

# Population Pharmacokinetics of Fenfluramine and Its Active Metabolite, Norfenfluramine, in Patients With CDKL5 Deficiency Disorder

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OVERVIEW

## QUESTION

How do the steady-state systemic exposure measures for fenfluramine and norfenfluramine in patients with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) compare with those in patients with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS)?

## RESULTS

- ▶ A PopPK model for fenfluramine and norfenfluramine was developed and qualified using data from healthy participants and patients with CDD, DS, and LGS, enabling robust exposure estimation across these populations.
- ▶ Exposure distributions for fenfluramine and norfenfluramine overlapped between participants with CDD and those with DS and LGS, indicating similar systemic exposure across syndromes.
- ▶ Statistically significant relationships were identified between PopPK parameters and coadministration of stiripentol and proton pump inhibitors, as well as syndrome, supratherapeutic dosing, and Japanese ethnicity, with effects on clearance, absorption, and distribution parameters.
- ▶ Despite statistical significance, most covariate effects were not clinically meaningful; only stiripentol coadministration produced changes of sufficient magnitude to warrant dose adjustment; all other simulated exposures remained within the 5th-95th percentile range of healthy, non-Japanese, 70-kg participants not receiving concomitant medications.

## CONCLUSIONS

- ▶ Pharmacokinetic exposures in patients with CDD were comparable to those observed in DS and LGS, supporting use of the same dosing regimen without adjustment for CDD patients ≥1 year of age.

## INVESTIGATION

Data from a Phase III CDD clinical trial, Phase I studies in healthy adults, and Phase III DS and LGS clinical trials were pooled to develop an integrated population pharmacokinetic (PopPK) model that was used to estimate steady-state exposure to fenfluramine and norfenfluramine across syndromes.

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## Background

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare, drug-resistant, X-linked developmental and epileptic encephalopathy caused by *CDKL5* gene mutations.<sup>1-3</sup>
- CDD is associated with infantile-onset epilepsy and global developmental delay.<sup>2-4</sup>
- There is an unmet need for effective holistic treatment options that address both seizures and other clinically relevant outcomes in this patient population.
  - Effective, well-tolerated treatment options for CDD are limited.<sup>5</sup>
- Fenfluramine, a multimodal serotonergic and sigma-1 receptor modulator, is approved for the treatment of seizures in patients (≥2 years of age) with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in the European Union, United States, Japan, and many other countries worldwide.<sup>6-8</sup>
- In a Phase III randomised placebo-controlled trial in patients with CDD, fenfluramine provided significantly greater reduction in the frequency of countable motor seizures compared with placebo; treatment-emergent adverse events were consistent with the known safety profile of fenfluramine in DS and LGS.<sup>9</sup>

## Objective

- To characterise pharmacokinetics and steady-state systemic exposures to fenfluramine and norfenfluramine in patients with CDD and compare them with those in patients with DS and LGS.

## Methods

### TRIAL DESIGN

- EP0216 (ClinicalTrials.gov: NCT05064878) Part 1 was a Phase III randomised controlled trial in children and adults (1-35 years of age) with a confirmed or likely pathogenic *CDKL5* mutation, a clinical CDD diagnosis with epilepsy onset in the first year of life, ≥4 countable motor seizures/week as reported by caregivers, and treatment with ≥1 ASM and ≤4 concomitant ASMs (not including rescue medications).
- The trial design was described in detail previously.<sup>9</sup> After a 4-week baseline period, patients were randomised 1:1 to receive fenfluramine 0.7 mg/kg/day (maximum 26 mg/day) or placebo over a 2-week titration, followed by a 12-week maintenance period.
- Plasma samples were collected from each participant 4 weeks into the maintenance period.

### MODEL DEVELOPMENT

- Data from the Phase III CDD trial (n=37; 1-29 years), Phase I studies in healthy adults (n=187; 18-55 years), and Phase III DS (NCT02682927, NCT02926898; n=247; 2-19 years) and LGS (NCT03355209; n=164; 2-35 years) trials were pooled (dose range: 0.2-0.7 mg/kg/day) to develop a population pharmacokinetic (PopPK) model for fenfluramine and norfenfluramine.
- The PopPK model evaluated the effects of age, sex, race, body mass index, creatinine clearance (CL<sub>Cr</sub>), concomitant medications, and syndrome (DS, LGS, and CDD).
- Allometric scaling coefficients (0.75 and 1.00 for rates and volumes, respectively) were used to relate weight to fenfluramine and norfenfluramine apparent clearance and volume of distribution.
- Inter-individual variability was estimated for fenfluramine and norfenfluramine apparent clearance and volume of distribution, as well as for the fenfluramine absorption rate constant and the stiripentol effect on fenfluramine apparent clearance.

