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Zuranolone as the First Oral Neuroactive Steroid for Postpartum Depression: Pharmacology, Clinical Efficacy, and Lactation Safety

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ABSTRACT

Introduction: Postpartum depression is one of the most common mental illnesses associated with childbirth that occurs in about one out of every six mothers and has an impact on their offspring and relatives. For decades, pharmacologic treatment options were scant: SSRIs took weeks to work, and brexanolone, the only drug for PPD approved by the FDA, worked quickly but had a 60-hour inpatient infusion protocol that very few women got access to. FDA-approved in August 2023 as the first pill to treat postpartum depression, the drug acts as a positive allosteric modulator for GABA-A receptors and does everything that brexanolone was able to do, but is available to patients. *Methods:* A comprehensive search of PubMed and Google Scholar was done to find articles regarding randomized controlled trials, pharmacokinetics, safety studies, and lactation pharmacology related to zuranolone at phase 3. *Results*: Improvement in the 17-item Hamilton Depression Rating Scale (HAM-D-17) score is observed from days 3 to 15 for both phase 3 RCTs, while effects lasted up to day 45. Similar conclusions are drawn in a meta-analysis, and fewer antidepressants are used as concomitant medication. No serious adverse events occurred, and patients remained conscious and did not show increased suicidality from baseline. In light of the RIDs obtained in lactation data, it can be assumed that breastfeeding can be maintained during therapy. *Conclusions*: Zuranolone is a novel agent for the treatment of PPD, acting via a target-specific mechanism, with rapid onset and an oral route of administration.

Keywords: postpartum depression; zuranolone; neuroactive steroids; GABA-A receptor; allopregnanolone

1. INTRODUCTION

Postpartum depression should be distinguished from the "baby blues," although the two conditions are often confused. Contrary to the baby blues, which tend to fade away in about two weeks following birth, postpartum depression is more durable and clinically important. Postpartum depression is far from the transient

mood swings commonly experienced by new mothers. Postpartum depression is a major depressive disorder that may affect a woman's emotional well-being and interfere with her ability to perform everyday duties and take care of her baby. Research indicates that the incidence of postpartum depression ranges from 13–19%, with a worldwide figure of about 17.2% (Wang et al., 2021; Liu et al., 2022; Al-Abri et al., 2023; Amer et al., 2024). In high-income countries, it is now considered the most common serious medical complication of childbirth — more common than postpartum hemorrhage, more common than eclampsia, more common than thromboembolism (Stewart and Vigod, 2019; ACOG, 2023). The clinical picture is wide: persistent sadness, low mood, profound despair, severe anxiety, and a loss of the everyday ability to manage daily life (Stewart and Vigod, 2019).

Without treatment, the disorder causes substantial harm. Cognitive, affective, and social developmental problems in children over time. Disturbances in the mother-infant attachment relationship. An increased chance of maternal suicide, which constitutes as much as one-fifth of all postpartum deaths (Gelaye et al., 2016; Deligiannidis et al., 2021; Saharoy et al., 2023). For a condition with this kind of clinical weight, the pharmacological response has been remarkably stuck. SSRIs are the default. They are also the wrong tool — they act on serotonin reuptake, not on the neurosteroid-GABAergic deficit that actually drives PPD, and they take four to eight weeks to produce a meaningful effect. Four to eight weeks during which a postpartum mother is still struggling, still at risk (Stewart and Vigod, 2019; ACOG, 2023). When brexanolone was approved by the FDA in 2019, it confirmed the GABAergic hypothesis of PPD and offered a treatment that genuinely worked. But the 60-hour intravenous infusion required to deliver it — at a certified facility, with continuous monitoring — kept it out of reach for the vast majority of women who could have benefited (Meltzer-Brody et al., 2018; Reddy et al., 2023a).

