**Request for Copy of Published Material**

The materials provided in response to your request, unless otherwise stated, are the property of the copyright holder. Copyright and other intellectual property laws protect these materials. Reproduction or retransmission of the materials, in whole or in part, in any manner, without the prior written consent of the copyright holder, is a violation of copyright law. A single copy of the materials is provided to you pursuant to a license to do so that has been granted by the copyright holder to us. You may not redistribute or reproduce the materials in any forms without prior written consent of the copyright holder of the materials.

Enclosure:

POSTER: Cotero-Lefevre V, Hogan M, Parks GS, et al. Presented at: Psych Congress 2026, September 15-19, 2026; New Orleans, LA, USA.

# Pharmacokinetic Comparability of Once-Daily Extended-Release Centanafadine Dosing in Children with ADHD and Healthy Adults

Viki Cotero-Lefevre[1], Mike Hogan[1], Gregory S. Parks[1], Lenika Lopez[1], Caroline L. Ward[1]

[1]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, United States

Scan for Full Poster

## Introduction

- Centanafadine is a norepinephrine-dopamine-serotonin reuptake inhibitor and central nervous system stimulant approved as a once-daily extended-release (QD XR) formulation for the treatment of attention-deficit/hyperactivity disorder (ADHD) in pediatric and adult populations[1]
- Pediatric dosing of centanafadine was established using a weight-based approach intended to approximate systemic exposures achieved with adult therapeutic doses
- Characterizing pediatric QD XR pharmacokinetics and confirming that weight-banded dosing produces consistent exposure across the pediatric age range is needed to support the pediatric dosing approach

## Objective

- To characterize single- and multiple-dose pharmacokinetics of centanafadine QD XR in children aged 6–12 years with ADHD and compare steady state exposures with those observed in adults

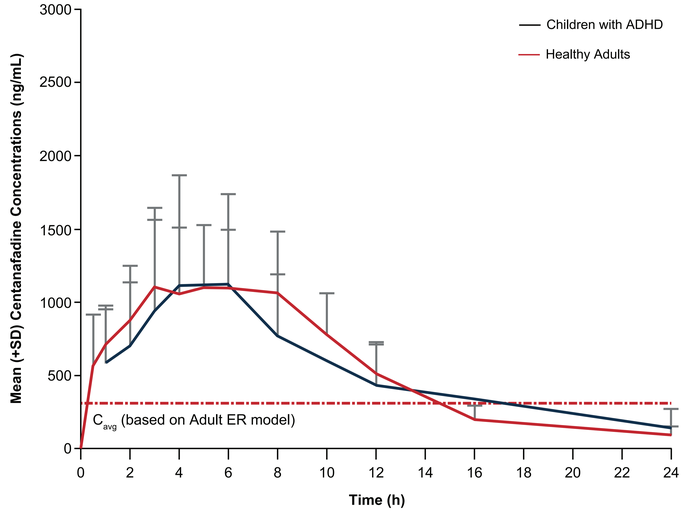
## Methods

- **Study:** A Phase 1b, multicenter, open-label, multiple ascending dose trial (NCT04786730) to assess the pharmacokinetics, safety, and tolerability of centanafadine QD XR capsules after oral administration in children with ADHD
- **Participants:** Children (aged 6–12 years) with a primary diagnosis of ADHD (of any presentation) according to *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) criteria, as confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)
- **Treatment and dosing:** Eligible participants received doses of weight-banded centanafadine QD XR (each capsule contains a combination of immediate release, extended release, and delayed release beads) in the morning on Days 1 through 14 (weight bands were <35, 35–50, and >50–89 kg)
- **Outcomes:** Pharmacokinetic sampling occurred after single and repeated dosing and included:
  - Maximal peak plasma concentration ($C_{max}$)
  - Area under the concentration-time curve from time 0 to 24 hours ($AUC_{0-24h}$) on Day 14
  - Apparent clearance and volume of distribution of centanafadine on Day 14
  - Steady-state exposures were used as the primary basis for comparison with adult exposures observed after administration of the 328.8-mg QD XR centanafadine capsule

