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ORIGINAL RESEARCH ARTICLE

# A Pharmacokinetic Study of Methylphenidate Hydrochloride Multilayer Extended-Release Capsules (Aptensio XR®) in Preschool-Aged Children with Attention-Deficit/Hyperactivity Disorder

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## Abstract

**Objective** This was a single-dose, one-period, multicenter, pharmacokinetic (PK) study to evaluate the PK of methylphenidate (MPH) hydrochloride multilayer extended-release capsules (MPH-MLR) in preschool children aged 4 to < 6 years, previously diagnosed with attention-deficit/hyperactivity disorder (ADHD), and on a stable dose of MPH.

**Methods** Preschool-aged children ($N = 10$) received a single oral dose of MPH-MLR (10, 15, or 20 mg) sprinkled over applesauce; a dose equivalent to their pre-enrollment daily dose of MPH. Blood samples for the measurement of MPH concentrations were obtained pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h post-dose. No structural model was assumed in the derivation of PK values for analysis. Maximum plasma concentration ($C_{max}$), area under the concentration–time curve (AUC), elimination half-life, clearance (CL), and volume of distribution ($V_d$) data were compared with a historical group of older children aged 6–11 years ($N = 11$) and analyzed by bodyweight. Safety (adverse event monitoring, vital signs, electrocardiogram, clinical laboratory testing, physical examination) was assessed.

**Results** Mean dose-normalized $C_{max}$ and area under the curve to the last measurable observation ($AUC_{0-t}$) values were similar across dose groups, ranging from 0.67 ng/mL/mg (MPH 15 mg) to 0.81 ng/mL/mg (MPH 10 mg) for $C_{max}$/dose, and from 7.80 h × ng/mL/mg (MPH 20 mg) to 8.92 h × ng/mL/mg (MPH 10 mg) for $AUC_{0-t}$/dose. PK results were integrated into a previously described pharmacostatistical population PK model. Visual predictive check plots showed greater variability in the 6- to 11-year-old group than the 4- to < 6-year-old group, and CL increased with increasing body weight in a greater than dose-proportional manner. Mean CL, normalized for body weight, was constant for all dose groups, ranging from 4.88 L/h/kg to 5.80 L/h/kg. Median time to $C_{max}$ ranged from 2.00 to 3.00 h post-dose, and overall, dose-normalized $C_{max}$ concentrations indicated greater systemic exposures of MPH-MLR in preschool children aged 4 to < 6 years compared with children aged 6–11 years. Children aged 4 to < 6 years had a lower $V_d$ than children aged 6–11 years. There were no unexpected safety signals.

**Conclusion** The PK of MPH-MLR in preschool children demonstrated the biphasic absorption profile described earlier in older children, and the PK profile in children with ADHD aged 4 to < 6 years was similar to the profile in those aged 6–11 years, apart from a lower $V_d$ and relatively higher systemic MPH levels for children in the preschool group.

**Trial registration** Clinicaltrials.gov Identifier: NCT02470234.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s40272-020-00409-z) contains supplementary material, which is available to authorized users.

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**Key Points**

Pharmacokinetics of methylphenidate (MPH) hydrochloride multilayer extended-release capsules (MPH-MLR) in children are well described by a one-compartment disposition model with two parallel absorption compartments.

Mean dose-normalized maximum plasma concentration ($C_{max}$) and area under the curve to the last measurable observation ($AUC_{0-t}$) values in preschool children were similar across dose groups, ranging from 0.67 ng/mL/mg (MPH 15 mg) to 0.81 ng/mL/mg (MPH 10 mg) for $C_{max}$/dose, and from 7.80 h × ng/mL/mg (MPH 20 mg) to 8.92 h × ng/mL/mg (MPH 10 mg) for $AUC_{0-t}$/dose.

Mean apparent clearance, normalized for body weight, was constant for all dose groups, ranging from 4.88 L/h/kg to 5.80 L/h/kg. Median time to $C_{max}$ ranged from 2.00 to 3.00 h post-dose, and overall, dose-normalized peak plasma concentrations indicated greater systemic exposures of MPH-MLR in preschool children aged 4 to < 6 years compared with children aged 6–11 years.

