Anxiety & Depression Association of America Annual Conference

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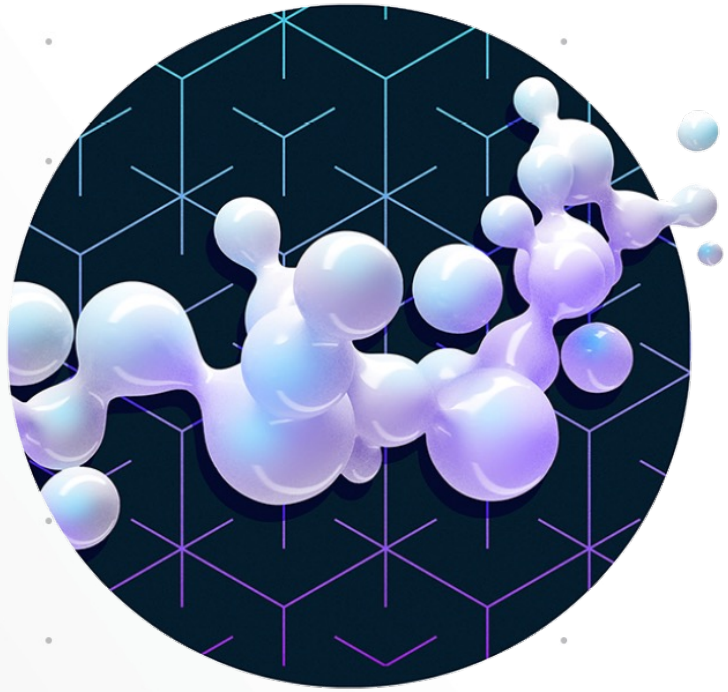
RE104—A Novel, Shorter-Acting Psychedelic for Postpartum Depression



Robert Alexander, MD

Reunion Neuroscience

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- I am employee of Reunion Neurosciences, Inc, and may hold stock or stock options in the company.

Reunion's Focus: Serotoninergic Psychedelics Present Advantages Over Other Treatment Options for Postpartum Depression

Current therapies used for PPD have limitations

- SSRIs (off label)[1-5]
  - Risk-based labeling for breastfeeding
  - Do not offer fast relief or significant response rates
  - Require continuous dosing
- Approved BZD-like therapies offer more rapid responses[6,7]
  - No fast return to breastfeeding (zuranolone, 14-d oral QD; brexanolone, 60-h IV infusion)
  - Boxed warning for excessive sedation (brexanolone) and driving impairment due to CNS depressive effects (zuranolone)

Serotonergic agonism with psychedelics may offer advantages

- Fast onset (<24 h) with durable efficacy after a single dose[8-10]
- Few AEs (acute, related to psychedelic pharmacology); not shown to be addictive[8,10]
- Psilocybin and DMT provide favorable reductions in depressive symptoms[8-10]
  - A single dose of COMP360 (synthetic psilocybin) for treatment-resistant MDD resulted in 29% remission rates at week 3 and a sustained response at week 12 in 20% of participants[11]

