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

Mark Pollack, Jasna Hocevar-Trnka, Nathan Bryson, Beatrix Taylor, Robert Alexander

Reunion Neuroscience, Inc; Morristown, NJ

Presenting Author: Mark Pollack, MD; Reunion Neuroscience, Inc

CONCLUSIONS

1. Overall, RE104 was generally well tolerated with robust pharmacodynamic (PD) effects observed at doses ≥30 mg that closely aligned with the pharmacokinetic (PK) profile of 4-OH-DiPT
2. The modified Drug Effect Questionnaire (DEQ) scores and Mystical Experience Questionnaire (MEQ) responder rates observed with RE104 doses ≥30 mg indicate potential for therapeutic effect in treatment trials, given that the intensity and quality of the subjective drug experience may predict treatment response[1-3]
3. The mean duration of the subjective experience as measured by DEQ was 3.6 hours following administration of 30 mg RE104, representing a 50% reduction in psychoactive experience duration relative to historical evidence with psilocybin and a more convenient duration for clinical monitoring
4. The adverse effect (AE) profile of RE104 is similar to psilocybin,[4,5] with no serious AEs and no clinically significant vital sign, clinical laboratory, or electrocardiogram findings at doses up to and including 40 mg
   - At doses ≥35 mg, 2 challenging experiences were observed
5. These data informed dose selection of RE104 at 30 mg for a randomized, active dose–controlled, phase 2 trial in women with moderate to severe postpartum depression (PPD), currently underway

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INTRODUCTION

- Approximately 1 in 8 women experience symptoms of PPD following delivery[6]
- PPD is associated with negative impacts to both maternal mental health (including increased risk for suicide) and infant development (including delays)[6,7]
- The classical serotonergic psychedelic psilocybin has exhibited therapeutic promise in recent early-phase clinical trials in depressive disorders[4,8] but is associated with a long psychoactive state (6-8 hours) that requires extensive monitoring of participants by clinic staff,[4,5,8] posing scalability challenges with broader use
- RE104, a unique, proprietary, subcutaneously administered 4-OH-DiPT prodrug, is a novel psychedelic investigational compound being developed for the treatment of postpartum depression and other mental health conditions
  - The prodrug design of RE104 overcomes the solubility, stability, and bioavailability challenges with 4-OH-DiPT[9]
- 4-OH-DiPT has similar pharmacology to the well-characterized psychedelic active form of psilocybin (4-OH-DMT), with a significantly shorter and more reproducible psychedelic experience

OBJECTIVES

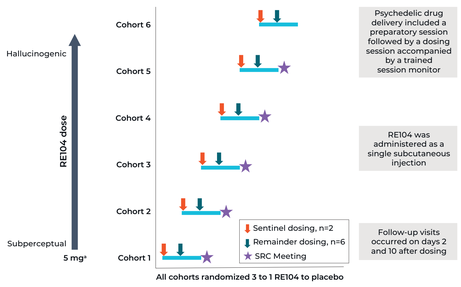
- To characterize the safety, tolerability, PD, and PK of RE104 in a phase 1, first-in-human (FIH) study and to present an overview of the phase 2 trial in PPD

METHODS

STUDY DESIGN

- This phase 1, FIH, double-blind, parallel group, single-ascending dose trial enrolled healthy adult volunteers with prior psychedelic experience
- Participants were randomized 3 to 1 RE104 to placebo in 6 cohorts (**Figure 1**)
- The study was conducted at PARC Clinical Research, University of Adelaide, Australia, with the first patient dosed in July 2022 and the last patient dosed in April 2023

Figure 1. Study design.



SRC, safety review committee. *5 mg was the maximum recommended safe starting dose for RE104.

OUTCOMES

- Study outcomes are shown in **Table 1**

Table 1. Study Outcomes

Safety and tolerability		
▪ Vital signs	▪ Electrocardiography	▪ Injection site reactions
▪ Clinical laboratory assessments	▪ AE reporting	
PK		
▪ RE104 and 4-OH-DiPT C_{max}, T_{max}, and $t_{1/2}$		
PD		
Modified DEQ administered as 2 questions: ▪ 1) "Do you feel a drug effect right now?" (DEQ-Feel) 2) "Are you high right now?" (DEQ-High) ▪ Responses ranged from 0 (not at all) to 10 (extremely) ▪ DEQ assessments were performed before dosing, before PK blood sampling, and at 14, 29, 44, 59, 74, 89, 119, 179, 209, 239, 299, and 359 minutes after dosing ▪ DEQ response score ≤1 is suggestive of the end of the psychoactive experience and is used to define mean experience duration	MEQ ▪ Validated 30-item questionnaire composed of 4 domains of psychedelic experience (mystical, positive mood, transcendence of time and space, and ineffability); scores range from 0 (none/not at all) to 5 (extreme)[10] ▪ MEQ total score was the sum of response scores from all items and calculated as a percent of the maximum total score ▪ MEQ responders were defined as participants who had an MEQ total score ≥60% of the maximum score (also referred to as a "complete mystical experience")	