## 1 Introduction

Sufficient evidence has accumulated documenting the presence of signs and symptoms of attention-deficit/hyperactivity disorder (ADHD) that require treatment in preschool-aged children, such that, beginning in 2011, the American Academy of Pediatrics expanded the age group addressed in their ADHD guidelines [1]. For preschool-aged children, non-pharmacologic therapy is considered a first-line intervention, treatment with the stimulant methylphenidate (MPH) is recommended if symptoms and functional deficits persist or a behavioral therapy option is not available. Stimulants, including MPH, are also first-line treatment options for children, adolescents, and adults with ADHD [2–4]. Although compared with school-aged children, far fewer well-controlled studies of preschoolers with ADHD have been conducted, efficacy and safety data from this age group are comparable. The National Institute of Mental Health-funded Preschool ADHD Treatment Study (PATS) reported that immediate-release (IR) MPH resulted in significant reductions in ADHD symptoms and functioning and was generally well tolerated [5, 6]. Despite the relatively frequent use of stimulants in children aged < 6 years, few data describe the pharmacokinetics (PK) of IR MPH in this population [7], and preschool-aged children have been largely excluded from PK studies of extended-release (ER) MPH formulations as well as systematic reviews or meta-analyses [8]. A subset of preschool children from the PATS study demonstrated higher maximum concentration ($C_{max}$) and slower clearance (CL) for comparable weight-adjusted doses of IR MPH compared with school-aged children [7]. Globally, MPH dosing recommendations vary and interpatient differences necessitate an individualized approach to dose optimization [9].

The mechanism of action of MPH in ADHD is not completely understood, but it is believed to block dopamine and norepinephrine reuptake into the presynaptic neuron and increase their release into the extraneuronal space [10]. The PK profile of MPH has been summarized [8, 11, 12]. IR MPH is rapidly absorbed and has a half-life of 3–4 h. The PK properties of MPH have been described as age- and dose-dependent [7, 11]. IR MPH requires two- or three-times-a-day drug administration; this requirement has been associated with non-adherence, administration during time away from home, and on–off responses resulting from fluctuating drug concentrations [10, 13–15]. Currently marketed ER MPH formulations provide an initial pulse of MPH, followed by a prolonged drug delivery phase; they are generally administered once daily [16, 17].

Aptensio XR® (methylphenidate hydrochloride multilayer extended release capsules [MPH-MLR]; Rhodes Pharmaceuticals L.P., Coventry, RI, USA) contains ~ 40% and ~ 60% of IR and ER MPH, respectively, and is approved for oral administration as an intact capsule or sprinkled on applesauce as the PK properties are similar for both routes of administration [18]. It has demonstrated efficacy from 1 to 12 h after dose administration [18–20]. MPH-MLR comes in seven strengths (10, 15, 20, 30, 40, 50, and 60 mg) in a hard gelatin capsule, and is labeled for children aged ≥ 6 years [19].

This study in children aged 4 to < 6 years with ADHD was undertaken to assess MPH PK following a single oral dose of MPH-MLR and (1) to investigate comparability with PK parameters previously obtained in children aged 6–11 years with ADHD and (2) to determine if results in the preschool-aged children fit a general pharmacostatistical population PK model developed for MPH-MLR in an earlier modeling study [21].

## 2 Methods

### 2.1 Study Design

This was a single-dose, open-label, one-period, multicenter study (NCT02470234). Children of both sexes who were aged 4 to < 6 years and had a history consistent with ADHD of ≥ 6 months were considered for enrollment. To be

considered, children had to meet criteria for ADHD diagnosis according to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, criteria for inattentive, hyperactive, or combined ADHD, as well as the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version, and participate in a clinical interview conducted by an experienced clinician. Children were excluded for a medical history that included motor or vocal tics, Tourette's syndrome, serious hypertension, agitation, glaucoma, thyrotoxicosis, tachyarrhythmias, and severe angina pectoris, or serious or unstable medical illness such as asthma, diabetes mellitus, or seizures. Children with other serious or unstable psychiatric conditions requiring treatment were also excluded. Current treatment with monoamine oxidase inhibitors, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), coumarin anticoagulants, presser agents (e.g., guanethidine), tricyclic antidepressants (e.g., imipramine, desipramine, selective serotonin reuptake inhibitors), or herbal remedies (e.g., melatonin) also prevented enrollment. No over-the-counter medications were permitted in the 7 days before study drug dosing. Grapefruit-, caffeine-, or xanthine-containing compounds, and poppy seeds, were prohibited in the 48 h before study drug dosing, with the latter being prohibited until the end-of-study visit. There was a minimum washout period of 5 days between any previously administered methylphenidate formulation and MPH-MLR.