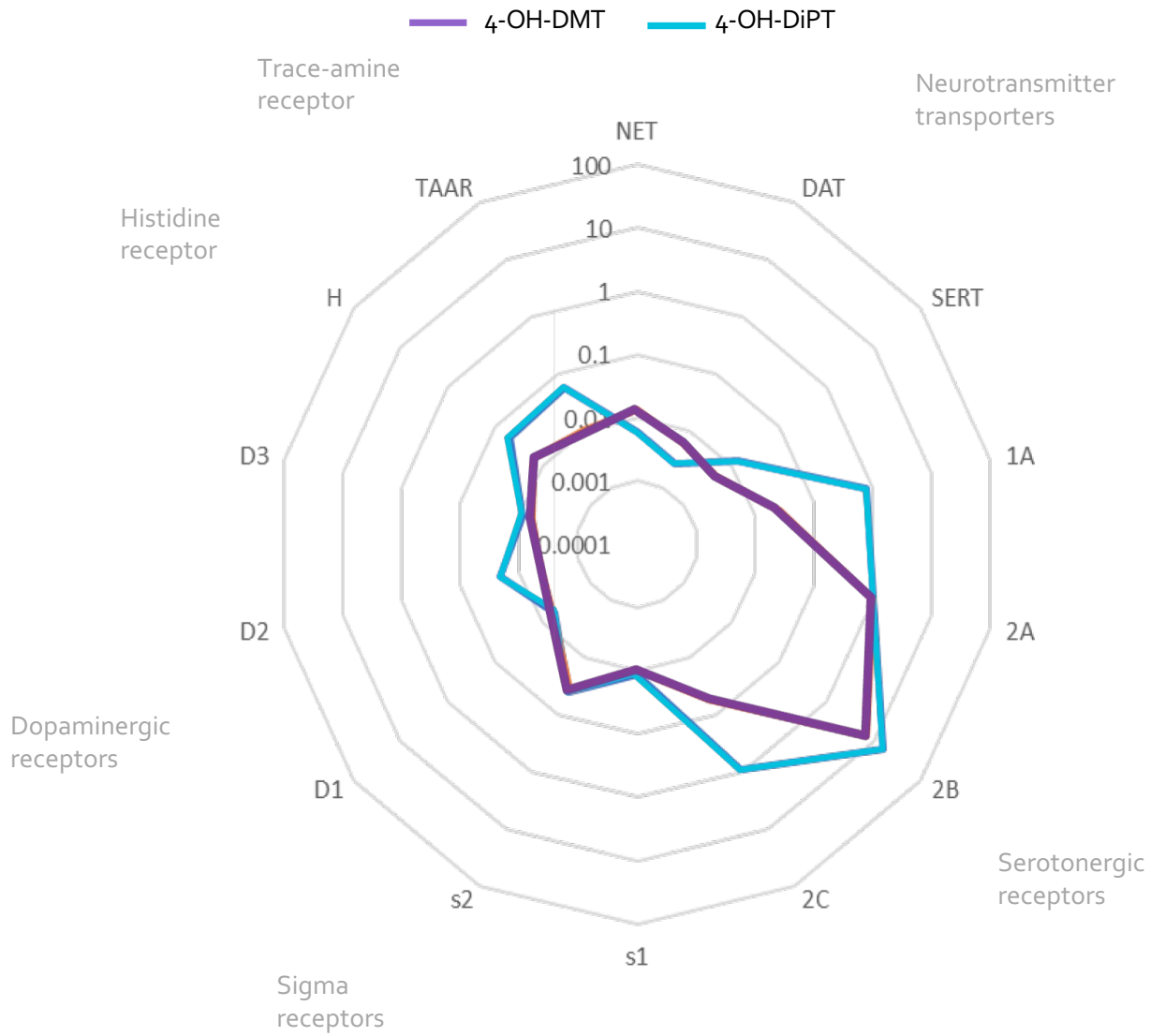
AE, adverse event; BZD, benzodiazepine; CNS, central nervous system; DMT, dimethyltryptamine; IV, intravenous; MDD, major depressive disorder; PPD, postpartum depression; QD, once daily; SSRI; selective serotonin reuptake inhibitor.

1. Prozac (fluoxetine) [package insert]. Eli Lilly and Company; 2023. **2.** Zoloft (sertraline hydrochloride) [package insert]. Viatris, Inc; 2023. **3.** Brown et al. *Cochrane Database Syst Rev*. 2021;2:CD013560. **4.** Papakostas GI. *J Clin Psychiatry*. 2010;71(suppl E1):e03. **5.** American Psychiatric Association. https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines. Accessed March 12, 2024. **6.** Zurzuvae (zuranolone) [package insert]. Biogen, Inc; 2023. **7.** Zulresso (brexanolone) [package insert]. Sage Therapeutics, Inc; 2022. **8.** Galvão-Coelho et al. *Psychopharmacology (Berl)*. 2021;238:341-354. **9.** Griffiths et al. *J Psychopharmacol*. 2016;30:1181-1197. **10.** Ross et al. *J Psychopharmacol*. 2016;30:1165-1180. **11.** Goodwin et al. *New Engl J Med*. 2022;387:1637-1648.

RE104, a New Chemical Entity With a Similar Pharmacological Profile to Psilocybin

- RE104: injectable prodrug of 4-OH-DiPT that is cleaved rapidly by endogenous enzymes
  - Prodrug design overcomes solubility, stability, and bioavailability challenges with 4-OH-DiPT
- The active forms of RE104 (4-OH-DiPT) and psilocybin (4-OH-DMT) have similar pharmacology, including comparable 5HT2A binding affinities

