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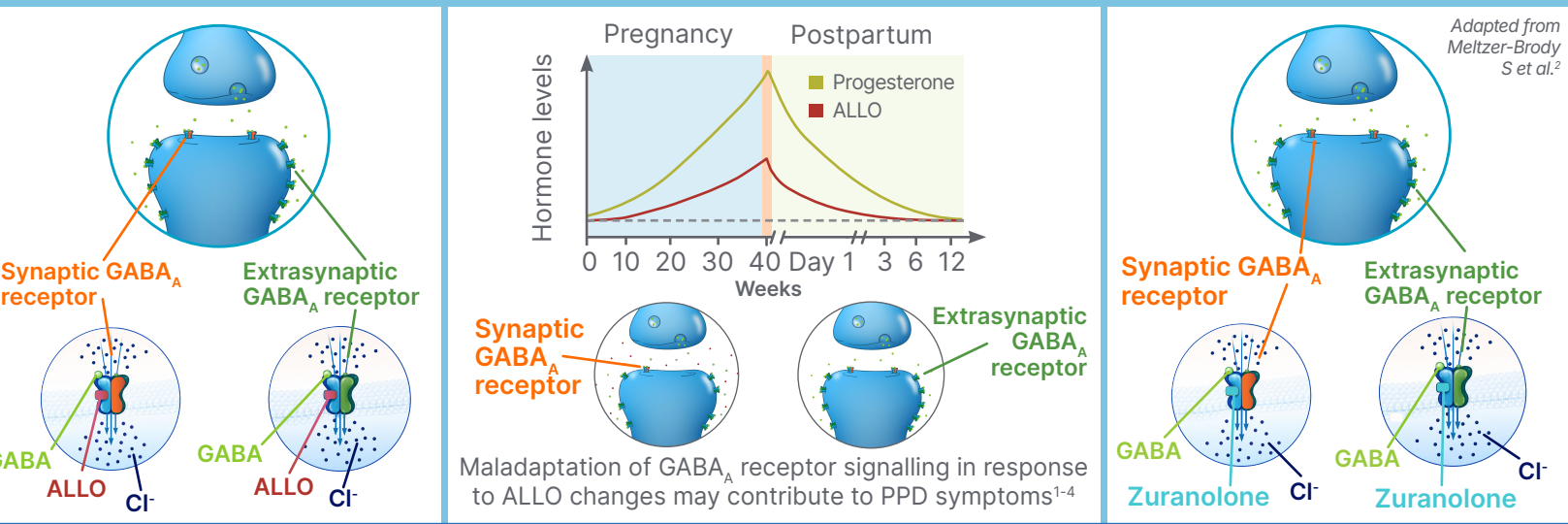
Mechanism of Action of Zuranolone

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 brain¹⁻³

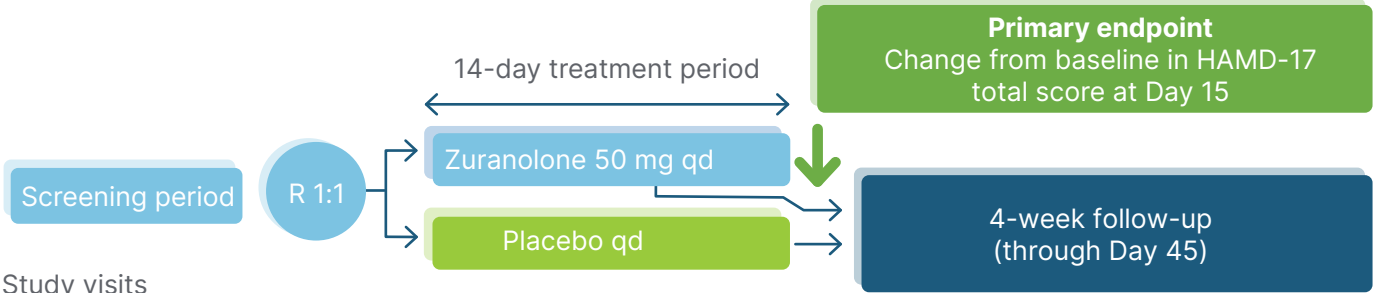
GABA_A receptor expression is hypothesised to adapt to fluctuations in ALLO in the perinatal period²

