

RE104: A Novel, Fast-Acting Psychedelic for Postpartum Depression

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Experts share the results from the first-in-human phase 1 study of this treatment, plus a preview of its upcoming phase 2 trial.



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The Anxiety and Depression Association of America Annual Conference in Boston, Massachusetts, in April 2024, showcased encouraging results from the first-in-human phase 1 study of RE104 in healthy adult participants.^{1,2}

The positive results of this study have served as the foundation for an upcoming phase 2 trial (the RECONNECT study; NCT06342310) of a single-dose subcutaneous RE104 administration in women suffering postpartum depression (PPD). The RECONNECT trial is set to begin recruiting in mid-2024.^{1,2}

What is RE104?

RE104 is a unique, proprietary prodrug that is converted in vivo to an active drug metabolite, 4-hydroxy-diisopropyltryptamine, or 4-OH-DiPT. Although it possesses pharmacology and intense psychedelic effects similar to those of the active metabolite of psilocybin, the psychoactive state lasts for only about half as long.³⁻⁶

RE104 is formulated as a subcutaneous (SC) injection to ensure optimal absorption, as well as rapid and reproducible conversion to its active metabolite.

RE104 is being developed as a single-dose, fast-acting, durable treatment for individuals suffering from PPD and other mental health conditions.^{5,6}

Psilocybin for the Treatment of Depression

After years of prohibition, dating back to the 1970s, psychedelics such as psilocybin and RE104 are now being enthusiastically pursued as therapies for a multitude of disorders, including depression.⁷ Psilocybin, a classical serotonergic psychedelic agent, has demonstrated therapeutic potential in early-phase clinical trials in various types of depression.^{8,9}

For example, a single dose of a synthetic psilocybin (COMP360) administered with psychological support to participants with treatment-resistant major depressive disorder (MDD) was associated with a 29% remission rate at 3 weeks and a sustained response in 1 out of 5 participants at week 12.⁸

Results from a systematic review of 19 studies evaluating psychedelics in treating unipolar mood disorders, which included MDD and persistent depressive disorder, showed that as many as 79.2% of individuals had clinician-judged improvement after treatment.¹⁰

Limitations of Psilocybin

Although the clinical benefits of psilocybin in treating depression are emerging, this agent has important limitations that could potentially impact its clinical utility. For example, psilocybin induces a psychoactive state lasting a full day (up to 8 hours) during

which patients must be monitored by health care professionals for safety reasons, thereby posing resource challenges when scaled up for broader use.^{8,9,11}

RE104, which has a shorter, but intense psychoactive state (~4 hours), has the potential for psilocybin-like therapeutic activity but could halve the clinical resource burden.

First-in-Human Phase 1 Study of RE104

Subcutaneous RE104 was first evaluated in humans for its safety, tolerability, pharmacodynamics (PDs), and pharmacokinetics (PKs) in a double-blind, randomized, placebo-controlled, single-ascending dose trial. The study enrolled a total of 48 healthy volunteers who had prior experience with psychedelics and involved the administration of placebo or 6 active dose levels of RE104 ranging from a low, subperceptual (non-psychedelic, 5 mg) dose to high, very intense (40 mg) doses.

Consistent with the findings in preclinical studies,⁵ RE104 was rapidly converted to its active metabolite, 4-OH-DiPT, which had a half-life of roughly 3 hours and a peak plasma concentration at approximately 1.25 hours of administration, corresponding to the peak of the psychedelic effects of the drug. Overall, RE104 was generally well tolerated with no serious adverse effects and no unexpected adverse effects relative to the safety profile seen with psilocybin as reported in other studies.^{8,9}

For the 30 mg RE104 dose, the psychedelic experience was generally equivalent to the 25 mg COMP360 psilocybin dose shown to be therapeutically useful in clinical studies when measured using the Mystical Experience Questionnaire (MEQ)—however, the duration of the overall altered state of consciousness was halved.

The potential for a therapeutic benefit in treatment trials of patients with depression is suggested by the strong MEQ response rates with 30 mg RE104, which are thought to predict response to psychedelic therapy in depression.^{10,12,13}

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Suitability of RE104 for PPD

The robust pharmacodynamic effects of RE104 may translate into rapid and sustained relief in depression after a single dose. The pharmacokinetics of RE104 are consistent with the possibility of a fast return to breastfeeding for the mother. The shorter duration of the psychoactive experience (vs psilocybin) should allow reduced use of health care resources with less time required to monitor patients during administration in the clinic setting.

Postpartum Depression: A Common, Disabling Complication of Childbearing

PPD (also referred to more recently as perinatal depression) is a serious psychological condition that afflicts as many as 1 in 7 new mothers.¹⁴ PPD presents as a persistent low mood, sleep impairment, feelings of inadequacy or guilt, and a sense of detachment from the newborn.⁷ It is not uncommon for some mothers with PPD to have feelings of self-harm (~19%) and even to experience thoughts of infanticide.^{15-17,18}

PPD is to be distinguished from the “baby blues,” which is typically a transient condition characterized by crying without an apparent reason, irritability, restlessness, and anxiety, which occurs in as many as 85% of new mothers.¹⁹

Treatment Options for PPD: An Unmet Medical Need

New mothers experiencing moderate or severe PPD have very few options. The current standard of care relies primarily on selective serotonin reuptake inhibitors (SSRIs) administered either alone or in combination with psychological counseling.¹⁶

SSRIs are not specifically approved for PPD and may be associated with slow onset and poor therapeutic response, as well as unwanted adverse effects. According to a population-based retrospective cohort study of more than 3 million pregnant women with PPD, 1 in 20 women developed treatment-resistant depression (TRD) within the first year of diagnosis due to inadequate treatment.²⁰

In 2019, brexanolone, a GABA-A modulator of the benzodiazepine type, was the first drug approved by the US Food and Drug Administration (FDA) specifically to treat PPD; however, it has several limitations and is only available as part of a restricted program.²¹ This agent is given as an extended 60-hour intravenous (IV) infusion with several dose titration steps.²² It has a black box warning for excessive sedation and sudden loss of consciousness, requiring continuous pulse oximetry monitoring.