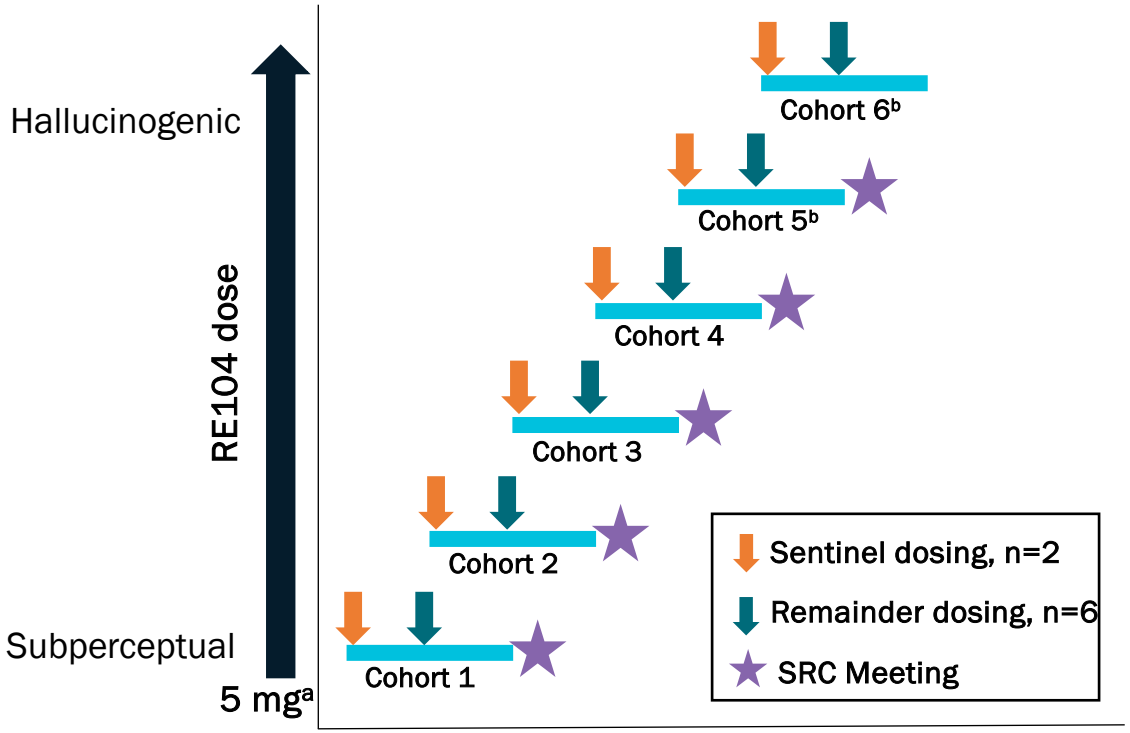
Relative binding constants[1,2]



PK, pharmacokinetic. **1.** Klein et al. *ACS Pharmacol Transl Sci.* 2021;4:533-542. **2.** Rickli et al. *Eur Neuropsychopharmacol.* 2016;26:1327-1337.

Study Design for First-in-Human Phase 1 Study of RE104

- Double-blind, randomized, placebo-controlled single ascending subcutaneous dose study (July 2022-April 2023)
- Healthy volunteers with prior psychedelic experience randomized 6:2 (RE104:placebo) per cohort
- Preparatory session followed by RE104 dosing session with trained session monitor
- Cohort dose selection determined after SRC meetings



Study Endpoints

Primary: Safety and tolerability

Secondary: PK (RE104, 4-OH-DiPT)

Exploratory: Pharmacodynamic PROs
- **DEQ:** intensity, duration of experience
- **MEQ:** quality of subjective feelings during experience

DEQ, modified drug effects questionnaire; MEQ, mystical experience questionnaire; PK, pharmacokinetic; PRO, patient-reported outcome; SRC, safety review committee [a]5 mg was the maximum recommended safe starting dose for RE104. [b]Cohort optional based on safety, tolerability, and PK data from initial cohorts.

Participant Demographics and Characteristics Were Well Balanced Between RE104 and Placebo

48 participants were enrolled and dosed

RE104 5 mg (n=6)	RE104 10 mg (n=6)	RE104 20 mg (n=6)	RE104 30 mg (n=9)	RE104 35 mg (n=6)	RE104 40 mg (n=3)	Placebo (n=12)

Participant demographics were well balanced between participants receiving RE104 versus placebo

	Mean age	Sex	Race	Mean weight	Mean BMI
RE104 (n=36)	36.0 y	75% male 25% female	92% White 8% Other[a]	79.9 kg	26.0 kg/m^2
Placebo (n=12)	40.1 y	67% male 33% female	100% White	78.9 kg	25.7 kg/m^2

BMI, body mass index. [a]Including 1 participant each for Black or African American, Asian, or other.