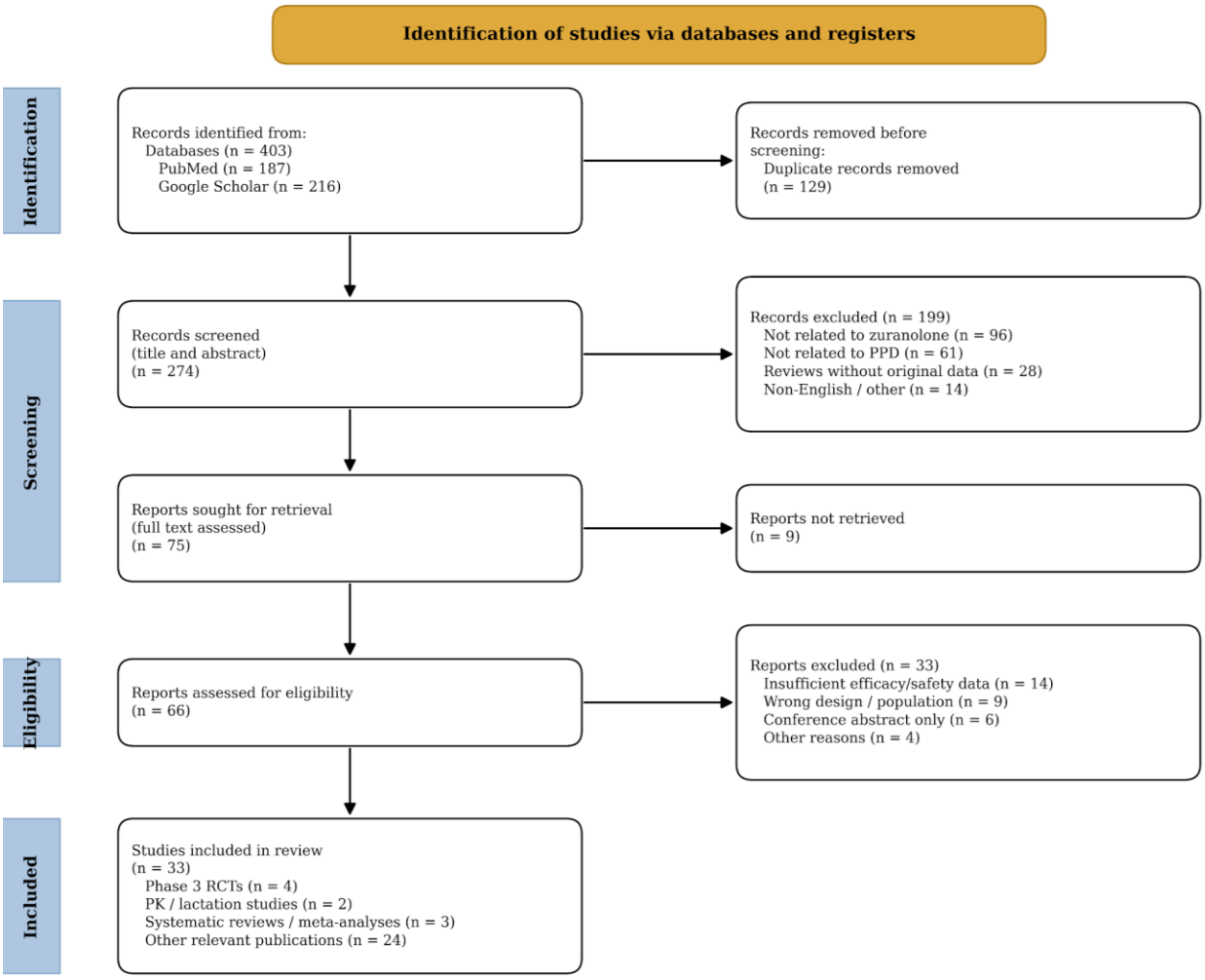

Figure 1. PRISMA flow diagram of the literature search and study selection process

Zuranolone (ZURZUVAE™) is what the field has been waiting for. The FDA approved it on August 4, 2023, as the first oral medication specifically indicated for PPD in adults (Deligiannidis et al., 2021; Giannopoulos et al., 2025). The mechanism is the one brexanolone already proved — positive allosteric modulation of GABA-A receptors, restoring the neurosteroid signaling that crashes after delivery — but delivered as 14 days of capsules taken at home (Meltzer-Brody and Kanes, 2020; Reddy, 2023b). In what follows, we walk through phase 3 trial results, the safety picture, what has been worked out about co-initiation with standard antidepressants, and what the breast milk data show.

