An Open-Label Study to Evaluate Concentrations of Zuranolone in the Breast Milk of Healthy Lactating Women

P8

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Introduction

- Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy, with a global prevalence of 17.2%.[1-8]
- Symptoms of PPD can be associated with a significant impairment in mother-infant bonding and maternal function, including breastfeeding and caring for the child, with implications for the child's health and development.[1,9-12]
- Zuranolone is a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ receptors and a neuroactive steroid currently in clinical development as an oral, once-daily, 14-day treatment for major depressive disorder and PPD in adults.[13,14]
- Two Phase 3, double-blind, randomized, placebo-controlled trials of zuranolone 30 mg and 50 mg in adult women with PPD (ROBIN [NCT02978326] and SKYLARK [NCT04442503], respectively) met their primary endpoints: treatment with zuranolone demonstrated a statistically significant improvement in depressive symptoms compared with placebo at Day 15 as assessed by the 17-item clinician-rated Hamilton Rating Scale for Depression.[14,15]
- Given the importance of breastfeeding to a new mother and her infant, this Phase 1 study was designed to evaluate the extent of zuranolone transfer into breast milk.

Methods

- This single-center, open-label study included healthy female participants, aged 18 through 45 years who were ≥ 12 weeks postpartum, actively lactating, and pumping or breastfeeding ≥ 3 times per day (**Figure 1**).[16]
- Baseline frequency and volume of breastfeeding/pumping of breast milk were determined during the Screening Period (Day −28 to Day −4). Participants were expected to maintain at least the baseline frequency of breast milk expression throughout the study.
- Beginning after midnight on Day −3, participants were asked to temporarily stop breastfeeding so that all breast milk could be pumped and collected. Volume was recorded through the end of the study (Day 12).
- Participants orally self-administered zuranolone 30 mg once-daily on an outpatient basis in the evening with food for 5 days (Days 1-5).
- Blood samples for pharmacokinetic (PK) and plasma protein binding analysis were collected on Days -1, 5-7, 9 and 12. Participants were brought into the clinic on Day 5 for overnight assessment and discharged after completion of the assessments on Day 6.

FIGURE 1: Study Design

ENDPOINTS AND ASSESSMENTS

- Primary endpoint
  - Concentration of zuranolone transferred into the breast milk.
- Secondary endpoints
  - Determination of the relative infant dose (RID) and daily infant dose (mg/kg/day) of zuranolone; RID was computed as the infant dose divided by maternal dose.
  - Characterization of the time course of zuranolone in milk and plasma using model-based approaches.
  - Change from baseline in breast milk volume.
  - PK parameters in maternal plasma.
  - Fraction of zuranolone unbound in plasma.
  - Incidence of treatment-emergent adverse events (TEAEs).
- Data from this study (milk and plasma) and from the broader clinical development program (plasma) were used to generate a population PK model to characterize the pharmacokinetics of zuranolone, including excretion into breast milk.
  - The model enabled simulation of plasma and breast milk concentrations following 14 days of drug administration at 30 mg and 50 mg dose levels.

Results

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- A total of 15 participants (**Table 1**) were enrolled and received ≥ 1 dose of zuranolone, and 14 (93.3%) completed the study; 1 participant was lost to follow-up and therefore not included in the PK or breast milk analyses.

TABLE 1: Demographic and Baseline Clinical Characteristics

Screening measurement	Zuranolone 30 mg (n=15)
Age, mean (SD), years	30.1 (4.67)
Race, n (%)	
White	11 (73.3)
Black or African American	3 (20.0)
Native Hawaiian or other Pacific Islander	1 (6.7)
Ethnicity, n (%)	
Not Hispanic or Latino	13 (86.7)
Hispanic or Latino	2 (13.3)
Height, mean (SD), cm	166.1 (7.2)
Weight, mean (SD), kg	85.4 (12.4)
Body mass index, mean (SD), kg/m²	30.9 (4.4)

SD = standard deviation.

- Six participants (40.0%) experienced ≥ 1 TEAE; all were mild (**Table 2**).
- No deaths, serious adverse events (SAEs), or TEAEs leading to discontinuation or study withdrawal were reported.

TABLE 2: Overview Of TEAEs

TEAE, n (%)	Zuranolone 30 mg (n=15)
Any TEAE	6 (40.0)
TEAE by severity	
Mild	6 (40.0)
Moderate	0
Severe	0
TEAE by preferred term	
Dizziness	3 (20.0)
Headache	1 (6.7)
Memory impairment	1 (6.7)
Nausea	1 (6.7)
Vomiting	1 (6.7)
Fatigue	1 (6.7)
Any TEAE related to zuranolone	4 (26.7)
SAE	0
Discontinuation due to AEs	0

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

ZURANOLONE PHARMACOKINETICS

- Individual zuranolone plasma concentrations were measurable over 92 to 168 hours postdose.
- In plasma, zuranolone was highly protein bound; the unbound fraction was similar at time near t_{max} and 24 hours postdose, with a free fraction ≤ 0.52% across participants.
- Key plasma PK parameters obtained on Day 5 (**Table 3**) were similar to those observed in other clinical studies.[17]
- A good concordance was observed between the time course of plasma zuranolone concentration and breast milk zuranolone concentration, although zuranolone concentrations in breast milk were variable.