AEs Were Self-Limited and Mostly Mild to Moderate in Severity, With a Similar Safety Profile to Psilocybin

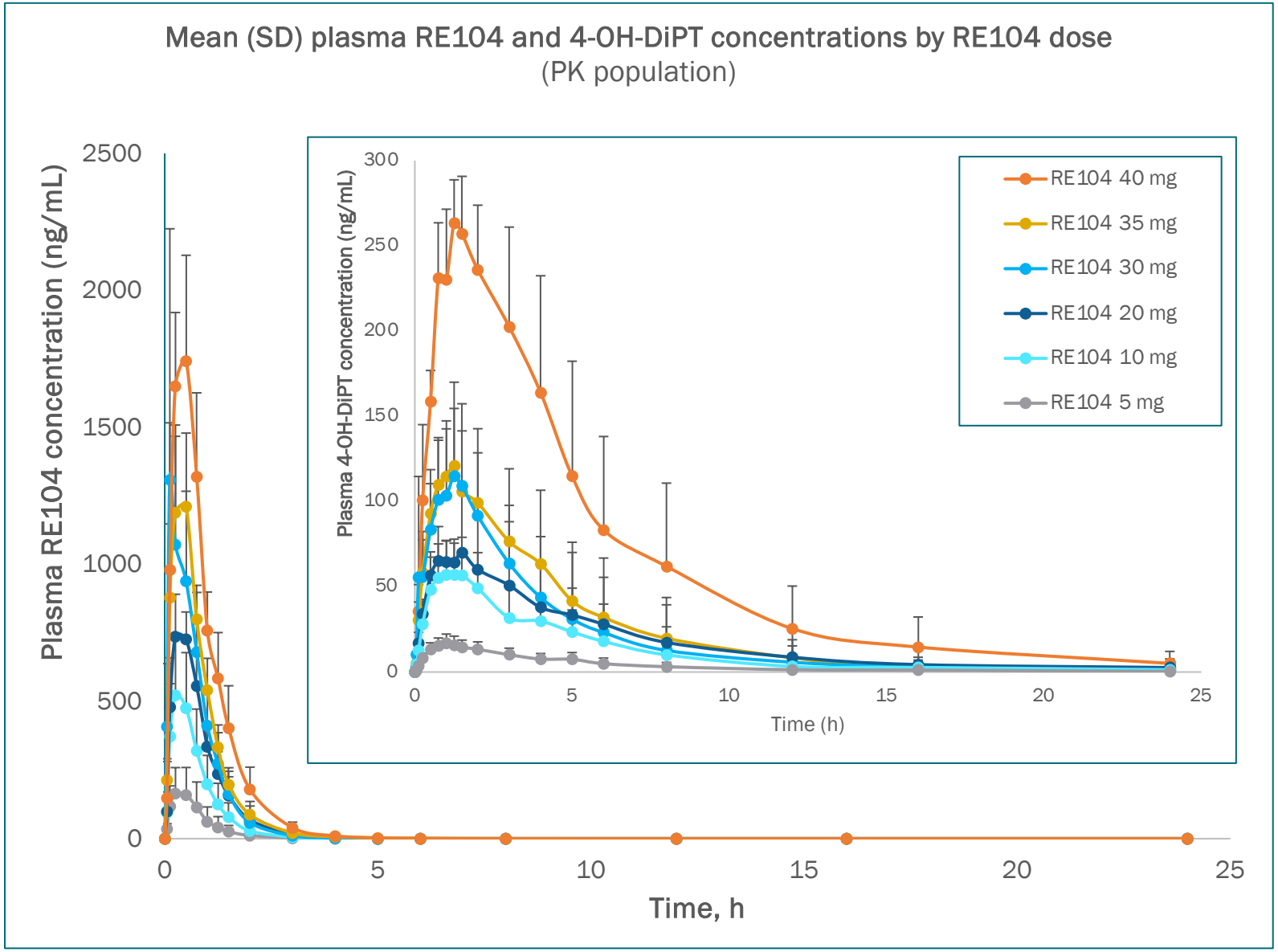
- AEs were transient, self-limiting, and mostly mild to moderate in severity
  - 2 severe AEs of agitation (n=1 each in 35-mg and 40-mg dose groups)
- No serious AEs were observed
- No clinically significant vital sign, clinical laboratory, or ECG findings were observed