2. REVIEW METHODS

To conduct a literature review on zuranolone for postpartum depression, searches were done in PubMed and Google Scholar using keywords that focused on articles in the English language on zuranolone for postpartum depression. Searches included phase 3 randomized controlled trials, systematic reviews and meta-analyses, pharmacology studies, and research studies related to the mode of action, effectiveness, pharmacokinetics, and breastfeeding safety of zuranolone. The sources were selected based on the title, abstract, and full text content. The article selection was based on the PRISMA protocol (Figure 1).

3. RESULTS AND DISCUSSION

Epidemiology

The global statistics for postpartum depression (PPD) are dramatic. Approximately 17.2% of all women worldwide have clinically significant levels of depression during their postpartum experience (Wang et al., 2021; Liu et al., 2022). However, the average differs from region to region. It is quite close to 11.9% in developed countries, but for poor or developing nations, it is greater than 19% (Al-Abri et al., 2023; Amer et al., 2024). The results of another cross-sectional multinational study conducted in six countries across three continents are even more shocking: about half of all cases remain undiagnosed by the time of the postpartum checkup (Amer et al., 2024). There are cases of this disorder. The system fails to recognize them.

Pathophysiology of Postpartum Depression

To understand why zuranolone works where SSRIs often do not, it helps to understand what postpartum depression actually is at the biological level. It is not an ordinary major depressive disorder that happens to arise after childbirth. It is a distinct condition driven by one of the most dramatic hormonal transitions in human physiology. Through pregnancy, progesterone and its neuroactive metabolite allopregnanolone rise steadily — by the third trimester, both are several times above the non-pregnant baseline. These neurosteroids are powerful enhancers of inhibitory GABAergic signaling, and they help buffer the maternal brain against the physiological and emotional stressors of pregnancy (Meltzer-Brody and Kanes, 2020; Maguire, 2019; Pinna et al., 2022). Then comes delivery. Within hours of placental expulsion, both progesterone and allopregnanolone collapse — sometimes to levels below the follicular phase. Most women adapt. The brain remodels its GABA-A receptors, the system rebalances, and life goes on. In neurobiologically vulnerable individuals, that adaptation fails.

The GABAergic deficit that follows expresses itself as the clinical picture of PPD: persistent low mood, hyperarousal, insomnia, severe anxiety, and emotional dysregulation (Walton and Maguire, 2019; Zawilska and Zwierzyńska, 2025). This is also why SSRIs frequently miss the mark — they target the serotonin system rather than the neurosteroid mechanism that has actually gone wrong (Stewart and Vigod, 2019). Inhibitory GABA-A receptors come in two functional flavors. Synaptic receptors handle fast phasic inhibition — the brief, point-to-point dampening that follows each release of GABA. Extrasynaptic receptors do something different: they sit slightly outside the synapse and produce a steady tonic inhibitory current that sets the baseline excitability of the neuron (Meltzer-Brody and Kanes, 2020; Pinna et al., 2022). Allopregnanolone — and, by design, zuranolone — bind to interfacial transmembrane sites present on both populations. The result is simultaneous enhancement of phasic and tonic inhibition (Pinna et al., 2022; Althaus et al., 2020).

One additional feature that came out of in vitro work is worth flagging: zuranolone also drives an increase in surface GABA-A receptor expression through metabotropic receptor trafficking. Benzodiazepines do not do this, which may be one reason why the clinical response to zuranolone outlasts the 14-day dosing course (Althaus et al., 2020). There is a stress axis dimension to all of this as well. The hypothalamic-pituitary-adrenal (HPA) axis is normally held in check, at least in part, by inhibitory GABAergic input onto corticotropin-releasing hormone neurons. When allopregnanolone collapses postpartum, that brake weakens. Stress reactivity rises, cortisol responses become exaggerated, and the cycle that this sets up is particularly hard for serotonergic drugs to interrupt (Walton

and Maguire, 2019). On top of this, more recent work points to a role for neuroinflammation — cytokine activation modulating GABA and glutamate receptor expression and disturbing inhibitory tone (Zawilska and Zwierzyńska, 2025).

