Introduction

Postpartum depression (PPD) is one of the most common medical complications during and after pregnancy, with a global prevalence of 17.2%.1,2

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.1,3,4

Zuranolone is a positive allosteric modulator of both synaptic and extrasynaptic GABA<sub>A</sub> 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.1,5

Two Phase 3, double-blind, randomized, placebo-controlled trials of zuranolone 30 mg and 50 mg in adult women with PPD (ROBIN [NCT02978326] and SKYLRK [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.1,5,6

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).7

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.

Before beginning 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 analyses were collected on Days 1, 5, 7, and 12. Participants were brought into the clinic on Day 5 for overnight assessment and discharged after completion of the assessments on Day 6.

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

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>ZURANOLONE PHARMACOKINETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</td>
<td>58.21</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;, median (range), h</td>
<td>12.00 (3.00 - 16.00)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;, mg/mL·h</td>
<td>924.4</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;, median (range), h</td>
<td>32.0 (16.4 - 41.3)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>32.45</td>
</tr>
<tr>
<td>C&lt;sub&gt;0&lt;/sub&gt;, ng/mL</td>
<td>22.62</td>
</tr>
<tr>
<td>C&lt;sub&gt;0&lt;/sub&gt;, mg/L</td>
<td>38.52</td>
</tr>
<tr>
<td>Overall fraction unbound*</td>
<td>0.327</td>
</tr>
</tbody>
</table>

*Values are 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<sub>max</sub> = maximum observed zuranolone concentration over the dosing interval; C<sub>0</sub> = steady-state plasma concentration; PK = pharmacokinetics; t<sub>1/2</sub> = estimate of the terminal elimination half-life of the drug; t<sub>max</sub> = time of maximum observed concentration.

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

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 0.217% 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 zuranolone 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