## Results

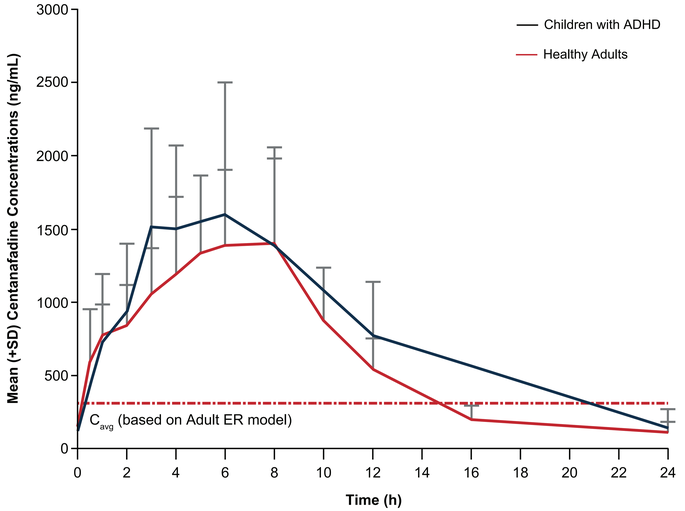
- In children and adults administered the centanafadine QD XR formulation, centanafadine concentrations increased rapidly after single dosing, reaching peak concentrations at a median of 4–6 hours, and declined below the exposure-response model $C_{avg}$ by 14–16 hours post dose (**Figure 1**)
  - A similar pharmacokinetic profile was observed after multiple doses (**Figure 2**)
- Steady state was reached by Day 2, and exposures were consistent across pediatric cohorts
- Single-dose pediatric exposures were comparable to adult QD XR exposures (**Table 1**)
- At steady state, pediatric exposure was modestly higher than adults ($C_{max}$ 1770 vs 1510 ng/mL; $AUC_{0-24}$ 20,100 vs 14,000 h·ng/mL), reflecting somewhat greater accumulation in children (accumulation ratio up to 1.8 vs 1.4 in adults) (**Table 2**)
- Exposure, half-life, and time to peak were similar across the pediatric participants despite age as well as apparent clearance and volume, indicating no residual age effect once weight-adjusted
- Observed pediatric exposures fell within the range seen at the adult 400 mg total daily dose ($C_{max}$ 538–2320 ng/mL; $AUC_{0-24}$ 4790–26,900 h·ng/mL), the highest adult dose not associated with an increase in adverse events

**Figure 1. Mean (+SD) Plasma Centanafadine Concentrations Over 24 Hours Following a Single Dose of Centanafadine QD XR in Children With ADHD and Healthy Adults**




Data were derived from two separate trials and were not compared head-to-head. Children with ADHD (n=21) received a single dose of centanafadine QD XR (400 mg AED) on Day 1 in Trial 405-201-00046; healthy adults (n=132) received a single dose of 328.8 mg centanafadine QD XR in Trial 405-201-00157. Error bars represent +SD (upper bound shown only for clarity). The horizontal dashed line represents $C_{avg}$ predicted from the adult exposure response model. A flat relationship between centanafadine exposure ($C_{avg}$) and Adult ADHD Investigator Symptom Rating Scale (AISRS) total score was observed suggesting 200 mg and 400 mg total daily dose were equally efficacious. The exposure range was anchored at a lower bound of a $C_{avg}$ of 308 ng/mL, representing the model-derived steady-state average plasma concentration associated with the lowest efficacious adult dose. This value was used as an exposure benchmark and does not represent a minimum effective concentration. ADHD, attention-deficit/hyperactivity disorder; AED, Adult equivalent dose; $C_{avg}$, average steady-state plasma concentration; ER, extended release; QD XR: once-daily extended-release formulation; SD, standard deviation.