Preschool-aged children had to have had behavioral treatment, or symptoms severe enough to warrant treatment without previous behavioral intervention, and be on a stable dose of MPH. Included children had to have age- and sex-adjusted ratings of ≥ 90th percentile total score on the ADHD Rating Scale-IV—Preschool Version, a Clinical Global Impression scale score of ≥ 4, and a Children's Global Assessment Scale rating of < 65 after MPH washout and before study drug dosing.

The study was undertaken in compliance with the Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. The protocol (WIRB No. 20150806) was reviewed and approved by the Western Institutional Review Board® (Puyallup, WA, USA). Informed consent was provided verbally by children and a parent or guardian provided written consent prior to entry into the study.

## 2.2 Study Drug Administration and Blood Sampling

On the morning of dosing, children were fed a standard breakfast consisting of toast, jam, cereal with 2% milk, and orange juice, and thereafter administered a single MPH-MLR capsule (10, 15, or 20 mg) sprinkled over applesauce. The dose each child received was based on the severity of symptoms, not on age or weight. The administered dose was equivalent to their pre-study total MPH.

Blood samples were collected immediately before dosing (baseline) and at predetermined timepoints during the 24 h after dosing (0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h) into EDTA BD Vacutainer® (Becton, Dickinson, and Company, Franklin Lakes, NJ, USA) tubes. Blood samples were processed immediately by centrifugation, and plasma samples were frozen and stored at approximately − 20 °C before shipment on dry ice to Worldwide Clinical Trials (Austin, TX, USA) for bioanalysis.

## 2.3 Analytical Methods

Plasma samples were analyzed by high-performance liquid chromatography/mass spectrometry to determine concentrations of MPH by a validated method, as outlined by the US Food and Drug Administration (FDA) [22]. Samples were spiked with the deuterated analog ($d_3$-MPH) and extracted using a liquid–liquid extraction procedure. The quantification limit of the assay was 0.5 ng/mL. The calibration curve for MPH was linear, in the range of 0.5–50 ng/mL ($r \geq 0.99$).

## 2.4 PK Analysis

Individual plasma concentration–time data were used to calculate MPH-PK parameters using standard non-compartmental methods (Phoenix® WinNonlin® Version 6.3, Certara USA, Inc., Princeton, NJ, USA). PK endpoints included $C_{max}$ and partial area under the concentration–time curve (AUC) to specified times ($AUC_{0–4}$, $AUC_{0–8}$, $AUC_{8–12}$), to the last measurable observation ($AUC_{0–t}$), and extrapolated to infinity ($AUC_{0–inf}$). AUC values were calculated using the linear trapezoidal rule. The apparent clearance (CL/*F*) is the CL divided by the fraction of the dose determined by bioavailability (*F*); in both absolute and weight-adjusted terms, the CL/*F* was estimated as the quotient of the dose and $AUC_{0–inf}$. The apparent volume of distribution ($V_d/F$) is the volume of distribution ($V_d$) divided by *F*. The terminal phase rate constant (kel) was calculated as the negative of the slope of the log-linear terminal portion of the plasma concentration–time curve, using linear regression.

Comparison of the PK parameters $C_{max}$, $AUC_{0–t}$, and $AUC_{0–inf}$ was performed using an analysis of variance model, with dose group as the only factor in the model. The lowest dose group, MPH-MLR 10 mg, was selected as the reference group, and point estimates of the ratio of the dose-normalized PK parameters with associated 90% confidence intervals (CIs) were deduced. Additionally, as per the FDA guidance for pediatric studies, General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products (December 2014), the geometric means and 95% CIs were calculated for weight-normalized CL/*F*

and $V_d/F$ to determine whether the 95% CIs were within the target range of 60–140%.

### 2.5 Safety Assessments

Safety of MPH-MLR in the preschool-aged children was evaluated from vital signs and 12-lead electrocardiograms administered at screening, baseline, and 2, 4, 8, 12, and 24 h post-dose; clinical laboratory testing (hematology and chemistry) at screening and 24 h post-dose; and physical examination done at screening with a limited exam performed 24 h post-dose. The type, incidence, severity, and relationship of adverse events (AEs) to the study drug were assessed.