Current Therapeutic Options and Their Limitations

Psychotherapy remains a foundation for treating all levels of PPD. Existing guidelines on clinical practice suggest that cognitive-behavioral therapy be employed in the management process (ACOG, 2023; Wojcieszak et al., 2026). In addition to psychotherapies themselves, there is evidence for the use of prenatal exercise as a preventative strategy. Regular exercise during pregnancy lowers postpartum depression risk through several plausible mechanisms — HPA axis reactivity modulation, neurotrophin release, and dampening of inflammatory signaling (Czernic-Goławska et al., 2026). But they can be used along with pharmaceutical therapy and they do have an effect on a person's mental health, especially when combined properly. Sertraline and other SSRIs will still continue to be the mainstay in the pharmacologic treatment of PPD (ACOG, 2023). The biggest problem facing the treatment of this illness is the same one mentioned above: the wrong system and a slow onset, with four to eight weeks of latency before any meaningful relief (Stewart and Vigod, 2019). An indirect comparative treatment analysis carried out in 2024 quantified the difference. At day 15, the difference between zuranolone and SSRI users was a 4.22-point higher decrease in EPDS scores among the former. However, by day 45, the difference was even larger, amounting to 7.43 points (Meltzer-Brody et al., 2024). The difference between week two and week eight means everything to a new mother. While brexanolone validated the neurosteroid hypothesis, it also became a highly successful drug (Meltzer-Brody et al., 2018; Reddy et al., 2023a). However, the delivery mechanism posed an issue from the very beginning. Specifically, a six-day infusion via intravenous line at an approved REMS site with constant medical supervision due to the known potential for loss of consciousness. During the infusion, the mother cannot breastfeed and is separated from her newborn. Add a wholesale acquisition cost of about $34,000 per course, and a limited number of certified facilities, and the math is obvious — brexanolone only ever reached a small minority of the women who could have benefited (Reddy et al., 2023a). An oral alternative with equivalent pharmacodynamic activity was not a luxury. It was overdue. The main pharmacological options for PPD are summarized in Table 1.

Table 1. Comparison of pharmacological treatments for postpartum depression.

Route	**Oral (once daily)**	**IV infusion**	**Oral**
Course length	14 days	60 hours	Weeks to months
Onset of effect	Day 3	Within hours	4–8 weeks
Setting	Outpatient (home)	Inpatient (REMS required)	Outpatient
Breastfeeding	Compatible (RID <1%)	Interrupted during use	Generally compatible
Mechanism	GABA-A PAM (synaptic + extrasynaptic)	GABA-A PAM	Serotonin reuptake inhibition
PPD-specific FDA approval	2023	2019	No (off-label)
Loss of consciousness risk	None reported	Yes (monitoring required)	None

Zuranolone: Mechanism, Efficacy, Safety, and Lactation

Zuranolone belongs to the class of synthetic neurosteroids, and its structure contains a scaffold similar to that of allopregnanolone. The reason why the molecule can be ingested is due to the presence of a 4-cyanopyrazole group at position C21, which reduces first-pass metabolism and allows for once-daily administration (Zawilska and Zwierzyńska, 2025). Pharmacologically, the drug is an allosteric positive modulator of GABA-A receptors. Overall, there are nine human recombinant types of GABA-A receptor identified, among which include the synaptic and extrasynaptic types of the GABA-A receptors (Althaus et al., 2020).

The drug metabolism occurs via the CYP3A4 metabolism pathway; metabolites formed do not have any pharmacological activity (Giannopoulos et al., 2025). The approved dose is 50 mg once daily at night on a fatty diet over 14 days. A 30 mg alternative dose for use in cases where tolerance may be an issue is also available (Giannopoulos et al., 2025; Zawilska and Zwierzyńska, 2025). With respect to the clinical evidence for zuranolone, two randomized controlled studies have been conducted to support its application. The first randomized trial is ROBIN, which comprised 153 participants diagnosed with major depression. These patients were given random doses of either 30 mg zuranolone or placebo each day at night for 14 days (Deligiannidis et al., 2021).