### EXPOSURE ESTIMATION

- Post hoc steady-state exposures to fenfluramine, norfenfluramine, and the sum of fenfluramine and norfenfluramine were estimated using the PopPK model.

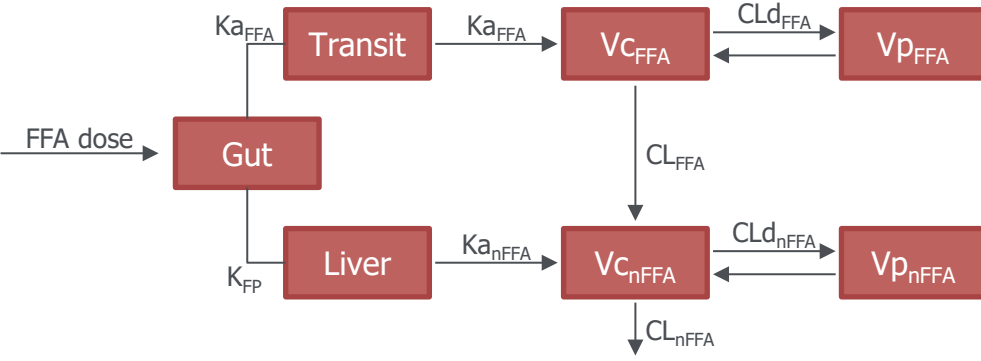
## Results

### DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- The overall pooled analysis population (N=635) had a wide range of age (1-55 years; median 14 years) and weight (7.7-127 kg; median 43.4 kg); 55.4% of patients were male; median (range) CL<sub>Cr</sub> was 117 (45.7-252) mL/min/1.73 m<sup>2</sup>.
- None of the patients with CDD received concomitant stiripentol.

### PopPK MODEL DEVELOPMENT

#### Schematic representation of the base structural PopPK model for fenfluramine and norfenfluramine

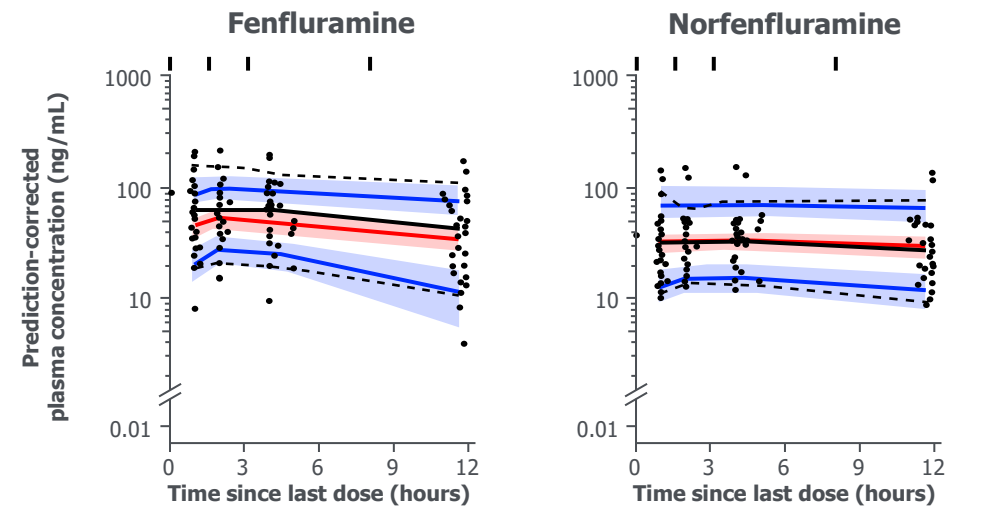


All clearance and volume terms were conditioned on the unknown absolute bioavailability of FFA.  $K_{FP}$  was set equal to  $CL_{FFA}/V_{C_{FFA}}$ , the elimination rate constant of FFA.  $CL$ , apparent oral systemic clearance (L/hr/70 kg);  $CL_d$ , apparent oral distributional clearance (L/hr/70 kg);  $FFA$ , fenfluramine;  $K_a$ , absorption rate constant (hr<sup>-1</sup>);  $K_{sp}$ , pre-systemic (first pass) metabolism;  $nFFA$ , norfenfluramine;  $PopPK$ , population pharmacokinetic;  $V_c$ , apparent oral central volume of distribution (L/70 kg);  $V_p$ , apparent oral peripheral volume of distribution (L/70 kg).