### 2.6 Population PK Model

A previous population PK model for MPH-MLR [21], developed in adults and children aged 6–11 years, was updated using data on the children enrolled in this study. This process included updating the analysis data set, refitting the existing population PK model to the new data set, evaluating potential new covariates, and confirming the final model fit with model-qualification activities. The overall structure of the final PK model and the model parameters has been previously published [21].

### 2.7 Pharmacostatistical Modeling

Plasma concentration–time course data were analyzed using a previously described non-linear mixed-effects modeling approach using Phoenix NLME® software, version 8.1 (Certara USA, Inc., Princeton, NJ, USA) [21]. First-order conditional estimation with interaction was the primary method used for PK model parameter estimation. The structural base model was a one-compartment disposition model with two parallel absorption compartments. One absorption compartment represented the fast or IR fraction, and the other represented the slow-release fraction, mimicking the design of the MPH-MLR formulation. The inter-individual random effects on the parameters were modeled assuming a log-normal distribution. The residual error structure used an additive error model.

### 2.8 Covariate Selection for the Population PK Model

Covariates of interest (body weight, body mass index, age group) were tested in a stepwise process. The covariate selection was performed using a forward addition process followed by backward deletion. The likelihood ratio test was used to evaluate the significance of incorporating fixed effects into or removing them from the population model, based on significance levels that are set a priori. For forward addition and backward deletion, significance levels of $p < 0.01$ and $p < 0.001$ were used, respectively. Improvement of the model relative to the base model was compared when each of the covariates were added univariately, and the model with the largest improvement was kept for the next evaluation step, given that there was an overall statistical significance supporting the inclusion of the respective covariate [23].

### 2.9 Evaluation of the Final Population PK Model

Several diagnostic plots were used during model development to assess the ability of each model to describe the observed data [24]. Visual prediction check plots (VPC) were used to evaluate the predictive ability of the final model, and were performed with prediction correction.

## 3 Results

Table 1 summarizes the demographic data on children in the study. Table 2 summarizes the mean PK parameters with descriptive statistics. Mean dose-normalized $C_{max}$ and $AUC_{0-t}$ values were similar across dose groups, ranging from 0.67 ng/mL/mg (MPH 15 mg) to 0.81 ng/mL/mg (MPH 10 mg) for $C_{max}$/dose, and from 7.80 h × ng/mL/mg (MPH 20 mg) to 8.92 h × ng/mL/mg (MPH 10 mg) for $AUC_{0-t}$/dose. Mean CL/$F$, normalized for body weight, was constant for all dose groups, ranging from 4.88 to 5.80 L/h/kg. Mean $V_d/F$/kg, normalized for body weight, was constant for all dose groups, ranging from 4.88 to 5.80 L/kg. Median time to $C_{max}$ ranged from 2.00 to 3.00 h post-dose. Some differences were observed for mean $AUC_{0-inf}$/dose, elimination half-life, CL/$F$, and $V_d/F$ values among dose groups; however, kel-dependent parameters were estimable for only one child in each of the 15-mg and 20-mg groups.

### 3.1 Statistical Analyses and Population PKs

VPC plots of the model (Fig. 1) show good agreement between the observed and predicted quantiles, suggesting that the final model accurately predicts the observed data. The VPC plots appear to show greater variability in children aged 6–11 years compared with children aged 4 to < 6 years. Comparison of the PK parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ was performed using an analysis of variance model, with dose group as the only factor in the model. The lowest dose group was selected as the reference group and compared with other dose groups in a pairwise fashion. The point estimate of the ratio of the dose-normalized PK parameters with associated 90% CI was presented. Additionally, as per the FDA guidance for pediatric studies, General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological

**Table 1** Demographics and baseline characteristics

| Parameter | MPH-MLR 10 mg $n=5$ | MPH-MLR 15 mg $n=3$ | MPH-MLR 20 mg $n=2$ | Total $N=10$ |
|---|---|---|---|---|
| Age at baseline, mean (SD), months | 61.0 (8.03) | 63.3 (5.51) | 70.5 (0.71) | 63.6 (7.06) |
| Age at baseline, median (min, max), months | 64.0 (49, 69) | 63.0 (58, 690) | 70.5 (70, 71) | 65.0 (49, 71) |
| Male, *n* (%) | 4 (80.0) | 2 (66.7) | 1 (50.0) | 7 (70.0) |
| Race, *n* (%) | | | | |
| White | 0 | 1 (33.3) | 1 (50.0) | 2 (20.0) |
| Black | 4 (80.0) | 1 (33.3) | 1 (50.0) | 6 (60.0) |
| Other | 1 (20.0) | 1 (33.3) | 0 | 2 (20.0) |
| Hispanic or Latino ethnicity, *n* (%) | 1 (20.0) | 1 (33.3) | 1 (50.0) | 3 (30.0) |
| Weight, mean (SD), kg | 19.7 (1.76) | 19.6 (2.65) | 21.3 (3.68) | 20.0 (2.22) |
| Body mass index, mean (SD), kg/m$^2$ | 15.3 (0.55) | 15.3 (0.98) | 15.3 (2.26) | 15.3 (0.96) |

*max* maximum, *min* minimum, *MPH-MLR* methylphenidate hydrochloride extended-release capsules, *SD* standard deviation

**Table 2** MPH PK after MPH-MLR single dose

| PK parameter, mean (SD) | MPH-MLR 10 mg $n=5$ | MPH-MLR 15 mg $n=3$ | MPH-MLR 20 mg $n=2$ | Total $N=10$ |
|---|---|---|---|---|
| Dose/weight, mg/kg | 0.51 ± 0.05 | 0.78 ± 0.11 | 0.95 ± 0.17 | 0.68 ± 0.21 |
| $C_{max}$, ng/mL | 8.07 ± 1.70 | 10.09 ± 0.62 | 15.45 ± 1.06 | 10.16 ± 3.18 |
| $C_{max}$/dose (ng/mL/mg) | 0.81 ± 0.170 | 0.67 ± 0.041 | 0.77 ± 0.053 | 0.76 ± 0.132 |
| $AUC_{0-4}$, h × ng/mL | 21.8 ± 7.06 | 25.69 ± 3.67 | 42.01 ± 2.93 | 27.01 ± 9.58 |
| $AUC_{4-8}$, h × ng/mL | 19.81 ± 3.14 | 25.72 ± 2.72 | 38.26 ± 10.71 | 25.27 ± 8.54 |
| $AUC_{8-12}$, h × ng/mL | 19.73 ± 5.10 | 20.73 ± 6.342 | 28.20 ± 9.48 | 21.72 ± 6.51 |
| $AUC_{0-t}$, h × ng/mL | 89.18 ± 25.05 | 118.49 ± 18.21 | 155.95 ± 35.21 | 111.33 ± 34.96 |
| $AUC_{0-inf}$, h × ng/mL | 105.26 ± 21.83 | 140.68 ± NE | 144.26 ± NE | 120.14 ± 25.60 |
| $T_{max}$, median (min, max), h | 2.00 (1.0, 3.0) | 3.00 (3.0, 12.0) | 2.00 (2.0, 2.0) | 2.50 (1.0, 12.0) |
| $t_{½}$, h | 4.80 ± 0.466 | 12.69 ± NE | 6.98 ± NE | 6.81 ± 3.436 |
| $V_d/F$ (L) | 682.49 ± 182.61 | 1952 ± NE | 1396.96 ± NE | 1079.32 ± 592.00 |
| $V_d/F$/kg | 4.88 ± 0.94 | 5.18 ± NE | 5.80 ± NE | 5.13 ± 0.776 |
| CL/*F*, L/h | 97.51 ± 18.10 | 106.63 ± NE | 138.64 ± NE | 107.56 ± 21.94 |
| CL/*F*/kg, L/h/kg | 4.88 ± 0.94 | 5.18 ± NE | 5.80 ± NE | 5.13 ± 0.78 |