TABLE 3: Participant Plasma PK Profiles Were Similar to Other Clinical Studies[18]

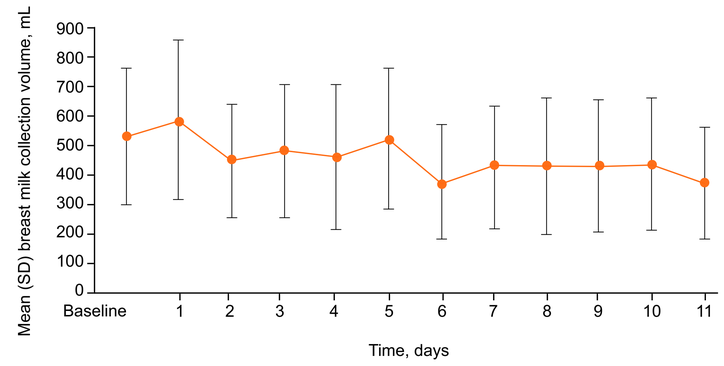
PK parameter, geometric mean[a]	Zuranolone 30 mg (n=14)
C_{max}, ng/mL	58.21
t_{max}, median (range), h	12.00 (3.00 - 16.00)
AUC_{0-24}, h•ng/mL	924.4
$t_{1/2}$, median (range), h	32.0 (18.4 - 41.3)
CL/F, L/h	32.45
C_{min}, ng/mL	22.62
C_{ss}, h•ng/mL	38.52
Overall fraction unbound[b]	0.327

AUC_{0-24} = area under the plasma concentration versus time curve from time 0 to 24 hours postdose; CL/F = apparent body clearance after oral administration of the study drug; C_{max} = maximum observed zuranolone concentration over the dosing interval; C_{min} = minimum observed zuranolone concentration over the dosing interval; C_{ss} = steady-state plasma concentration; PK = pharmacokinetics; $t_{½}$ = estimate of the terminal elimination half-life of the drug; t_{max} = time of maximum observed concentration.

[a]Data are geometric mean unless otherwise noted. [b]Overall is defined as the average of unbound values collected at 4 hours and 24 hours postdose on Day 5.

- At baseline, mean breast milk collection was 525.9 mL (range, 123.0-1100.0 mL) (**Figure 2**).
- A mean decrease of 41.2 mL (SD, 140.11 mL), or 8.3%, was observed in milk volume collected from baseline to steady state (mean of Day 3 to Day 5 of treatment).
- Mean variability in measurements was higher than nominal mean changes.

FIGURE 2: Daily Milk Collection Over Time

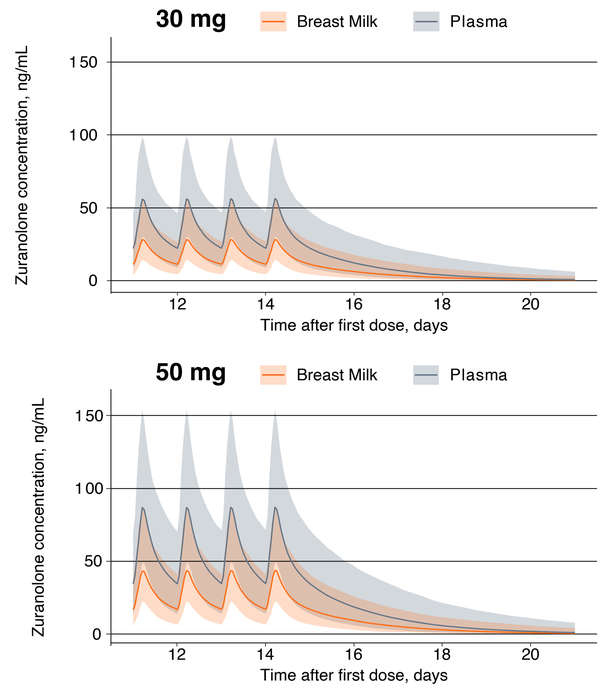


- Compared with maternal dose, amounts of zuranolone in breast milk were low.
  - Mean RID was 0.217% at Day 1 and 0.357% at Day 5.
  - Mean RID was 0.314% for Days 1 through 11.

POPULATION PHARMACOKINETICS MODEL

- In a population PK model, the partition ratio of breast milk and plasma concentrations was approximately 0.499.
- Simulated results predicted zurnanolone concentrations in plasma and breast milk for the administered dose of 30 mg/day and 50 mg/day.
- Concentrations in breast milk are expected to decrease at the same rate as in plasma (**Figure 3**).

FIGURE 3: Model-Predicted Zuranolone Plasma and Breast Milk Concentrations Following 14-Day, Once-Daily Dosing of 30 mg or 50 mg



Conclusions

- In healthy lactating participants:
  - The amount of zuranolone in breast milk following daily administration of zuranolone 30 mg over 5 days was very low compared with maternal dose.
  - The mean RID was 0.357% of the maternal dose and is consistent with a low fraction of unbound zuranolone in plasma.
  - Interpretation of the effect of zuranolone on milk production is limited due to variability in interpatient milk production at baseline, lack of a placebo arm, and the relatively small sample size.
  - Zuranolone 30 mg administered for 5 days was generally well tolerated in healthy lactating participants.
- In a population PK model:
  - Zuranolone breast milk concentrations were approximately 50% of plasma concentrations, with similar rates of decrease after the last dose.
  - Based on the PK characteristics of zuranolone, 30 mg and 50 mg doses are expected to exhibit similar behavior in plasma and milk, resulting in a dose-proportional increase in the total drug excreted in milk.

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