**Figure 2. Mean (+SD) Plasma Centanafadine Concentrations Over 24 Hours at Steady State Following Once Daily Centanafadine QD XR in Children With ADHD and Healthy Adults**




Data were derived from two separate trials and were not compared head-to-head. Children with ADHD (n=21) received once daily doses of centanafadine QD XR (400 mg AED) through Day 14 in Trial 405-201-00046; healthy adults (n=24) received once daily doses of 328.8 mg centanafadine QD XR through Day 4 in Trials 405-201-00154 and 405-201-00157. Error bars represent +SD (upper bound shown only for clarity). The horizontal dashed line represents $C_{avg}$ predicted from the adult exposure response model. A flat relationship between centanafadine exposure ($C_{avg}$) and Adult ADHD Investigator Symptom Rating Scale (AISRS) total score was observed suggesting 200 mg and 400 mg total daily dose were equally efficacious. The exposure range was anchored at a lower bound of a $C_{avg}$ of 308 ng/mL, representing the model-derived steady-state average plasma concentration associated with the lowest efficacious adult dose. This value was used as an exposure benchmark and does not represent a minimum effective concentration. Steady state previous established by the second dose. ADHD, attention-deficit/hyperactivity disorder; AED, Adult equivalent dose; $C_{avg}$, average steady-state plasma concentration; ER, extended release; QD XR: once-daily extended-release formulation;

**Table 1. Comparison of Pharmacokinetic Parameters Following a Single Dose of Centanafadine in Children and Adults**

| | Single Dose | |
|---|---|---|
| | Children | Adult |
| $C_{max}$ (ng/mL) | 1340 (689) | 1360 (443) |
| $AUC_t$ (h*ng/mL) | 12,300 (6360) | 13,800 (3930) |
| $AUC_\infty$ (h*ng/mL) | – | 14,100 (4010) |
| $t_{max}$ (h) | 6.0 (1.0–8.0) | 4.0 (0.50–12.00) |
| $t_{1/2}$ (h) | – | 6.3 (2.9) |
| CL/F (mL/min) | – | 380 (116) |

For children, weight bands were <35, 35–50, and >50–89 kg. $AUC_\infty$, area under the concentration–time curve from time 0 extrapolated to infinity; $AUC_t$, area under the concentration–time curve from time 0 to the last measurable concentration; CL/F, apparent clearance; $C_{max}$, maximum observed plasma concentration; $t_{1/2}$, terminal half-life; $t_{max}$, time to maximum observed plasma concentration.

**Table 2. Comparison of Pharmacokinetic Parameters Following Multiple Doses of Centanafadine in Children and Adults**

| | Multiple Doses | |
|---|---|---|
| | Children | Adult |
| $C_{max}$ (ng/mL) | 1770 (846) | 1510 (525) |
| $AUC_t$ (h*ng/mL) | 20,100 (7370) | 14,000 (4190) |
| $t_{max}$ (h) | 6.0 (2.0–12.0) | 5.0 (0.50–10.00) |
| $t_{1/2}$ (h) | 4.1 (1.5) | 5.2 (2.4) |
| CL/F (mL/min) | 340 (174) | 359 (524) |

For children, weight bands were <35, 35–50, and >50–89 kg. $AUC_t$, area under the concentration–time curve from time 0 to the last measurable concentration; CL/F, apparent clearance; $C_{max}$, maximum observed plasma concentration; $t_{1/2}$, terminal half-life; $t_{max}$, time to maximum observed plasma concentration.

## Conclusions

- **In children aged 6–12 years, centanafadine pharmacokinetics were comparable to adults, with centanafadine concentrations increasing rapidly after dosing, reaching peak concentrations at a median of 4–6 hours, and declining below the exposure-response model $C_{avg}$ by 14–16 hours postdose**
- **These findings support the weight-based pediatric dosing approach for once-daily extended-release centanafadine**

### References

1. SIMTRIYO® (centanafadine) extended-release capsules [prescribing information]. Princeton, NJ: Otsuka America Pharmaceutical, Inc.; 2026.

### Acknowledgements

The study and poster development support were sponsored by Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, United States. Medical writing and poster development support were provided by The Medicine Group, LLC (New Hope, PA, United States) in accordance with Good Publication Practice guidelines.

At Otsuka, we hold a deep respect for the value of every mind. We will not rest until mental illnesses and brain diseases are approached with the same priority and urgency as our physical health and recognized as chronic diseases that warrant early, equitable, and accessible intervention for patients and caregivers everywhere.

### Disclosures

**VCL**, **MH**, **GSP**, **LL**, and **CLW** are full-time employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

**Poster Number: 220**

Poster presented at Psych Congress 2026; September 15–19, 2026; New Orleans, LA, United States.