$AUC_{0-4}$ area under the concentration–time curve calculated to 4 h, $AUC_{4-8}$ area under the concentration–time curve calculated from 4 to 8 h, $AUC_{8-12}$ area under the concentration–time curve calculated from 8 to 12 h, $AUC_{0-inf}$ area under the concentration–time curve extrapolated to infinity, $AUC_{0-t}$ area under the concentration–time curve calculated to the last measurable observation, *CL/F* apparent clearance, $C_{max}$ maximum concentration, *max* maximum, *min* minimum, *MPH* methylphenidate, *MPH-MLR* methylphenidate hydrochloride extended-release capsules, *NE* not enough data points in the elimination phase to accurately calculate parameters, *PK* pharmacokinetic, *SD* standard deviation, $t_{½}$ elimination half-life; $T_{max}$ time to maximum concentration, *Vd/F* apparent volume of distribution

Products (December 2014), the geometric means and 95% CIs were calculated for weight-normalized CL/*F* and $V_d/F$ to determine whether the 95% CIs were within the target range of 60–140%.

As shown in Table 3, the geometric means (95% CI) reported for CL/*F*/kg and $V_d/F$/kg were 5.1 L/h/kg (4.2–6.2) and 45.9 L/kg (24.1–87.2), respectively. The 95% CI calculated for MPH CL/*F*/kg geometric mean fell entirely within the target CI range of 60–140% but the 95% CI for $V_d/F$/kg fell outside the target CI range of 60–140%.

Table 4 shows that comparisons of the $AUC_{0-t}$/dose and $C_{max}$/dose for the 15-mg and 20-mg doses with the 10-mg dose were similar, and the geometric mean (90% CI) ratios of the $C_{max}$/dose ranged from 0.85 (0.67–1.07) to 0.97 (0.74–1.27). $AUC_{0-inf}$/dose was similar for the MPH 15-mg and 20-mg doses, and was lower after the 20-mg dose than after the 10-mg dose. Geometric mean (90% CI) ratios for $AUC_{0-inf}$/dose were 0.90 (0.46–1.76) and 0.69 (0.36–1.35), respectively. Key covariate effects in the population PK model were that CL increased as weight increased and $V_d$ was lower in preschool children aged 4 to < 6 years.

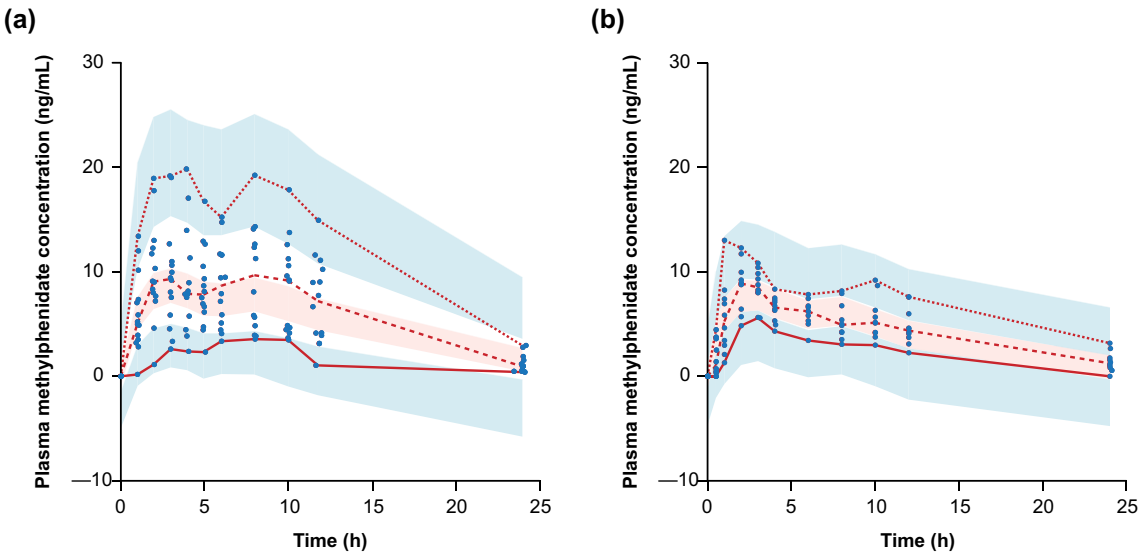


**Fig. 1** Visual prediction check plots for methylphenidate from the final population pharmacokinetic model for **a** children aged 6–11 years and **b** preschool children aged 4 to < 6 years. Blue dots represent the observed data; red lines represent the quantiles for the observed data. The 5th (solid red line), 50th (dashed red line), and 95th (dotted red line) quantiles are shown for the observed data. The blue shaded regions represent the 90% prediction interval for the 5th and 95th quantiles. The red shaded region represents the 90% prediction interval for the 50th quantile. Data are shown regardless of the administered dose

