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Phase 1 Results and Phase 2 Clinical Development of RE104: A Novel Serotonergic Psychedelic 4-OH-DiPT Prodrug

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CONCLUSIONS

1. Overall, RE104 was generally well tolerated with robust pharmacodynamic (PD) effects observed at doses ≥33 mg that closely aligned with the pharmacokinetic (PK) profile of 4-OH-DiPT
2. The Drug Effect Questionnaire (DEQ-High) scores and Mystical Experience Questionnaire (MEQ) responder rates observed with RE104 doses ≥33 mg indicate potential for therapeutic effect in treatment trials, given that the intensity and quality of the subjective drug experience may predict treatment response to psilocybin therapy in depression[1-3]
3. The mean duration of the subjective experience with RE104 at 33 mg was 3.7 hours, representing a 50% reduced psychoactive experience relative to historical evidence with psilocybin, and a 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 44 mg
   - At doses ≥38 mg, 2 challenging experiences were observed
5. These data informed dose selection of RE104 at 33 mg for a randomized, active dose–controlled, phase 2 trial in women with moderate to severe postpartum depression (PPD), with initiation planned for the second half of 2023

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The data presented herein are based on data generated from preliminary draft outputs of the final FT-104-101 study analysis; data are not final and may be subject to change.

INTRODUCTION

- The classical serotonergic psychedelic psilocybin has exhibited therapeutic promise in recent early-phase clinical trials in depressive disorders[4,6] but is associated with a long psychoactive state (6-8 hours) that requires extensive monitoring of participants by clinic staff,[4-6] posing scalability challenges with broader use
- RE104, a unique, proprietary 4-OH-DiPT prodrug, is a novel psychedelic investigational compound being developed for the treatment of postpartum depression and other mental health conditions
  - RE104 is composed of a glutarate moiety appended to the phenolic functional group of 4-OH-DiPT to improve solubility, stability, and reproducibility in PK and PD of the active compound[7]
- Preclinical characterization confirmed similar pharmacology of 4-OH-DiPT to the well-characterized psychedelic active form of psilocybin (4-OH-DMT), while in vivo studies demonstrated a significantly shorter and more reproducible psychedelic experience

OBJECTIVES

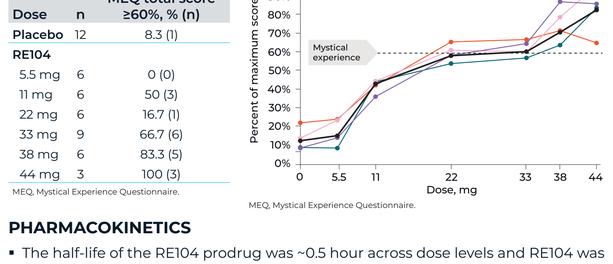
- To characterize the safety, tolerability, PD, and PK of RE104 in a phase 1, first-in-human (FIH) study and to present an overview of the phase 2 trial in PPD

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 on July 20, 2022, and the last patient dosed on March 23, 2023

Figure 1. Study design.



SRC, safety review committee.

OUTCOMES

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

Table 1. Study Outcomes

Safety and tolerability

- Vital signs
- Clinical laboratory assessments
- Electrocardiography
- AE reporting
- Injection site reactions

PK

- RE104 and 4-OH-DiPT C_{max}, T_{max}, and $t_{1/2}$
- Blood sampling for PK assessments was performed before dose and at 3, 7, 15, 30, 45, 60, 75, and 90 min, and 2, 3, 4, 5, 6, 8, 12, 16, and 24 h (day 2) post dose

PD

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 range from 0 (not at all) to 10 (extremely)
- DEQ assessments were performed before dose, before PK blood sampling, and at 14, 29, 44, 59, 74, 89, 119, 179, 209, 239, 299, and 359 minutes after dosing
- A DEQ ≤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 mystical, positive mood, transcendence of time and space, and ineffability factors of the psychedelic experience; score range from 0 (none/not at all) to 5 (extreme)[8]
- 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

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 5.5 mg, n=6 at 11 mg, n=6 at 22 mg, n=9 at 33 mg, n=6 at 38 mg, n=3 at 44 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 36 years, 27% of participants were female, 88% 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 38 mg and 1 at 44 mg, experienced distress 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

