) from just prior to receiving study drug on Day 1 until 7 days following the last dose of study drug.[7]

[a]Among 505 screened individuals, 200 met study criteria and were randomized. Of these 200 individuals, 196 received zuranolone (n=98) or placebo (n=98).

What is the HAMD-17?

- 17-item rating scale administered by clinicians.[8]
- Widely used in PPD and MDD clinical trials but less common in clinical practice due to complexity and administration time.[9,10]
- Scores range from 0–52.[9]

Participants enrolled in SKYLARK had HAMD-17 scores ≥26, which is associated with severe depressive symptoms.[7,9]

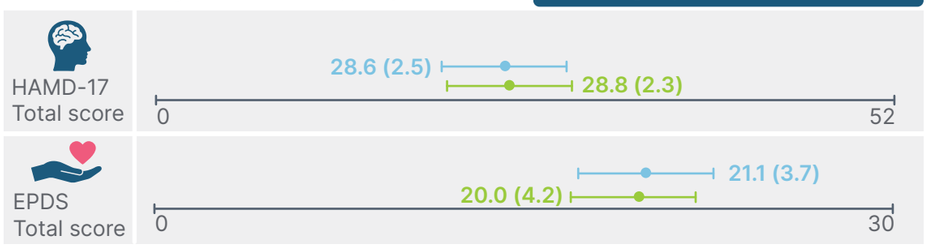
Patient Baseline Characteristics Were Balanced Between Groups[7]

Participants in both groups were similar in age (mean 30–31 years) and were predominantly White (~69–70%), with Black/African American participants making up roughly 18–26% of participants across the zuranolone 50 mg and placebo groups.

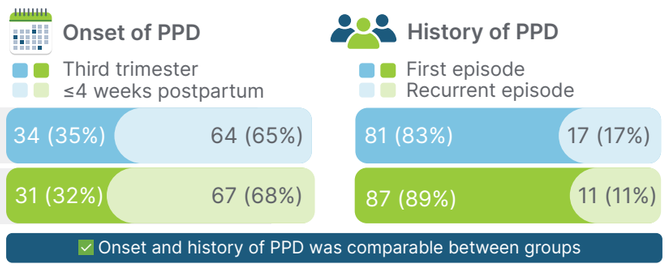
Zuranolone 50 mg, n=98 | Placebo, n=98

✓ Similar severity of depressive symptoms (HAMD-17, EPDS) and anxiety symptoms (HAM-A) (not shown) between groups.

Baseline severity scores, mean (±SD)



Categorical characteristics, n (%)



	Onset of PPD: Third trimester	Onset of PPD: ≤4 weeks postpartum	History of PPD: First episode	History of PPD: Recurrent episode
Zuranolone 50 mg n=98	34 (35%)	64 (65%)	81 (83%)	17 (17%)
Placebo n=98	31 (32%)	67 (68%)	87 (89%)	11 (11%)

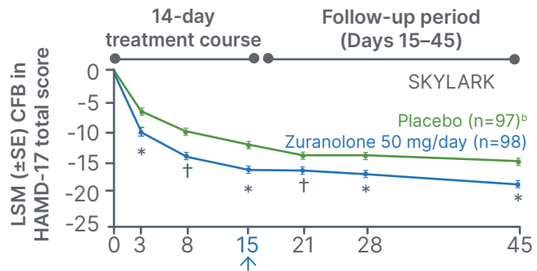
✓ Onset and history of PPD was comparable between groups

Effect of Zuranolone on Depressive Symptoms[7]

Statistically significant improvements were observed in change from baseline in HAMD-17 total scores to Day 15 in patients receiving zuranolone 50 mg vs placebo (p=0.001).

Improvements in HAMD-17 total scores from baseline with zuranolone relative to placebo were observed as early as Day 3 and sustained to Day 45.

Change from baseline in HAMD-17 total score over time



*p<0.05.
†Nominal p<0.05.
[b]One patient randomised to placebo had no post-baseline efficacy assessments

SKYLARK Study Safety Profile[7]

- Zuranolone was generally well tolerated, with most TEAEs being mild or moderate in severity.
- Maintenance or improvement from baseline in maximum severity score on the C-SSRS were observed in most patients and no evidence of withdrawal symptoms after the end of the 14-day treatment period.
- No TEAEs of sexual dysfunction or weight gain were spontaneously reported.[11]

[c]Over the SKYLARK study period, two patients (2%) experienced serious AEs in the zuranolone group considered unrelated to treatment.

	SKYLARK	
	Zuranolone 50 mg n=98	Placebo n=98
Overall rate of TEAEs, n (%)	65 (66)	52 (53)
Most common TEAEs (≥5% in any group)		
Somnolence, n (%)	26 (27)	5 (5)
Dizziness, n (%)	13 (13)	10 (10)
Sedation, n (%)	11 (11)	1 (1)
Headache, n (%)	9 (9)	13 (13)
Diarrhoea, n (%)	6 (6)	2 (2)
Nausea, n (%)	5 (5)	6 (6)
Urinary tract infection, n (%)	5 (5)	4 (4)
COVID-19, n (%)	5 (5)	0
Severe AE	3 (3)	1 (1)
Serious AE	2[c] (2)	0
AEs leading to treatment discontinuation	4 (4)	2 (2)
Death	0	0

Key takeaways

- The exact mechanism of action for zuranolone in PPD is not well understood but is thought to be related to restoration of $GABA_A$ receptor-mediated signalling.[1-6]
- In the Phase III SKYLARK trial, zuranolone significantly improved depressive symptoms versus placebo at Day 15, with effects observed from Day 3 and sustained to Day 45.[7]
- Zuranolone was generally well tolerated, with most TEAEs being mild or moderate in severity.[7]

Abbreviations:

ALLO: allopregnanolone; CFB: change from baseline; C-SSRS: Columbia-Suicide Severity Rating Scale; EPDS: Edinburgh Postnatal Depression Scale; GABAA: gamma-aminobutyric acid type A; HAM-A: Hamilton Anxiety Rating Scale; HAMD-17: 17-item Hamilton Depression Rating Scale; LSM: least squares mean; MDD: major depressive disorder; MDE: major depressive episode; NAS: neuroactive steroid; PAM: positive allosteric modulator; PPD: postpartum depression; qd: per day; SE: standard error; TEAEs: treatment-emergent adverse events; vs: versus.

References

1. Payne JL, Maguire J. Front Neuroendocrinol. 2019;52:165-80.
2. Meltzer-Brody S, Kanes SJ. Neurobiol Stress. 2020;12:100212.
3. Maguire J, Mody I. Neuron. 2008;59(2):207-13.
4. Feng YF et al. Mol Neurobiol. 2024;61(1):385-96.
5. Martinez Botella et al. J Med Chem. 2017;60(18):7810-9.
6. Althaus AL et al. Neuropharmacology. 2020;181:108333.
7. Deligiannidis KM et al. Am J Psychiatry. 2023;180(9):668-75.
8. Hamilton M. J Neurol Neurosurg Psychiatry. 1960;23(1):56-62.
9. Gerbasi ME et al. Arch Womens Ment Health. 2020;23(5):727-35.
10. FDA. Available at: https://www.fda.gov/media/113988/download. Last accessed: 13 August 2026.
11. Meltzer-Brody et al. Poster 15737. Psych Congress, 6-10 September, 2023.