- Fenfluramine absorption was described as a first-order process through a single transit compartment, with pre-systemic metabolism to norfenfluramine.
- The PopPK model demonstrated linear clearance for fenfluramine and norfenfluramine (each with a 2-compartment model).
- Of the covariates tested, the most clinically relevant were:
  - Body weight (allometric scaling), which is predictive of the variability in all systemic pharmacokinetic parameters for fenfluramine and norfenfluramine
  - Concomitant stiripentol administration, which is associated with reduced apparent oral clearance of fenfluramine
  - Concomitant administration of proton-pump inhibitors or other gastric acid suppression medications (eg, H<sub>2</sub>-antagonists), which is associated with a modest increase in fenfluramine clearance.

### POPPK MODEL EVALUATION

#### Diagnostic plots for the CDD population



Circles are observed concentrations, black solid lines are median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Black tick marks at top of figure indicate the times since last dose at which the data were binned for the calculation of summary statistics. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles of the simulations. CDD, cyclin-dependent kinase-like 5 deficiency disorder; PopPK, population pharmacokinetic.

- Based on model diagnostics, the fit of the PopPK model was robust with minimal bias overall and was deemed qualified for exposure estimation in patients with DS, LGS, and CDD.

## References

1. Weaving LS, et al. *Am J Hum Genet* 2004;75(6):1079-1093.
2. Olson HE, et al. *Pediatr Neurol* 2019;97:18-25.
3. Fehr S, et al. *Eur J Hum Genet* 2013;21(3):266-273.
4. Dell'Isola GB, et al. *Epilepsy Behav* 2025;171:110504.
5. Kalinowska-Doman A, et al. *Seizure* 2025;131:391-396.
6. FINTEPLA® (fenfluramine) EU Summary of Product Characteristics. UCB SA. 2026. [https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/fintepla-epar-product-information_en.pdf) Accessed 28 July 2026.
7. FINTEPLA® (fenfluramine) US Prescribing Information. UCB Inc. 2025. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/212102s016lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/212102s016lbl.pdf) Accessed 28 July 2026.
8. FINTEPLA® (fenfluramine) oral solution. The Pharmaceuticals and Medical Devices Agency. 2026. [https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530263\\_1139016S1020\\_2\\_01](https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530263_1139016S1020_2_01) Accessed 28 July 2026.
9. Specchio N, et al. American Epilepsy Society 79th Annual Meeting 2025; Abstract 2.429.