A comparison of zuranolone to placebo showed that participants treated with zuranolone were significantly better than those who received placebo at post-treatment (least squares mean difference = −4.2; 95% CI −6.9 to −1.5; p = 0.003). Differences between the two treatments became apparent by day 3 (difference −2.7; p = 0.03) and continued through day 45, about one month after discontinuation of treatment (Deligiannidis et al., 2021). Secondary outcomes supported the findings of the primary endpoint, with higher response (OR 2.63; p = 0.005) and remission rates (OR 2.53; p = 0.01) observed in the zuranolone group. Improvements were also seen in anxiety-related outcomes. The second trial — SKYLARK — tested the 50 mg dose in 196 women with severe PPD. Findings were essentially identical. HAM-D-17 difference at day 15: −4.0 (95% CI −6.3 to −1.7), onset at day 3, benefit sustained through day 45 (Deligiannidis et al., 2023). One thing about SKYLARK worth highlighting is the population — 38.3% Hispanic/Latina, 21.9% Black/African American — which substantially broadens generalizability over what the original 30 mg trial offered (Table 2).

Table 2. Summary of phase 3 clinical trial evidence for zuranolone in postpartum depression

Number randomized	153	196
Design	Phase 3, double-blind, RCT	Phase 3, double-blind, RCT
Dose / course	30 mg once nightly × 14 days	50 mg once nightly × 14 days
HAM-D-17 at day 15 (LSM diff)	−4.2 (95% CI −6.9 to −1.5); p = 0.003	−4.0 (95% CI −6.3 to −1.7); p < 0.001
Onset at day 3	−2.7 (p = 0.03)	Significant (p < 0.05)
Sustained effect (day 45)	Yes	Yes
Response rate (OR)	2.63 (p = 0.005)	—
Remission rate (OR)	2.53 (p = 0.01)	—
Most common Aes (≥10%)	Somnolence, dizziness, sedation	Somnolence, dizziness, sedation
Loss of consciousness	Not observed	Not observed
Suicidal ideation increase	Not observed	Not observed

Oliveira et al., (2024) analyzed data from both trials in a systematic review and meta-analysis of 346 women. The analysis showed consistent efficacy in terms of significantly increased proportions of patients with positive responses to treatment according to CGI scores (OR 2.31; 95% CI 1.49–3.58; p < 0.001; I^2 = 0%) and HAM-D scores indicative of remission at day 15 and 45 of the therapy. However, one particular result deserves special attention. The patients who were under zuranolone treatment needed a significantly lesser amount of concurrent antidepressant medications (OR 13.74; 95% CI 2.55–74.09; p=0.002) (Oliveira et al., 2024). From the practice standpoint, it can indicate the potential capacity of fast-acting neurosteroids to minimize the overall use of drugs. Furthermore, two additional systematic reviews on PPD and MDD were made by Winslow et al., (2024) and Raja et al., (2024). Across both phase 3 programs, the safety record has been consistent. The adverse events that showed up most often — somnolence, dizziness, sedation, headache — were almost always mild to moderate, and discontinuations on this basis were rare (Deligiannidis et al., 2021; Giannopoulos et al., 2025). There were no drug-induced vital sign alterations, ECG changes, or lab results detected (Giannopoulos et al., 2025). There are two aspects of importance here: first, none of the patients experienced loss of consciousness, and second, suicidal ideation remained unchanged throughout both trials (Deligiannidis et al., 2021; Deligiannidis et al., 2023). It is particularly significant that the drug did not exacerbate ideation. This would be valuable in individuals who are already at high risk for suicide. Some tips that could be conveyed to patients would include the following: take this medication at night; do not drive or use heavy machinery within 12 hours after taking it; and do not take it with alcohol (Giannopoulos et al., 2025).

The Schedule IV controlled-substance classification reflects mild dose-dependent euphoric effects seen in phase 1 — no clinically significant abuse signal appeared in the phase 3 populations (Barnes et al., 2024). Also, there is a black-box warning for central nervous system depression and risk to the fetus due to reproductive animal toxicology studies. Contraception should be recommended to reproductive-aged women who are not breastfeeding while undergoing the therapy (Giannopoulos et al., 2025). Last but not least, it is essential to mention that CYP3A4 inhibitors may elevate the plasma levels of zuranolone (Price and Price, 2024).