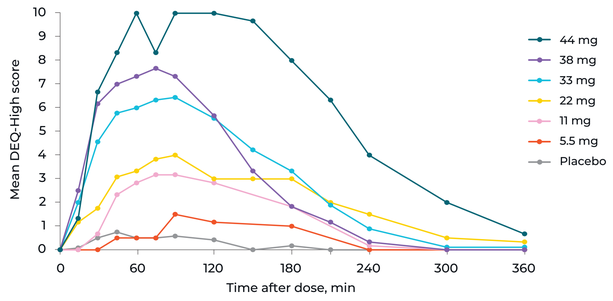
	RE104						
n (%)	5.5 mg (n=6)	11 mg (n=6)	22 mg (n=6)	33 mg (n=9)	38 mg (n=6)	44 mg (n=3)	Placebo (n=12)
Any AE	2 (33.3)	2 (33.3)	2 (33.3)	8 (88.9)	5 (83.3)	3 (100)	4 (33.3)
Any SAE	0	0	0	0	0	0	0
Severe AEs	0	0	0	0	1 (16.7)	1 (33.3)	0
AEs leading to withdrawal	0	0	0	0	0	0	0
AEs by preferred term (≥2 participants across all dose levels)							
Nausea	1 (16.7)	2 (33.3)	0	3 (33.3)	2 (33.3)	2 (66.7)	0
Sinus tachycardia	0	0	0	4 (44.4)	3 (50.0)	2 (66.7)	0
Restlessness	0	0	0	3 (33.3)	3 (50.0)	1 (33.3)	0
Headache	0	1 (16.7)	0	1 (11.1)	4 (66.7)	0	0
Agitation	0	0	0	0	2 (33.3)	2 (66.7)	0
Diarrhea	0	0	1 (16.7)	0	2 (33.3)	0	0
Hyperhidrosis	0	0	1 (16.7)	0	1 (16.7)	1 (33.3)	0
Muscle twitching	0	0	0	3 (33.3)	0	0	0
Abdominal pain	0	0	0	2 (22.2)	0	0	0
Distress	0	0	0	0	1 (16.7)	1 (33.3)	0
Fatigue	0	0	0	2 (22.2)	0	0	0
Feeling hot	0	0	1 (16.7)	0	0	0	1 (8.3)
Heart rate increased	0	0	1 (16.7)	0	0	0	1 (8.3)
Musculoskeletal injury	0	0	0	1 (11.1)	0	0	1 (8.3)
Thirst	0	0	0	0	2 (33.3)	0	0
Tremor	0	0	0	1 (11.1)	0	1 (33.3)	0
Vomiting	1 (16.7)	0	0	0	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 ≥33 mg, peak DEQ-High scores ranged from 7 to 10 and the mean time to peak score was 1.1 hours; the Mean Experience Duration at 33 mg was 3.7 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?").

- A dose-related increase in frequency of MEQ responders was observed, with 66.7%, 83.3%, and 100% of participants in the RE104 33-mg, 38-mg, and 44-mg treatment groups, respectively, having a "complete" mystical experience (defined as ≥60% of MEQ total score) predictive of clinical efficacy, 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		
5.5 mg	6	0 (0)
11 mg	6	50 (3)
22 mg	6	16.7 (1)
33 mg	9	66.7 (6)
38 mg	6	83.3 (5)
44 mg	3	100 (3)

MEQ, Mystical Experience Questionnaire.

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

MEQ, Mystical Experience Questionnaire.

PHARMACOKINETICS

- The half-life of the RE104 prodrug was ~0.5 hour across dose levels and RE104 was not detectable in plasma within 5 hours of administration at any dose
- The maximum plasma concentration of 4-OH-DiPT after administration of RE104 was proportional to the RE104 dose (**Table 4**)

Table 4. Mean PK Parameters for RE104 and 4-OH-DiPT After RE104 Administration

RE104 dose	5.5 mg (n=6)	11 mg (n=6)	22 mg (n=6)	33 mg (n=9)	38 mg (n=6)	44 mg (n=3)
RE104 (prodrug), mean (CV%)						
C_{max}, ng/mL	173 (60)	527 (39)	788 (16)	1461 (56)	1246 (22)	1805 (20)
T_{max}, h	0.42 (31)	0.33 (39)	0.38 (36)	0.25 (45)	0.38 (36)	0.42 (35)
$t_{1/2}$, h	0.53 (28)	0.48 (21)	0.50 (24)	0.43 (14)	0.64 (40)	0.52 (13)
4-OH-DiPT (active drug), mean (CV%)						
C_{max}, ng/mL	18 (29)	60 (35)	77 (42)	137 (38)	124 (28)	275 (9)
T_{max}, h	1.12 (23)	1.21 (40)	1.42 (58)	1.07 (42)	1.08 (48)	1.25 (20)
$t_{1/2}$, h	3.42 (63)	3.55 (51)	3.27 (83)	2.79 (52)	2.79 (49)	3.76 (54)

C_{max}, maximum plasma concentration; CV, coefficient of variation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

- The PK profile of 4-OH-DiPT was aligned with the PD profile, with the peak plasma concentration and PD effects coinciding; however, the subjective drug effect declined faster than the plasma levels of 4-OH-DiPT (example from the 33-mg dose group shown in **Figure 4A**)
- When PK-PD correlation was examined across all cohorts and dose levels, the mean 4-OH-DiPT concentration appeared to correlate with mean DEQ-High scores over a range of 40 to 100 ng/mL (**Figure 4B**)
- Below 40 ng/mL, mean DEQ-High score did not exceed a value of 2

Figure 4. RE104 pharmacokinetic and pharmacodynamic relationships.

A. Mean plasma 4-OH-DiPT concentrations and DEQ-High scores: RE104 33-mg dose group

B. Mean plasma 4-OH-DiPT concentrations versus DEQ-High scores: all cohorts

DEQ-High, Drug Effect Questionnaire question 2 ("Are you high right now?").

PHASE 2 TRIAL OVERVIEW

- A randomized, active dose–controlled trial of RE104 in participants with PPD is planned for initiation later this year (**Figure 5**)

Figure 5. Phase 2 trial overview.

CGI, Clinical Global Impression; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; PPD, postpartum depression. [a]Additional secondary and exploratory endpoints not shown.