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}



Study Design of the SKYLARK Study⁷

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}



Study visits: Day -28, Day -1, Day 1, Day 3, Day 8, Day 15, Day 18, Day 21, Day 28, Day 45

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

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

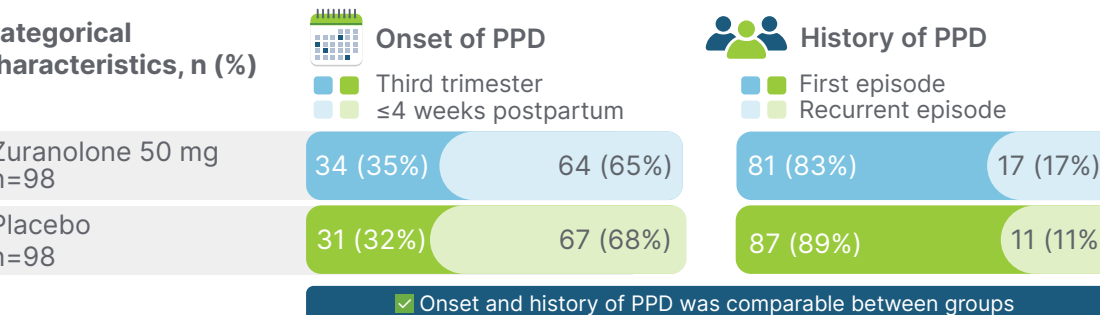
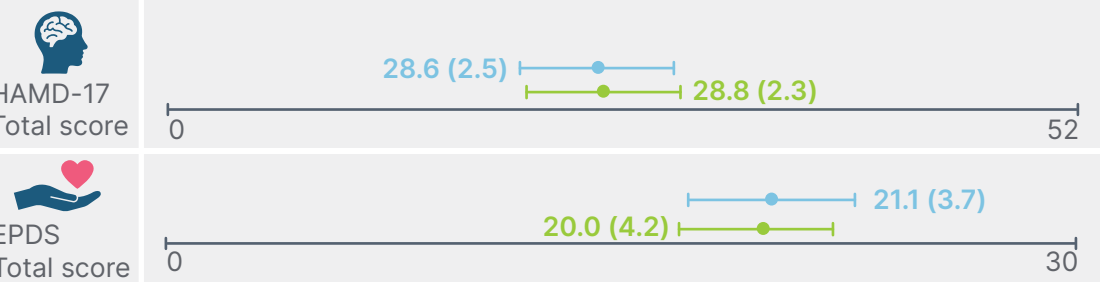
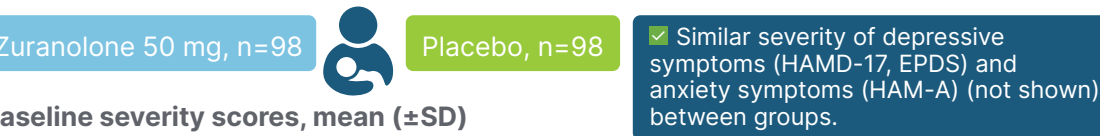
What is the HAMD-17?

- 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 Groups⁷

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.

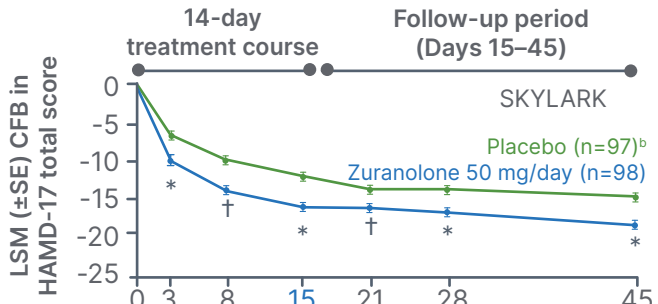


Effect of Zuranolone on Depressive Symptoms⁷

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



SKYLARK Study Safety Profile⁷

- 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

^cOver 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; GABA: 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
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