AE, adverse effect; C_{max}, maximum plasma concentration; DEQ, Drug Effect Questionnaire; MEQ, Mystical Experience Questionnaire; PD, pharmacodynamics; PK, pharmacokinetics; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

RESULTS

STUDY PARTICIPANTS

- A total of 48 participants were enrolled across 6 active dose levels of RE104 or placebo (n=6 at 5 mg, n=6 at 10 mg, n=6 at 20 mg, n=9 at 30 mg, n=6 at 35 mg, n=3 at 40 mg, and n=12 placebo)
  - Two participants were randomized to placebo in each of 6 serially enrolled cohorts and pooled to form a single placebo group
- Overall, the mean age was 37 years, 27% of participants were female, 94% were White, and mean body mass index was 26 kg/m^2

SAFETY AND TOLERABILITY

- There were no serious AEs in any treated participants and all completed dosing (**Table 2**)
- The most common treatment-related AEs for RE104 were nausea, sinus tachycardia (asymptomatic at a maximum recorded value of 115 beats per minute), restlessness, and headache
- Two participants, 1 at 35 mg and 1 at 40 mg, experienced agitation as a severe AE and received midazolam. Both AEs resolved after administration of concomitant medication
- No injection site adverse reactions were reported, but there was 1 AE of mild bruising related to the administration procedure
- There were no evident blood pressure effects or clinically significant vital sign, clinical laboratory, or electrocardiogram findings during the study

Table 2. Summary of AEs

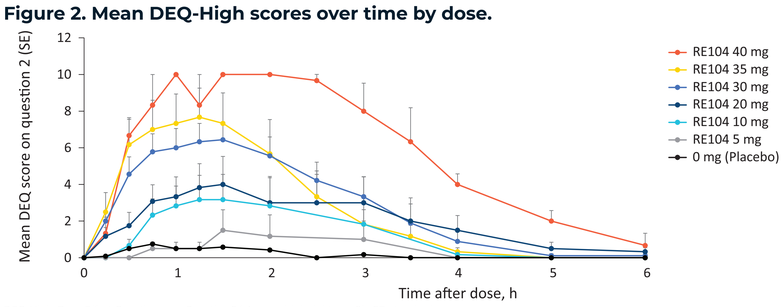
	RE104						
n (%)	5 mg (n=6)	10 mg (n=6)	20 mg (n=6)	30 mg (n=9)	35 mg (n=6)	40 mg (n=3)	Placebo (n=12)
Any AE	2 (33.3)	2 (33.3)	2 (33.3)	8 (88.9)	5 (83.3)	3 (100)	4 (33.3)
Any SAE	0	0	0	0	0	0	0
Severe AEs	0	0	0	0	1 (16.7)	1 (33.3)	0
AEs leading to withdrawal	0	0	0	0	0	0	0
AEs that occurred in ≥2 participants, preferred term by system organ class, n (%)							
Cardiac disorders							
Sinus tachycardia	0	0	0	4 (44.4)	3 (50.0)	2 (66.7)	0
Gastrointestinal disorders							
Abdominal pain	0	0	0	2 (22.2)	0	0	0
Diarrhea	0	0	1 (16.7)	0	2 (33.3)	0	0
Nausea	1 (16.7)	2 (33.3)	0	3 (33.3)	2 (33.3)	2 (66.7)	0
Vomiting	1 (16.7)	0	0	0	0	1 (33.3)	0
General disorders							
Fatigue	0	0	0	2 (22.2)	0	0	0
Feeling hot	0	0	1 (16.7)	0	0	0	1 (8.3)
Hyperhidrosis	0	0	1 (16.7)	0	1 (16.7)	1 (33.3)	0
Thirst	0	0	0	0	2 (33.3)	0	0
Injury, poisoning, and procedural complications							
Musculoskeletal injury	0	0	0	1 (11.1)	0	0	1 (8.3)
Musculoskeletal and connective tissue disorders							
Muscle twitching	0	0	0	3 (33.3)	0	0	0
Investigations							
Heart rate increased	0	0	1 (16.7)	0	0	0	1 (8.3)
Nervous system disorders							
Headache	0	1 (16.7)	0	1 (11.1)	4 (66.7)	0	0
Tremor	0	0	0	1 (11.1)	0	1 (33.3)	0
Psychiatric disorders							
Agitation	0	0	0	0	2 (33.3)	2 (66.7)	0
Restlessness	0	0	0	3 (33.3)	3 (50.0)	1 (33.3)	0

SAE, serious adverse event.

PHARMACODYNAMICS

- Average DEQ-High scores over time demonstrated a dose-dependent effect (**Figure 2**)
- For doses ≥30 mg, peak DEQ-High scores ranged from 7 to 10 and the mean time to peak score was 1.2 hours; the mean experience duration at 30 mg was 3.6 hours, and all participants had a score ≤1 at 4 hours post dose

Figure 2. Mean DEQ-High scores over time by dose.



