RE104: A Novel Serotonergic Psychedelic 4-OH-DiPT Prodrug for the Treatment of Postpartum Depression

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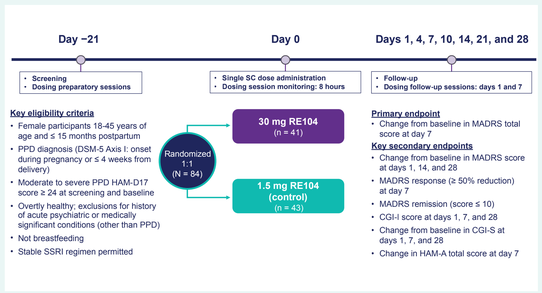
BACKGROUND

- Postpartum depression (PPD) is a serious pregnancy complication reported in approximately 15% of women in the US[1]
- PPD is associated with significant negative mental health impacts for mothers and can result in adverse effects on infant development[2,3]
- RE104, a unique, proprietary, subcutaneously administered prodrug of 4-OH-DiPT, is a novel psychedelic investigational compound being developed for the treatment of PPD and other mental health conditions[4]
- Preclinical and clinical characterization has confirmed that the pharmacology of RE104 is similar to that of the well-characterized psychedelic active form of psilocybin (4-OH-DMT); however, RE104 provides a significantly shorter and more reproducible acute psychedelic experience in the clinic[5]
- Given the critical adverse impact of PPD and continued need for rapidly effective and well-tolerated treatments, the RECONNECT study, a multicenter, randomized, double-blind, active dose-controlled Phase 2 clinical trial of RE104 for the treatment of PPD (NCT06342310), was initiated
- Here, we present efficacy and safety results from the Phase 2 RECONNECT study

METHODS

- The Phase 2 RECONNECT study evaluated the efficacy and safety of a single subcutaneous dose of 30 mg RE104 in participants with moderate to severe PPD vs a control dose of 1.5 mg RE104 at 37 sites across the US (**Figure 1**)
  - A dose of 30 mg of RE104 was selected based on the results of a Phase 1 trial in healthy volunteers, which suggested its potential for efficacy and tolerability as the target therapeutic dose[5]
  - A subperceptual dose of 1.5 mg RE104 was selected as the comparator in this study to reduce functional unblinding, as all participants were informed that they would receive RE104 (as opposed to an inert placebo)
  - Blinded, independent site raters were used to assess the primary endpoint
- The primary endpoint was the change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at day 7
- Key secondary endpoints are included in **Figure 1**
  - Change from baseline in Barkin Index of Maternal Functioning (BIMF) score was also assessed
- Safety was evaluated from dosing through study completion on day 28
- Discharge readiness was assessed based on clinically relevant safety parameters of the drugs in this class, including vitals (blood pressure/heart rate), physical stability, cognitive awareness, psychological factors, and patient self reports of functional capacity
- Session monitoring was conducted by qualified Session Monitors
  - Preparation, day-of-dosing monitoring, and follow-up was supportive only, without specific psychotherapy

Figure 1. RECONNECT study design



CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; DSM, Diagnostic and Statistical Manual of Mental Disorders; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Depression Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; PPD, postpartum depression; SC, subcutaneous; SSRI, selective serotonin reuptake inhibitor.

- A mixed model for repeated measures (MMRM) analysis with multiple imputation for missing data was used to evaluate the primary endpoint
  - The model included treatment, visit, and a treatment-by-visit interaction term, as well as baseline MADRS score using an unstructured covariance matrix
- Secondary endpoints were summarized using descriptive statistics
  - The normal approximation binomial test was used to evaluate MADRS response and remission rates
  - A 2-sample *t* test was used to evaluate the BIMF endpoint

RESULTS

- Most randomized participants completed the study, with lost to follow up being the most common reason for withdrawal. Retention was higher among those randomized to 30 mg vs 1.5 mg RE104 (**Table 1**)
- There were no study withdrawals due to adverse events

Table 1. Disposition

	30 mg RE104	1.5 mg RE104
Randomized, n	41	43
Completed study, n (%)	40 (97.6)	38 (88.4)
Study withdrawal, n (%)	1 (2.4)	5 (11.6)
Lost to follow-up, n (%)	1 (100)	3 (60.0)
Withdrawal by participant, n (%)	0	1 (20.0)
Other, n (%)	0	1 (20.0)

- Participant demographics and baseline characteristics were generally similar between groups; there were more participants in the 30 mg RE104 group who had concurrent treatment (SSRI and/or psychotherapy) at baseline (**Table 2**)

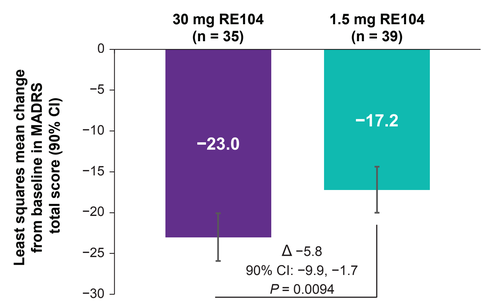
Table 2. Demographics and baseline characteristics