**Table 3** Statistical analysis of weight-normalized methylphenidate hydrochloride extended-release capsule clearance and volume of distribution ($n = 5$)

| Parameter | Geometric mean | 95% CI | Target CI range (60–140%) |
|---|---|---|---|
| $V_d/F$/kg, L/kg | 45.9 | 24.1–87.2 | 27.5–64.2 |
| CL/*F*/kg, L/h/kg | 5.1 | 4.2–6.2 | 3.0–7.1 |

Target CI range was calculated by multiplying the geometric mean by 0.6 for the 60% lower bound and 1.4 for the 140% upper bound

*CI* confidence interval, *CL/F* apparent clearance, $V_d/F$ apparent volume of distribution

Figure 2 shows a correlation of CL/*F* with age. The data, even with a small sample size, clearly indicate CL is constant in this age group. Also, CL and dose-normalized $C_{max}$ were strongly correlated with age, which was expected because weight is a function of age; CL/*F* and dose-normalized $C_{max}$ would be expected to vary directly with weight (and correspondingly with age).

The lower $V_d$ estimated for children aged 4 to < 6 years compared with children aged 6–11 years notably yielded similar MPH concentrations in both age groups, despite considerably lower (50–75%) doses administered to the younger age group (Fig. 3). Pharmacostatistical modeling of the data

**Table 4** Log-transformed systemic exposure parameters of MPH extended-release capsules

| Parameter | Comparison | Ratio[a] | 90% CI of ratio |
|---|---|---|---|
| $AUC_{0-t}$/dose, h × ng/mL/mg | MPH 15 mg vs MPH 10 mg | 0.91 | 0.64–1.29 |
| | MPH 20 mg vs MPH 10 mg | 0.89 | 0.60–1.33 |
| $AUC_{0-inf}$/dose, h × ng/mL/mg[b] | MPH 15 mg vs MPH 10 mg | 0.90 | 0.46–1.76 |
| | MPH 20 mg vs MPH 10 mg | 0.69 | 0.60–1.35 |
| $C_{max}$/dose, ng/mL/mg | MPH 15 mg vs MPH 10 mg | 0.85 | 0.67–1.07 |
| | MPH 20 mg vs MPH 10 mg | 0.97 | 0.74–1.27 |

$AUC_{0-t}$ area under the concentration–time curve calculated to the last measurable observation, $AUC_{0-inf}$ area under the concentration–time curve extrapolated to infinity, *CI* confidence interval, $C_{max}$ maximum concentration, *MPH* methylphenidate

[a]Ratio (%) is the geometric mean (test, 15 mg and 20 mg) divided by geometric mean (reference, 10 mg). Geometric means are based on least square mean of log-transformed parameter values

[b]Insufficient data points in the elimination phase for some subjects. $AUC_{0-inf}$ values were estimable for only 5 of the 10 subjects