In 2023, the FDA approved zuranolone, also a GABA-A modulator of the benzodiazepine type, for PPD. The recommended dosage of zuranolone is 50 mg taken orally for 14 days. Similar to brexanolone, zuranolone has a black box warning for excessive sedation, describing an impaired ability to drive and perform other potentially hazardous activities and that individuals may not be able to assess their own competence or degree of impairment.^{23,24}

Animal studies even indicate that this agent may cause fetal harm if taken during pregnancy. A clinical lactation study conducted in 14 healthy lactating women found that zuranolone administered at a dose of 30 mg for 5 days was excreted in breast milk at low levels (with maximum relative infant dose of <1% at steady state); however, no data exist on the impact of zuranolone on infant outcomes.²⁴

Despite the addition of these new agents to the therapeutic armamentarium, a significant unmet need still exists for additional treatment options for patients with PPD, particularly for agents that can produce safe and rapid symptom relief with an earlier return to routine maternal activities. Treatments are needed that not only are accessible, but also address the extremely important needs relevant to infant-maternal bonding, including breastfeeding, that can affect the child's long-term development.²⁵

Psychedelic Therapy for PPD Treatment

The neurobiology of PPD is not completely understood, but it is proposed that several underlying factors may collectively contribute, including changes in estrogen; progesterone, oxytocin, and stress hormone levels; genetic factors; neuroinflammatory changes; and neural circuit level changes.^{16,26} Evidence is also emerging that PPD is associated with a reduction in both amygdala response and corticolimbic activity.^{27,28}

Since serotonergic psychedelics enhance amygdala activity and corticolimbic circuitry,^{29,30} this mechanism of action could contribute to potential therapeutic effects in the treatment of PPD. A number of potential therapeutic benefits associated with use of psychedelics to treat PPD have been described in numerous clinical studies.⁷

Anecdotal reporting suggests that psilocybin therapy can promote a sense of reconnection and enhanced connectedness with the mother, the baby, and the mother's support network.⁷ This can be accompanied by an improvement in the interaction between mother and infant, as well as an enhanced sensitivity of the mother and the bond between mother and infant.

Phase 2 Study of RE104 in Individuals With PPD

The potential for rapid improvement in depressive symptoms and improved functioning shortly after the treatment with RE104 would be valuable to both mothers affected by PPD and their infants. To investigate the effects of RE104 on depressive symptoms, a phase 2, multicenter (~35 US study centers), randomized, double-blind, parallel-group, dose-controlled study involved adult female patients with PPD.

The study is designed to determine if treatment with a single SC dose of RE104 (30 mg) reduces depressive symptoms in participants with PPD compared with a subperceptual dose of RE104 (1.5 mg). The primary endpoint of the study is the change from baseline in total Montgomery-Åsberg Depression Rating Scale (MADRS) score.

The study is expected to begin enrolling in mid-2024, with an expected completion in 2025. Patients will be eligible to enroll in the study if they are female aged 18 to 45 years (inclusive), have a diagnosis of moderate to severe PPD, and are not breastfeeding. It is

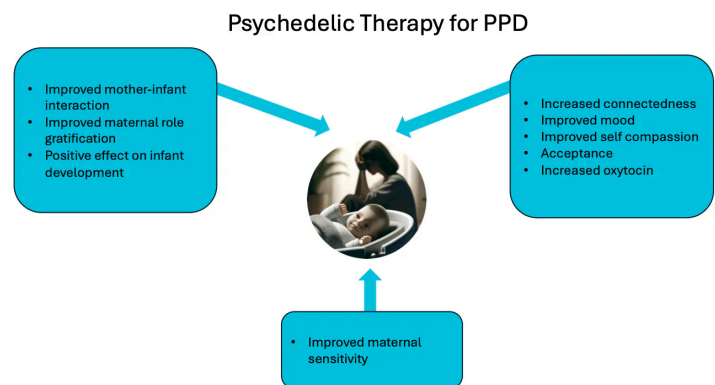


Figure. Clinical Benefits of Psilocybin Treatment in PPD Reported in Clinical Studies

important to note that the exclusion of women who are breastfeeding in this study may eliminate a number of women with PPD who could also benefit from treatment. Consequently, the safety of RE104 in breastfeeding mothers will be assessed in a future study.

Concluding Thoughts

The clinical research and development program at Reunion Neuroscience is focused on extending the frontiers of neuroscience to develop innovative, serotonergic psychedelic therapies for mothers with PPD and individuals with other mental health disorders. Reunion's leading clinical drug candidate, RE104, is a patented prodrug of 4-OH-DiPT with 5HT_{2A} agonist activity that produces a brief, but intense, psilocybin-like psychedelic activity that lasts only ~4 hours.

Data from the phase 1 study in healthy adults show a favorable safety profile compared with available PPD treatments. When phase 2 is completed and analyzed, it is hoped that the results will demonstrate beneficial effects of RE104 including a rapid and long-term relief of depressive symptoms with improved functioning, which could be beneficial for mothers and their infants.

Drs Alexander, Hocevar-Trnka, and Bryson and Ms Taylor are employees of Reunion Neuroscience, Inc, in Morristown, New Jersey.

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