Parameter	30 mg RE104 (n = 41)	1.5 mg RE104 (n = 43)
Age, mean (SD), years	33.3 (5.3)	31.2 (5.9)
Duration of PPD, mean (SD), months	7.6 (3.9)	7.0 (3.5)
MADRS total score, mean (SD)	33.4 (6.9)	33.2 (5.0)
HAM-A score, mean (SD)	21.8 (6.3)	21.1 (7.1)
Onset of PPD—post-partum, n (%)	26 (63.4)	24 (55.8)
History of prior PPD episodes, n (%)	13 (31.7)	12 (27.9)
Prior hallucinogenic agent experience, n (%)	4 (9.8)	4 (9.3)
SSRI use, n (%)	5 (12.2)	4 (9.3)
Concomitant psychotherapy, n (%)	8 (19.5)	2 (4.7)

HAM-A, Hamilton Rating Scale for Anxiety; MADRS, Montgomery-Åsberg Depression Rating Scale; PPD, postpartum depression; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor.

- The primary endpoint was met. There was a statistically significant and clinically meaningful reduction from baseline in MADRS total score in participants receiving 30 mg vs 1.5 mg RE104 on day 7 (**Figure 2**)

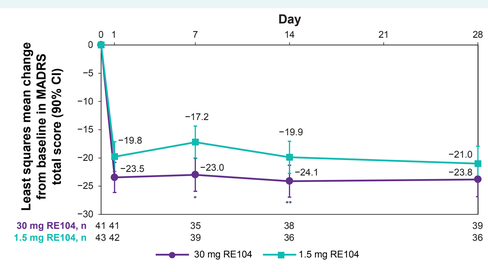
Figure 2. Change from baseline in depression by MADRS total score at day 7



Powered at 80% for 6-point effect size. One-sided *P* value.
MADRS, Montgomery-Åsberg Depression Rating Scale.

- Clinically meaningful reductions in MADRS score were observed with 30 mg RE104 on day 1, with significantly greater reductions associated with 30 mg vs 1.5 mg RE104 at days 7 and 14 with effects maintained through day 28 (**Figure 3**)

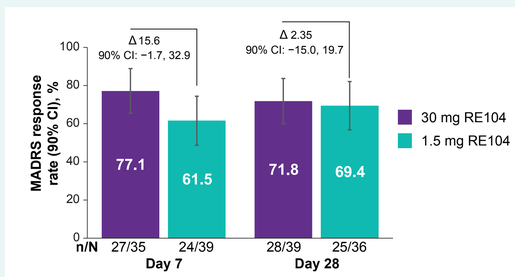
Figure 3. Change from baseline in depression by MADRS total score through day 28



*$P < 0.01$; **$P < 0.05$; one-sided *P* values.
MADRS, Montgomery-Åsberg Depression Rating Scale.

- At day 7, MADRS response was observed in 77.1% of participants receiving 30 mg RE104 compared with 61.5% of participants receiving 1.5 mg RE104 (**Figure 4**)
- Response rates were maintained through day 28 (**Figure 4**)

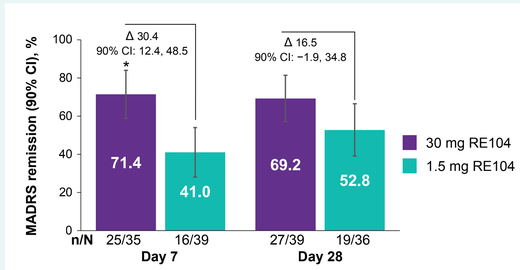
Figure 4. Improvement in depression as measured by MADRS response at days 7 and 28



MADRS, Montgomery-Åsberg Depression Rating Scale.

- At day 7, 71.4% of participants receiving 30 mg RE104 achieved MADRS remission compared with 41.0% of participants receiving 1.5 mg RE104 (**Figure 5**)
- High remission rates were maintained through day 28 (**Figure 5**)

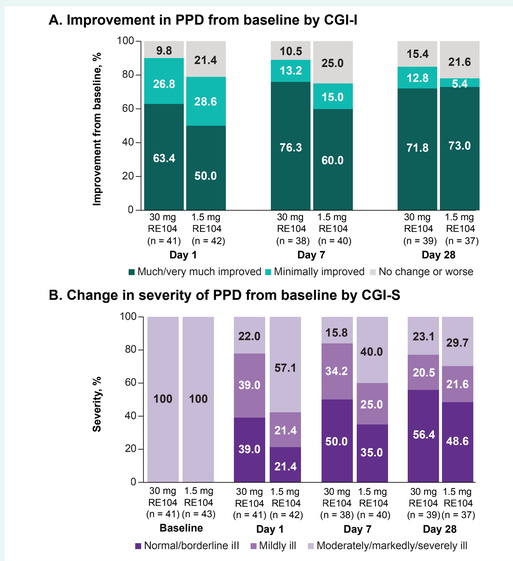
Figure 5. Depression remission by MADRS total score at days 7 and 28



*$P < 0.01$; one-sided *P* value.
MADRS, Montgomery-Åsberg Depression Rating Scale.