AEs, 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)
Participants with ≥1 AE, n (%)	2 (33)	2 (33)	2 (33)	8 (89)	5 (83)	3 (100)	4 (33)
AEs that occurred in ≥2 participants, preferred term by system organ class, n (%)							
Cardiac disorders							
Sinus tachycardia[a]	-	-	-	4 (44)	3 (50)	2 (67)	-
Gastrointestinal disorders							
Abdominal pain	-	-	-	2 (22)	-	-	-
Diarrhea	-	-	1 (17)	-	2 (33)	-	-
Nausea	1 (17)	2 (33)	-	3 (33)	2 (33)	2 (67)	-
General disorders							
Fatigue	-	-	-	2 (22)	-	-	-
Hyperhidrosis	-	-	1 (17)	-	1 (17)	1 (33)	-
Musculoskeletal and connective tissue disorders							
Muscle twitching	-	-	-	3 (33)	-	-	-
Nervous system disorders							
Headache	-	1 (17)	-	1 (11)	4 (67)	-	-
Psychiatric disorders							
Agitation	-	-	-	-	2 (33)	2 (67)	-
Restlessness	-	-	-	3 (33)	3 (50)	1 (33)	-

AE, adverse event; ECG, electrocardiography. [a]Events of sinus tachycardia were asymptomatic, transient, and resolved spontaneously.

RE104 Demonstrates Predictable Pharmacokinetics With Rapid Conversion of RE104 to Active 4-OH-DiPT

- RE104 is rapidly converted to 4-OH-DiPT ($t_{1/2}$ ~30 min)
- Peak concentrations achieved rapidly with RE104 (~15 min) and 4-OH-DiPT (~65 min)
- 4-OH-DiPT cleared rapidly ($t_{1/2}$ ~3 h)
- RE104 and 4-OH-DiPT exposure was dose proportional across the RE104 dose range (5 mg–40 mg)



PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, half-life.

DEQ Data Reflected a Strong Dose Dependence for Peak Intensity, With a Mean Experience Duration of ~4 Hours at 30 mg

- Questionnaire to assess perceived drug effects on scale of 0 (“not at all”) to 10 (“extremely”)
  - **Question 2:** “Are you HIGH right now?”

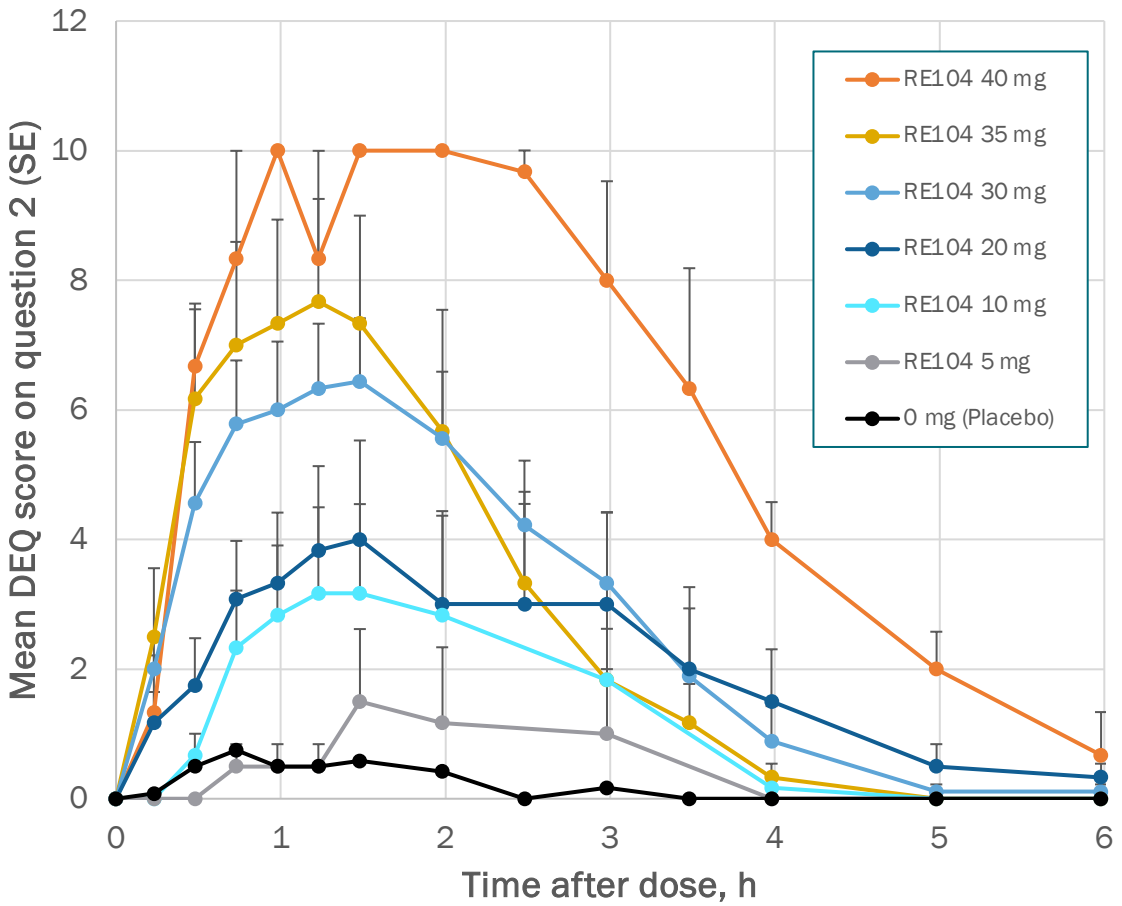
At 30 mg dose:

1.2 h Mean time to peak experience

3.6 h Mean experience duration[a]

3.5 h Median experience duration[a]

RE104 experience duration compares favorably with psilocybin experience duration (~6-8 hours)[1]

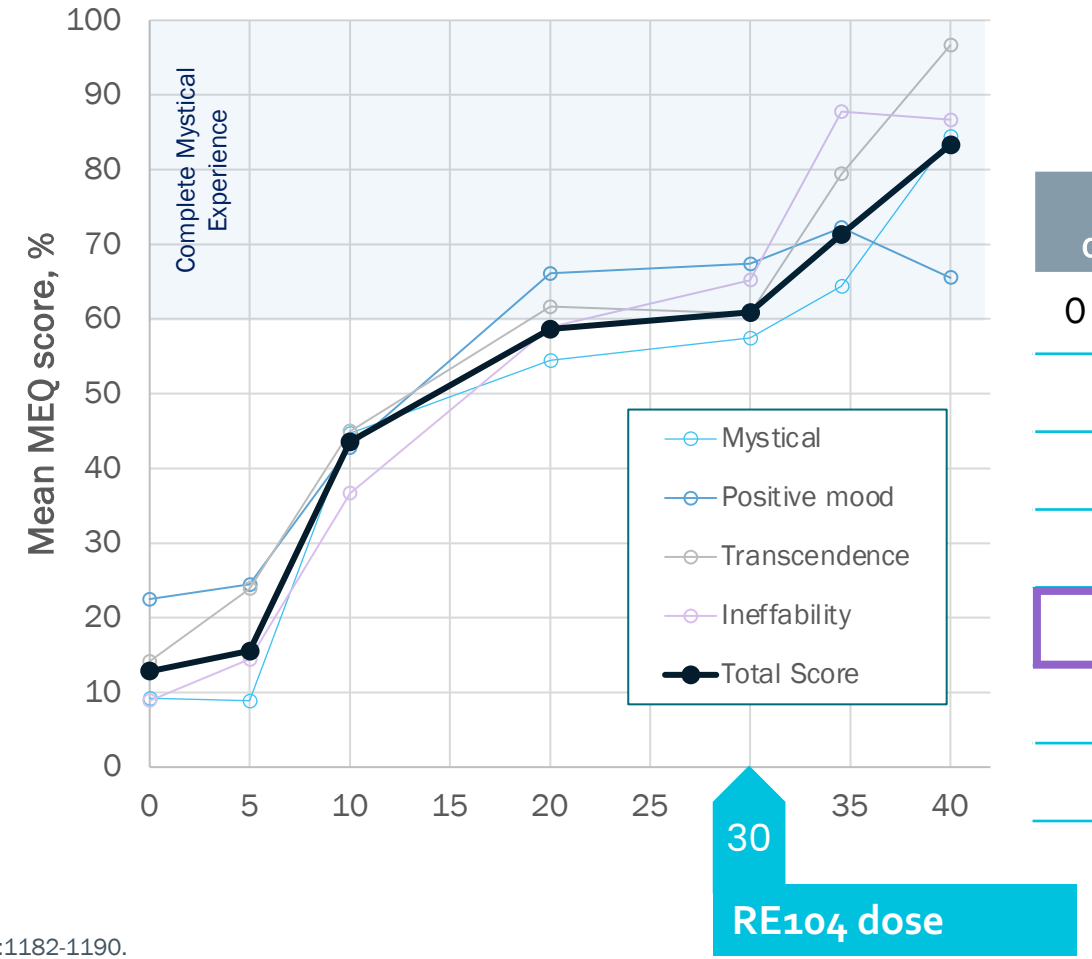


DEQ, Modified Drug Effects Questionnaire. [a]Defined as time to return to a DEQ score of ≤1. **1.** Goodwin et al. *New Engl J Med*. 2022;387:1637-1648.