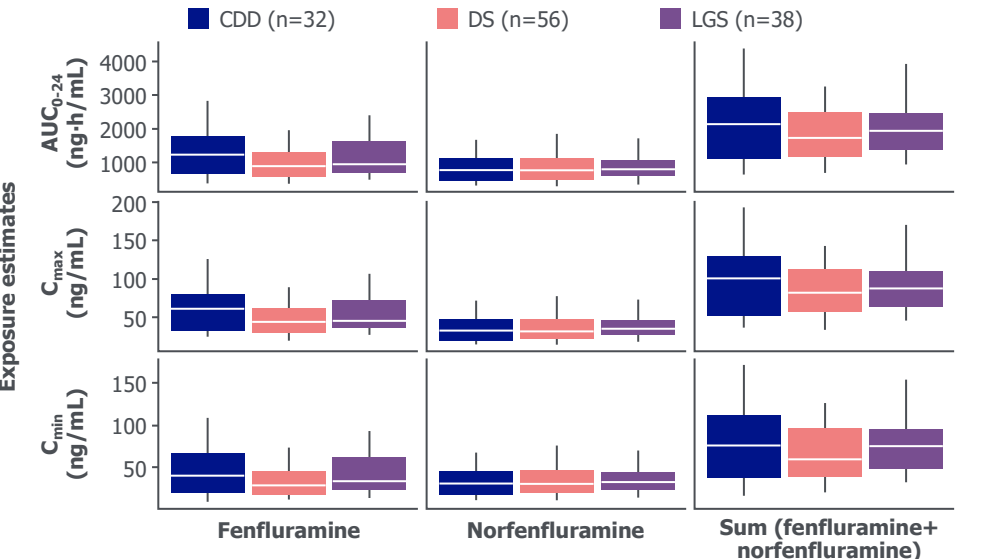
### STEADY-STATE EXPOSURE ESTIMATES

#### Geometric mean (geometric CV%) estimates, derived from the fit of the PopPK model, stratified by syndrome

| Parameter                                 | CDD (n=32)  | DS (n=56)   | LGS (n=38)  |
|-------------------------------------------|-------------|-------------|-------------|
| <b>Fenfluramine</b>                       |             |             |             |
| <b>AUC<sub>0-24</sub> (ng·h/mL)</b>       | 1130 (67.6) | 883 (52.2)  | 1030 (55.0) |
| <b>C<sub>max</sub> (ng/mL)</b>            | 57.2 (57.7) | 44.3 (46.8) | 49.7 (48.1) |
| <b>C<sub>min</sub> (ng/mL)</b>            | 35.5 (85.2) | 28.2 (63.3) | 34.3 (68.2) |
| <b>Norfenfluramine</b>                    |             |             |             |
| <b>AUC<sub>0-24</sub> (ng·h/mL)</b>       | 746 (62.2)  | 733 (60.3)  | 809 (50.6)  |
| <b>C<sub>max</sub> (ng/mL)</b>            | 32.8 (57.9) | 32.2 (57.1) | 35.1 (47.8) |
| <b>C<sub>min</sub> (ng/mL)</b>            | 28.6 (69.0) | 28.2 (65.4) | 31.7 (55.3) |
| <b>Sum (fenfluramine+norfenfluramine)</b> |             |             |             |
| <b>AUC<sub>0-24</sub> (ng·h/mL)</b>       | 1940 (61.7) | 1660 (52.6) | 1890 (47.9) |
| <b>C<sub>max</sub> (ng/mL)</b>            | 92.2 (54.3) | 78.1 (47.9) | 86.9 (42.9) |
| <b>C<sub>min</sub> (ng/mL)</b>            | 67.0 (73.5) | 58.2 (60.7) | 68.5 (56.4) |

Summary statistics are based on patients with a body weight <37.5 kg and age <18 years who received an FFA dose of 0.7 mg/kg/day and did not receive concomitant stiripentol. AUC<sub>0-24</sub>, area under the concentration-time curve from time 0 to 24 hours; CDD, cyclin-dependent kinase-like 5 deficiency disorder; C<sub>max</sub>, maximum concentration; C<sub>min</sub>, minimum concentration; CV, coefficient of variation; DS, Dravet syndrome; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; PopPK, population pharmacokinetic.

#### Distributions of steady-state AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> stratified by syndrome



Horizontal line through box is median, box extends from 25th to 75th percentile, whiskers extend from 5th to 95th percentile. Exposures in all 3 populations are compared using patients with a body weight <37.5 kg and age <18 years who received fenfluramine 0.7 mg/kg/day and did not receive concomitant stiripentol. AUC<sub>0-24</sub>, area under the concentration-time curve from time 0 to 24 hours; CDD, cyclin-dependent kinase-like 5 deficiency disorder; C<sub>max</sub>, maximum concentration; C<sub>min</sub>, minimum concentration; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

- Exposure distributions of fenfluramine, norfenfluramine, and the sum of fenfluramine and norfenfluramine overlapped across patients with CDD, DS, and LGS (body weight <37.5 kg; <18 years of age; no stiripentol use).
- The observed differences in geometric mean AUC<sub>0-24</sub>, C<sub>max</sub>, and C<sub>min</sub> among patients with CDD, DS, and LGS are not considered clinically meaningful.
- Among the 37 patients with CDD receiving fenfluramine, 2 were <2 years of age, and their pharmacokinetic exposures were comparable to those of patients ≥2 years of age.

## CONCLUSIONS

- ▶ In patients with CDD, exposures to fenfluramine and norfenfluramine were in the range of those observed in Phase III trials of DS and LGS at comparable doses.
- ▶ The overall results and inferences from this PopPK model are consistent with previous findings.<sup>7</sup>
- ▶ The PopPK model provides a platform for predicting exposure in future patients with CDD, DS, or LGS, and in other disease populations of similar demographic characteristics.

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