- Most participants who received 30 mg RE104 reported improvement on the Clinical Global Impression - Improvement (CGI-I; **Figure 6A**) and Clinical Global Impression - Severity (CGI-S; **Figure 6B**) scales, and improvement appeared greater among those who received 30 mg vs 1.5 mg RE104 (**Figure 6**)

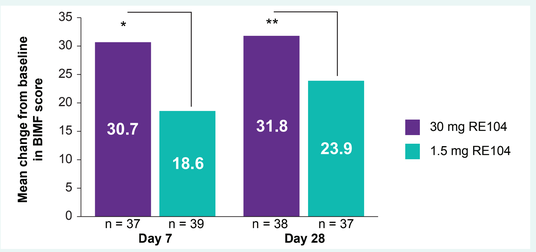
Figure 6. Change from baseline in CGI scores



CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; PPD, postpartum depression.

- Maternal well-being and function (including care of the infant) as assessed by change from baseline in BIMF were also substantially improved with 30 mg vs 1.5 mg RE104 at days 7 and 28 (**Figure 7**)

Figure 7. Mean change from baseline in maternal well being and function at days 7 and 28



*$P < 0.01$; **$P < 0.05$; one-sided *P* values. Baseline scores (SD): 30 mg RE104, 65.4 (16.0); 1.5 mg RE104, 68.6 (16.2).
BIMF, Barkin Index of Maternal Functioning.

- Among all participants, there was a change from baseline to day 7 in HAM-A score of −10.6 with 30 mg RE104 and −9.6 with 1.5 mg RE104, with sustained reductions through day 28
- On day 7, 65.7% of participants receiving 30 mg RE104 and 52.6% of participants receiving 1.5 mg RE104 achieved a HAM-A response, which was maintained through day 28
- In a post hoc analysis, among participants with a baseline HAM-A score ≥ 22, significantly greater reductions in HAM-A were observed with 30 mg RE104 (−17.7 [6.7]) compared with 1.5 mg RE104 (−9.6 [8.4]) on day 7; reductions were maintained through the day 28 follow-up visit

Safety and Tolerability

- There were no serious treatment-emergent adverse events (TEAEs) or deaths, and no evidence of treatment-related suicidal ideation or behavior in either arm (**Table 3**)
- The majority of TEAEs occurred on day 0, were mild to moderate in intensity, transient, and resolved spontaneously on the day of dosing (**Table 3**)
- The most common TEAEs for 30 mg RE104 were nausea, headache, dizziness, vomiting, visual hallucinations, and anxiety (**Table 3**)

Table 3. Overall safety summary

TEAE, n (%)	30 mg RE104 (n = 41)	1.5 mg RE104 (n = 43)
Any TEAE	38 (92.7)	27 (62.8)
TEAEs (≥ 10% in any arm)		
Nausea	18 (43.9)	7 (16.3)
Headache	14 (34.1)	8 (18.6)
Dizziness	11 (26.8)	3 (7.0)
Vomiting	10 (24.4)	1 (2.3)
Hallucinations, visual	9 (22.0)	2 (4.7)
Anxiety	8 (19.5)	3 (7.0)
Illusion	6 (14.6)	2 (4.7)
Tremor	5 (12.2)	1 (2.3)
Feeling abnormal	5 (12.2)	1 (2.3)
Chills	5 (12.2)	0
Treatment-related TEAEs	37 (90.2)	23 (53.5)
Serious TEAEs	0	0
TEAEs leading to withdrawal	0	0
TEAEs by maximum severity		
Mild	24 (58.5)	21 (48.8)
Moderate	12 (29.3)	6 (14.0)
Severe	2 (4.9)[a]	0
TEAEs of special interest		
Psychiatric	31 (75.6)	15 (34.9)
Seizure related	0	0

[a]2 events of nausea: 1 event on day 0 was treatment related, and 1 event on day 28 was not treatment related (attributed to cannabis use).
TEAE, treatment-emergent adverse event.

- Consistent with its pharmacokinetics,[5] 93% of participants receiving 30 mg RE104 were clinically assessed by the investigator as presenting no signs or symptoms posing a risk for discharge at 4 hours after treatment (the first time point at which discharge readiness was assessed in this study)

CONCLUSIONS

- In RECONNECT, the first randomized controlled trial of a psychedelic agent evaluated for the treatment of PPD, a single subcutaneous dose of 30 mg RE104 showed substantial and clinically meaningful efficacy, and favorable safety and compliance in treating PPD symptoms
  - The primary endpoint of significant change from baseline in MADRS total score at day 7 was met
    - A rapid improvement in MADRS total score was observed as early as day 1
    - Approximately 70% of participants receiving 30 mg of RE104 were in remission by day 7 and through day 28
  - Efficacy was durable and stable through day 28 with no indication of waning of efficacy
- 30 mg RE104 was generally well tolerated through day 28
  - AEs were consistent with the Phase 1 study[5] and pharmacology observed with other agents in the class[6]
  - Most participants were medically stable and fit for discharge at 4 hours after the single dose of RE104
- Findings support further evaluation of RE104 for the treatment of PPD in a Phase 3 study, as well as development in other mood and anxiety disorders

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