Lactation compatibility was always going to be the question that decided whether zuranolone could be used in real-world postpartum populations. In the United States, around 83% of postpartum women initiate breastfeeding, and 60% are still breastfeeding at six months (Giannopoulos et al., 2025). A drug that requires breastfeeding interruption — as brexanolone did — limits itself by design. A Phase I PK study was conducted to fill this void with 15 lactating healthy individuals receiving the drug in doses of 30 mg

per day for five days (Deligiannidis et al., 2024). RID in the case of 30 mg is 0.357%, while for 50 mg it was calculated to be 0.984%. Both values lie far below 10%, considered to be the acceptable level for indicating breastfeeding compatibility. Breast milk concentrations went below the limit of quantification in 4–6 days from the last dose (Deligiannidis et al., 2024). Another point worth mentioning is the following. The recommendations of the manufacturer do not allow breastfeeding while under treatment. At the same time, LactMed recommends not stopping breastfeeding just because the woman takes zuranolone; however, monitoring of infant sedation should be performed, especially in the case of newborn or premature infants (National Library of Medicine, 2006). Clinical practice currently has not registered any adverse outcomes for babies due to zuranolone use by their mothers (Price and Price, 2024).

Clinical Implications and Future Directions

Since FDA approval in August 2023, clinical guidelines from the American College of Obstetricians and Gynecologists have been updated to recommend zuranolone for PPD occurring in the third trimester or up to four weeks after childbirth, within one year following childbirth (ACOG, 2023). EPDS will still serve as the main screening instrument, as it is a 10-item self-reported survey that is a reliable measure of PPD in this patient population, with a sensitivity of 0.79 and a specificity of 0.92 (Cox et al., 1987; Park and Kim, 2023). A recent addition to this list, which is not necessarily related to PPD specifically, was the phase 3 CORAL study. The results of CORAL indicate that combining zuranolone therapy with an established antidepressant led to quicker improvement in symptoms compared to using a placebo along with an established antidepressant (Parikh et al., 2024). With respect to the patients suffering from postnatal disorders that need prolonged management for depression, co-medication would be considered rational since it allows the patient to gain relief through the chronic process of treatment (Giannopoulos et al., 2025; Parikh et al., 2024).

The overall scenario appears to be much easier. First and foremost, zuranolone gets rid of all possible limitations that could make brexanolone unattainable. It is not necessary to be admitted to the hospital or REMS facilities. A frank appraisal would be that this body of research is still quite immature. Two studies, which only provide results up to day 45, cannot offer information on the sustainability of the effect over time, nor about relapse, nor what should be done if patients have to be retreated for recurring symptoms. There is also a lack of comparative data when compared to both SSRIs and brexanolone (Price and Price, 2024). It is also important for future research to consider the safety of the babies being breastfed — infant blood levels, as well as standard measures of development (Deligiannidis et al., 2024; National Library of Medicine, 2006). There are a few other areas that remain on the wish list. Pharmacoeconomics — the wholesale cost runs about $15,900 per 14-day course (Meltzer-Brody et al., 2024). And biomarker-guided selection using peripartum allopregnanolone levels (Meltzer-Brody and Kanes, 2020; Maguire, 2019).

4. CONCLUSION

Postpartum depression treatment has, for many years, been hindered by drugs that are either slow in providing results, are not easily accessible, or do not target the specific neurobiological processes that cause postpartum depression. SSRIs are an inappropriate treatment. Brexanolone is an appropriate treatment, but it is administered improperly. Zuranolone is the first treatment that pairs a mechanism actually matched to the biology of PPD — positive allosteric modulation of both synaptic and extrasynaptic GABA-A receptors — with a delivery system patients can use without giving up their daily life. Fourteen days of an oral capsule taken at home, with or without a concomitant antidepressant. No hospitalization. No separation from the newborn. The available evidence is consistent. Two phase 3 trials. Meaningful improvement starting at day 3 and holding through day 45 — a month after the last dose. A pooled meta-analysis with zero between-trial heterogeneity that also documents a reduction in concomitant antidepressant requirements. Lactation data that are, on every reasonable read, reassuring. Information regarding long-term infant safety remains limited. So are real-world effectiveness data. Direct comparative studies evaluating these therapies against currently established treatment options are still limited. Therapeutic decisions should continue to be tailored to the individual patient, taking into account breastfeeding, chronic disease, and treatment availability. At the same time, ongoing advances in the field have led to a broader range of therapeutic options.

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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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