# Effects of Ecopipam on Growth and Development in Juvenile Rats

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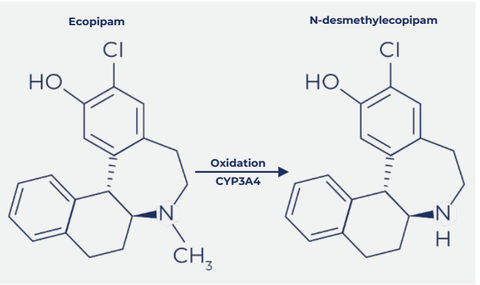
## BACKGROUND

- Ecopipam is a first-in-class dopamine $D_1$ receptor antagonist (**Figure 1**) under investigation in a Phase 3 trial (NCT05615220) as a potential treatment for Tourette syndrome (TS)[1]

### Figure 1. Structure of Ecopipam and N-desmethylecopipam (Active Metabolite)




- The pharmacology, absorption, distribution, metabolism, excretion, and toxicology of ecopipam are well-characterized across multiple species, and clinical investigations have included healthy volunteers and patients with TS[1,2]
- In a phase 2b randomized trial, ecopipam tablets (2 mg/kg/day) improved the Yale Global Tic Severity Scale-Total Tic Score by 30% from baseline at Week 12 in children and adolescents with TS, with significance versus placebo ($P$=0.01)[1]
  - The most frequent treatment-related adverse events in ecopipam group were headache, insomnia, fatigue, anxiety/restlessness, and somnolence; no increased weight gain versus placebo, metabolic side effects, or drug-induced movement disorders were observed with ecopipam
- Despite extensive clinical experience with ecopipam, and given the intended clinical indication for ecopipam is for treatment of TS in pediatric patients aged ≥6 years, preclinical data were needed on the impact of ecopipam treatment on juvenile growth and maturation

## OBJECTIVE

- To evaluate the effects of ecopipam on growth and development and determine potential toxicity of ecopipam and its active metabolite in a juvenile rat model (dosing postnatal days [PND] 28-84 to represent the age range and developmental milestones of a pediatric patient population)

## METHODS

- Repeated once-daily oral (gavage) dosing was administered to Sprague-Dawley rats during PND 28 through 84 (**Table 1**)

### Table 1. Study Design

| GROUP | ECOPIPAM HCl DOSE, mg/kg/day* | MAIN STUDY, n† | TOXICOKINETIC STUDY, n |
|---|---|---|---|
| 1 (control)‡ | — | 40/sex | 6/sex |
| 2 | 6 | 40/sex | 18/sex |
| 3 | 36 | 40/sex | 18/sex |
| 4 | 216 | 40/sex | 18/sex |

*Dose concentration and volume: Group 1 (control; 5 mL/kg); Group 2 (1.2 mg/mL; 5 mL/kg); Group 3 (7.2 mg/mL; 5 mL/kg); Group 4 (43.2 mg/mL; 5 mL/kg).
†Subset in 4 groups followed during ~4-week treatment-free recovery period (n=20/sex/group).
‡Aqueous 0.4% (w/v) methylcellulose.

- Various parameters were measured including viability, sexual maturation, behavioral and laboratory results, and gross necropsy and histopathology findings, as well as reproductive capacity (PND 115-119 [recovery phase animals only])
- Toxicokinetic evaluation
  - In humans, ecopipam is the primary active moiety in plasma with an active metabolite, N-desmethylecopipam (circulating at ~10% of ecopipam concentration in plasma); in rats, it is well-established that N-desmethylecopipam is the primary active entity measured in plasma
    - Both analytes are approximately equipotent across various in vitro and in vivo assays
    - Therefore, toxicokinetic exposures in the current study were presented as a combination of the 2 moieties (ecopipam + N-desmethylecopipam)
  - Blood samples were collected from 3 animals/sex on PND 28 and 84, at 1, 3, 6, and 24 hours postdose, and ecopipam + N-desmethylecopipam concentrations were determined using validated liquid chromatography with tandem mass spectrometry methodology

## RESULTS

- There were no ecopipam-related deaths at any dose level, and ecopipam-related clinical signs were dose-dependent and occurred in the 2 highest dose groups (**Table 2**)
  - Complete recovery from clinical signs occurred for all affected animals during the recovery phase, except for hunched posture in some animals (partial recovery)

### Table 2. Clinical Signs

| CLINICIAL SIGN | ANIMAL AFFECTED, n (PND RANGE*) | |
|---|---|---|
| | ECOPIPAM, 36 mg/kg/day | ECOPIPAM, 216 mg/kg/day |
| Salivation | 5 females (40-85) | 11 males (77-82)<br>13 females (40-85) |
| Hunched posture | 2 males (78-85) | 8 males (78-85)<br>2 females (84-85) |
| Hyperreactivity | 8 males (77-81) | 2 males (77-81) |
| Decreased activity | 0 | 10 males (77-85) |
| Suspected dehydration | 3 males (33-85) | 5 males (33-85) |
| Abnormal breathing sounds | 0 | 3 males (30-85) |

*Range during which sign was observed.
PND = postnatal day.