MEQ Data Also Exhibited a Dose Response, With Two-Thirds of Participants Experiencing Complete Mystical Experiences at 30 mg

- 30-item questionnaire collected after session[1]
  - 4 domains (mystical, positive mood, transcendence of space and time, and ineffability)
  - Item rated from 0 (“none”/“not at all”) to 5 (“extreme”/”more than any other time in my life and stronger than 4”)
  - Total score calculated as average response to all items

Complete mystical experience:
(≥60% of maximum possible score)

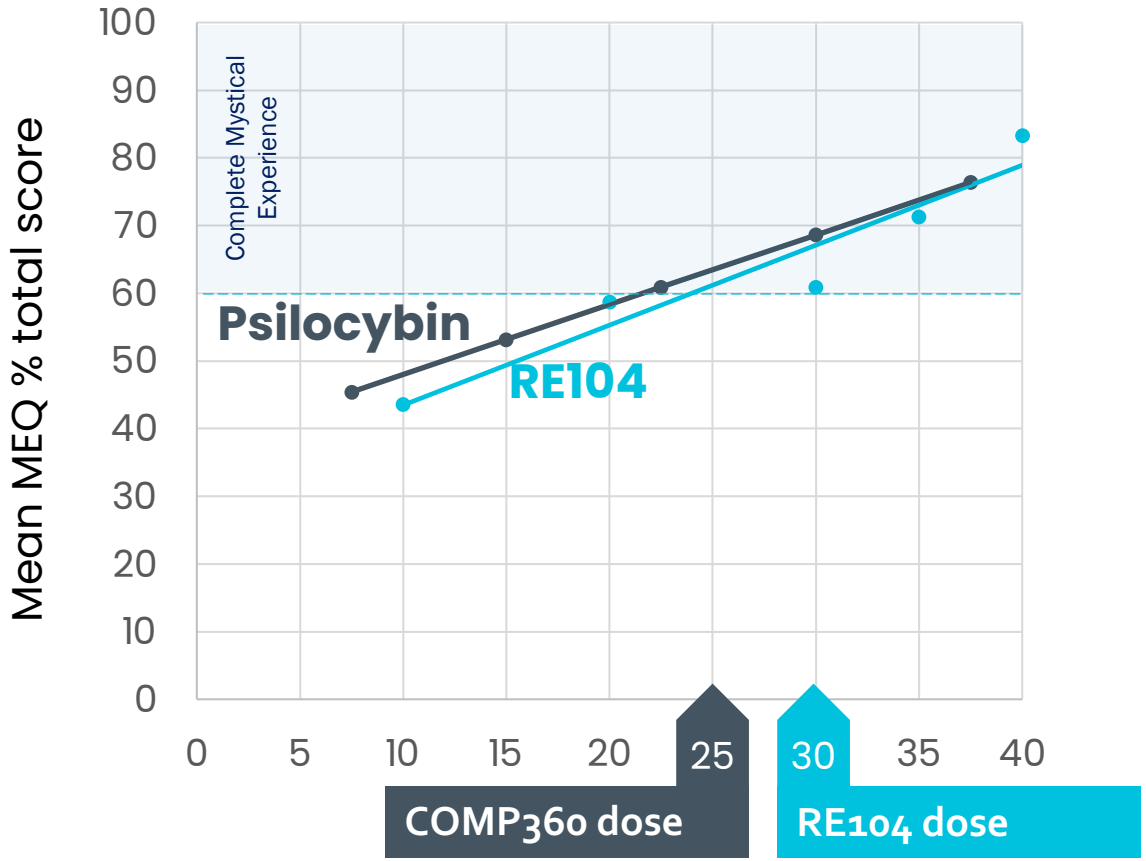


RE104 dose, mg	Response rate, % (n/N)
0 (placebo)	8 (1/12)
5	0 (0/6)
10	50 (3/6)
20	17 (1/6)
30	**67 (6/9)**
35	83 (5/6)
40	100 (3/3)

MEQ, Mystical Experience Questionnaire. **1.** Barrett et al. *J Psychopharmacol*. 2015;29:1182-1190.