DEQ-High, Drug Effect Questionnaire Question 2 ("Are you high right now?"); SE, standard error.

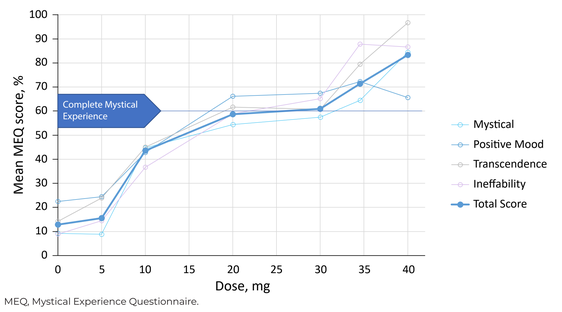
- A dose-related increase in frequency of MEQ responders was observed, with 66.7%, 83.3%, and 100% of participants in the RE104 30-mg, 35-mg, and 40-mg treatment groups, respectively, having a "complete mystical experience" (defined as ≥60% of MEQ total score) predictive of clinical efficacy,[10] based on MEQ total scores (**Table 3**)
  - The proportion of MEQ responders by domain and dosing group is shown in **Figure 3**

Table 3. Summary of MEQ Responders by Dose

Dose	n	Participants with MEQ total score ≥60%, % (n)
Placebo	12	8.3 (1)
RE104		
5 mg	6	0 (0)
10 mg	6	50 (3)
20 mg	6	16.7 (1)
30 mg	9	66.7 (6)
35 mg	6	83.3 (5)
40 mg	3	100 (3)

MEQ, Mystical Experience Questionnaire.

Figure 3. Mean MEQ score by individual domain and total score per RE104 dose level.[10]



MEQ, Mystical Experience Questionnaire.

PHARMACOKINETICS

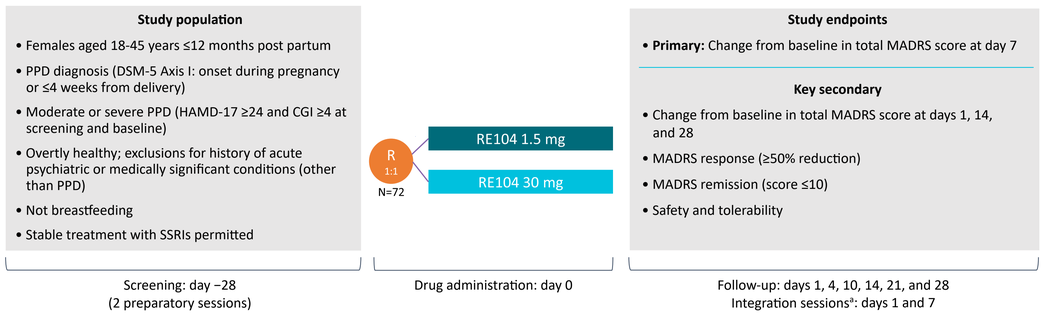
- RE104 was rapidly converted into 4-OH-DiPT, which had a time to maximum plasma concentration of approximately 1.25 hours and a half-life of approximately 2 to 3 hours across dose levels. PK characterization was consistent with prior preclinical data

PHASE 2 TRIAL OVERVIEW

- A randomized, active dose–controlled trial of RE104 in participants with PPD has been initiated (**Figure 4**)

Figure 4. Phase 2 trial overview.

RECONNECT is a multicenter, randomized, double-blind, active dose–controlled phase 2 study evaluating the efficacy and safety of a single dose of RE104 for subcutaneous injection in the treatment of adult female patients with PPD



CGI, Clinical Global Impression; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; PPD, postpartum depression; SSRI, selective serotonin reuptake inhibitor. [a]Integration sessions are supportive, without formal or manualized psychotherapy.

- RE104 has a potential role in the treatment of PPD as a novel serotonergic antidepressant therapeutic candidate with potential for rapid symptom relief after a single treatment period of 2 to 4 hours, shorter than other available treatments (**Table 4**)

Table 4. Target Profile of RE104 Compared With Other Treatments for Postpartum Depression

Parameter	Investigational RE104 PPD	Investigational Psilocybin TRD	FDA approved Zurzuvae® (zuranolone) PPD	FDA approved Zulresso® (brexanolone) PPD	Off-label clinical use SSRI: TRD, PPD
Pharmacology	Serotonergic psychedelic	Serotonergic psychedelic	Neuroactive steroid	Neuroactive steroid	Classical antidepressant
Single dose	✓	✓	Once daily oral; 14 d	60 h infusion	
Short psychoactive state (<4 h)	✓		n/a	n/a	n/a
Fast relief	✓	✓	✓	✓	
Significant response rates	✓	✓	✓	✓	✓
Fast return to breastfeeding (24-48 h)	✓				Risk-based labeling for breastfeeding
Durable response (>28 d)	✓	✓	✓	✓	Only with continuous dosing
Composition of matter patent	✓		✓	✓	

PPD, postpartum depression; SSRI, selective serotonin reuptake inhibitor; TRD, treatment-resistant depression.