- Mean body weight gains were significantly reduced in the 2 highest dose groups (ecopipam 36 and 216 mg/kg/day) in males and females during the overall dosing period (PND 28-84), with signs of recovery post-treatment (**Figures 2 and 3**)
- A summary of additional observations and assessments is shown in **Table 3**

### Table 3. Summary of Outcomes

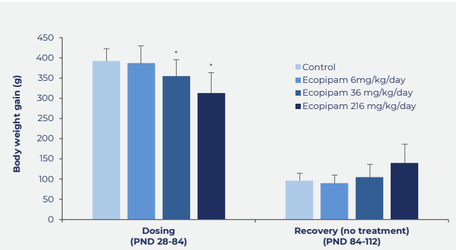
| | |
|---|---|
| BEHAVIORAL ASSESSMENTS | • No adverse ecopipam-related effects on functional observational battery testing, motor activity, or acoustic startle habituation<br>• For Morris water maze testing, latency time was substantially prolonged during dosing period at ecopipam 216 mg/kg/day in males and females |
| LABORATORY PARAMETERS | • No ecopipam-related effects on hematologic parameters at any dose level<br>• At end of dosing period, there were reversible increases in APTT time in males and females treated with ecopipam ≥36 mg/kg/day, in GGT and cholesterol levels in males treated with ecopipam 216 mg/kg/day, and in ALP and triglyceride levels in females treated with ecopipam ≥36 mg/kg/day and 216 mg/kg/day, respectively, compared with controls (effects were not considered adverse)<br>• At end of dosing period, there were reversible reductions in urine volume in males at all ecopipam dose levels and in females treated with ecopipam 216 mg/kg/day compared with controls (effects were not considered adverse) |
| DEVELOPMENT AND MATURATION ENDPOINTS | • No ecopipam-related effects on vaginal patency at any dose level<br>• Mean age of balano-preputial separation was higher ($P$≤0.01) at all dose levels compared with controls; however, this was considered secondary to reduced body weight, and results were within the range of historical control data<br>• No ecopipam-related effects on estrous cycling, mating and fertility, and sperm, ovarian, and uterine parameters at any dose level<br>• No ecopipam-related effects on femur lengths at any dose level |
| OPTHALMOLOGIC EXAMINATIONS | • No ecopipam-related effects at any dose level |
| TERMINAL PROCEDURES | • No ecopipam-related effects on organ weight, except decreased absolute and relative (to body and/or brain) spleen weights in males and females treated with ecopipam 216 mg/kg/day<br>– However, there were no microscopic correlates to account for the decrease, and these weight differences were not observed by the end of the recovery period<br>• No ecopipam-related macroscopic or microscopic changes at any dose level |

ALP = alkaline phosphate; APTT = activated partial thromboplastin time; GGT = gamma glutamyltransferase.

- Systemic exposure to ecopipam and N-desmethylecopipam increased as ecopipam dose level increased in both males and females, with greater than dose-proportional results observed between ecopipam 6 and 36 mg/kg/day (**Figure 4**)
- For ecopipam, the time to maximum concentration ($t_{max}$) on PND 84 for all 3 dose groups was 1 hour for males (half-life [$t_{1/2}$] range, 6.5–7.7 hours) and females ($t_{1/2}$ range, 6.7–7.9 hours); for N-desmethylecopipam, $t_{max}$ was also generally 1 hour postdose

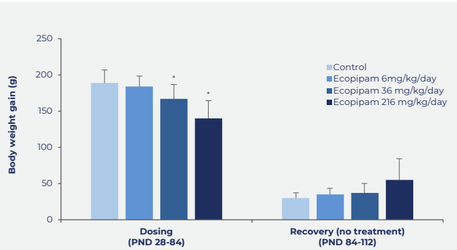
## RESULTS

### Figure 2. Mean Body Weight Gain in Males



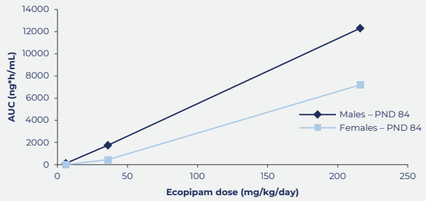

*$P$<0.01 versus control group.
PND = postnatal day.

### Figure 3. Mean Body Weight Gain in Females




*$P$<0.01 versus control group.
PND = postnatal day.

### Figure 4. Ecopipam and N-desmethylecopipam Exposure (Combined) at PND 84




AUC = area under the concentration-time curve; PND = postnatal day.

## CONCLUSIONS

- There were no unexpected toxicities related to ecopipam, and all ecopipam-related effects were consistent with its pharmacologic action (eg, sedation, decreased body weight gain)
  - All ecopipam-related effects completely or near-completely resolved after dosing cessation
- Exposure to ecopipam and N-desmethylecopipam at PND 84 in juvenile rats at oral ecopipam doses of 6, 36, or 216 mg/kg/day represented a ~0.12-fold, ~2.4-fold, and ~16-fold greater exposure, respectively, than exposure reported for healthy adults after single-dose oral administration of ecopipam 200 mg[2]
- There were no untoward effects of ecopipam, at any dose level, on growth, development, sexual maturation, and mating/fertility in juvenile rats

**REFERENCES** **1.** Gilbert DL, et al. *Pediatrics*. 2023;151(2):e2022059574. **2.** Schmith VD, et al. Presented at American Society for Clinical Pharmacology & Therapeutics 2023 Annual Meeting; March 22-24, 2023; Atlanta, GA.

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