RE104 30 mg Pharmacodynamics Compare Favorably With Psilocybin/COMP360 25 mg, With a Shorter Duration of Action

	RE104 30 mg	Psilocybin
Duration (DEQ-High returns to ≤1), h	3.6	"6-8" (25 mg)[1] >8.3[2]
Peak drug effects[a]	8.5/10	~8/10 (30 mg)[2] ~3.5/4 (30 mg)[3]
Mean MEQ % total score	60%	64% (0.45 mg/kg)[4] 69%[5]



DEQ, Modified Drug Effects Questionnaire; MEQ, Revised Mystical Experience Questionnaire. [a]For RE104, ratings reflect highest average peak score (range of 7-10). For psilocybin, ratings reflect hallucinogen rating scale[2] and monitor rating.[3] **1.** Goodwin et al. *New Engl J Med*. 2022;387:1637-1648. **2.** Carbonaro et al. *Psychopharmacol (Berl)*. 2018;235:521-534. **3.** Griffiths et al. *Psychopharmacology (Berl)*. 2011;218:649-655. **4.** Nicholas et al. *J Psychopharmacol*. 2018;32:770-778. **5.** Hirschfeld and Schmidt. *J Psychopharmacol*. 2021;35(4):384-397.

Phase 1 RE104 Data Support Favorable Safety, Tolerability, PK, and PD Profiles Compared With Available PPD Therapies

A favorable safety/tolerability profile was observed, with no serious AEs and no unexpected AEs relative to the safety profile of other psychedelic therapies including psilocybin

PK was well behaved, without excessive variability and with dose proportionality

- Although not explicitly investigated in this study, the short $t_{1/2}$ of RE104 may support a fast return to breastfeeding

MEQ total score reached ≥60% for RE104 30 mg in most patients, which may be predictive of clinical efficacy

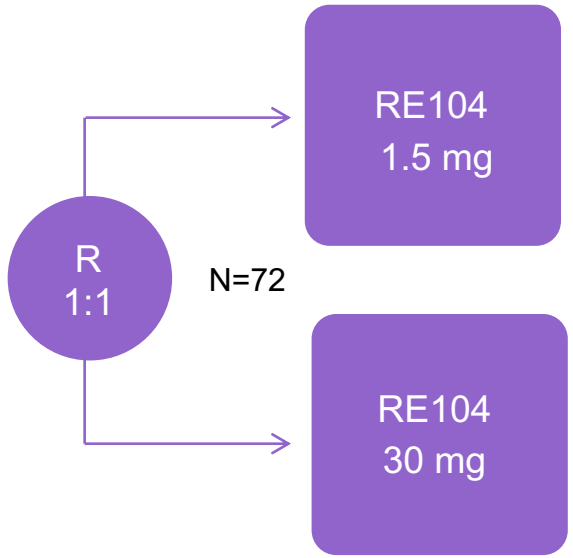
The robust pharmacodynamic effects of RE104 30 mg, with a shorter duration of experience that could support a fast return to breastfeeding and reduced healthcare resource burden, support further investigation of RE104

AE, adverse event; MEQ, MEQ, mystical experience questionnaire; PD, pharmacodynamic; PK, pharmacokinetic; PPD, postpartum depression; $t_{1/2}$, half-life.

RECONNECT Is a Multicenter, Randomized, Double-Blind, Active Dose–Controlled Phase 2 Study of Subcutaneous RE104 for Adult Females With PPD

Study population

- Females aged ≥18-45 years; ≤12 months post partum
- PPD diagnosis (DSM-5 Axis 1: onset during pregnancy or ≤4 weeks from delivery)
- Moderate or severe PPD (HAMD-17 ≥24, CGI ≥4 at screening and baseline)
- Overtly healthy; exclusions for history of acute psychiatric or medically significant conditions rendering unsuitable for study (other than PPD)
- Not breastfeeding
- Stable treatment with SSRIs permitted



Study endpoints

Primary: Change in total MADRS score from baseline at day 7

Key secondary

- Change in total MADRS score from baseline at day 1, 14, and 28
- MADRS response (≥50% reduction)
- MADRS remission (score ≤10)
- Safety and tolerability (AEs, clinical laboratory, vitals, ECGs, suicidality)

Screening: day –28
2 preparatory sessions

Administration: day 0

Follow-up: days 1, 4, 10, 14, 21, and 28
Integration sessions: day 1 and 7[a]

AE, adverse effect; CGI, clinical global impression; ECG, electrocardiography; HAMD-17, 17-item Hamilton Depression Rating Scale for Depression; MADRS, Montgomery- Åsberg Depression Rating Scale; PPD, postpartum depression; SSRI; selective serotonin reuptake inhibitor. [a]Integration sessions were supportive, without formal or manualized psychotherapy.

Thank you!

We would like to thank the Royal Adelaide Hospital, Principal Investigator Professor Guy Ludbrook, the RE104 study personnel, and study participants in the phase 1 study.