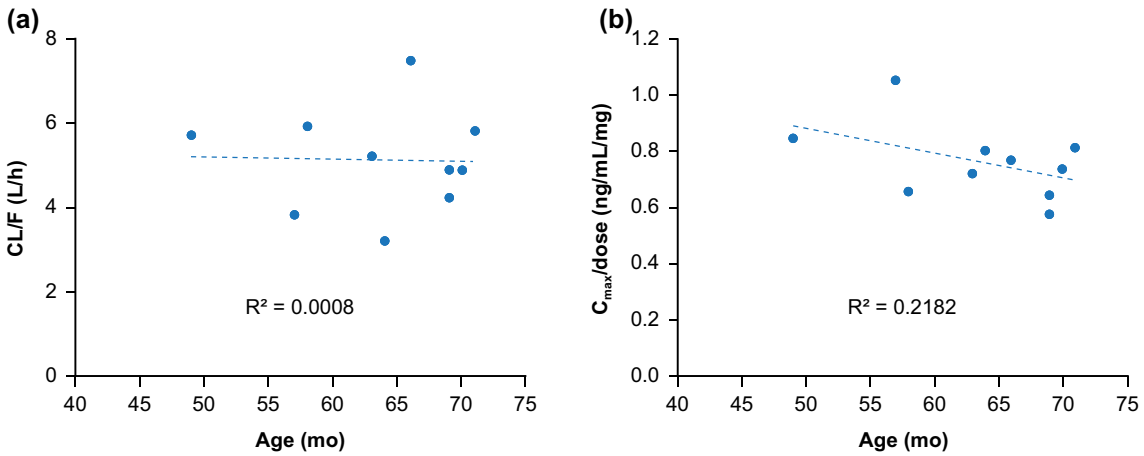


**Fig. 2** Correlation of **a** CL/*F* with age and **b** $C_{max}$ with age. $C_{max}$ maximum concentration, *CL/F* apparent clearance

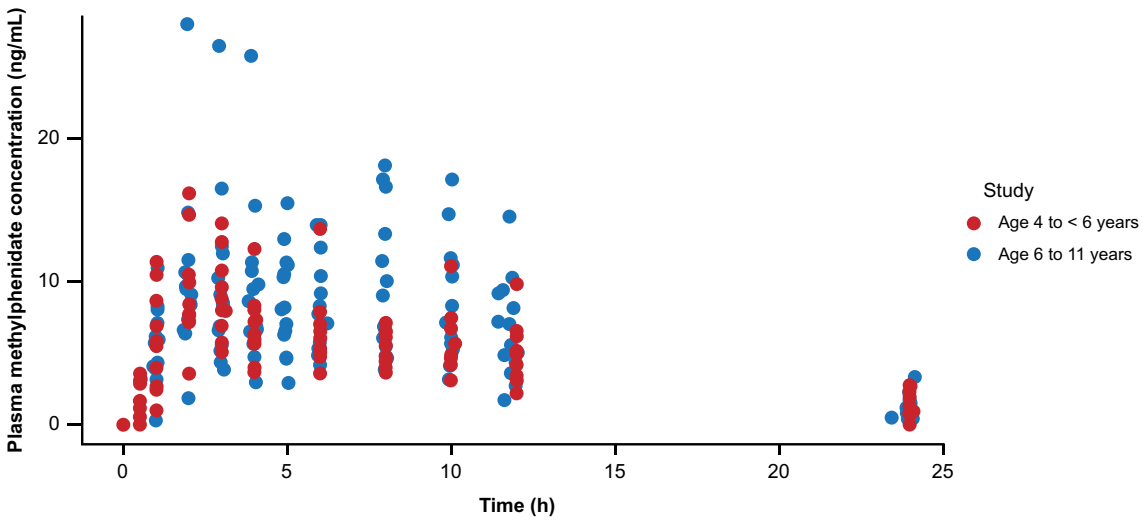


**Fig. 3** Relationship between plasma methylphenidate concentrate and time in children aged 4 to < 6 years and in children aged 6–11 years

based on observed and simulated data from a previous analysis [21] yielded mean dose-normalized MPH concentration profiles, respectively, for (1) children 4 to < 6 years of age and (2) children aged 6–11 years (Fig. 4a). Overlay of the model-based, dose-normalized simulations for the two age groups shows concordance between the PK profiles of the two simulations (Fig. 4b) but also unexpectedly demonstrates approximately a doubling in MPH exposures in the preschool group compared with the age 6–11 years group.

### 3.2 Safety

Overall, there were no AEs that were severe or serious, or led to discontinuation from the study. One AE (respiratory tract infection) that occurred during the study, 3 days before administration of the study drug, resolved without intervention after ~ 7 days; the investigator assessed this AE as moderate in severity and not related to study treatment. No clinically significant findings were noted for laboratory tests, vital signs (Supplementary Table S1, see electronic supplementary material [ESM]), 12-lead electrocardiograms (Supplementary Table S2, see ESM), or physical examinations during the study.

## 4 Discussion

Overall, dose-normalized maximum and total MPH exposure, as measured by $C_{max}$/dose and $AUC_{0-t}$/dose, were similar across doses in children aged 4 to < 6 years. $AUC_{0-inf}$/dose was similar for MPH-MLR 15-mg and 20-mg doses, and was lower after the 20-mg dose than after the 10-mg dose. Furthermore, the geometric mean (90% CI) ratios of the Cmax/dose ranged from 0.85 (0.67–1.07) to 0.97

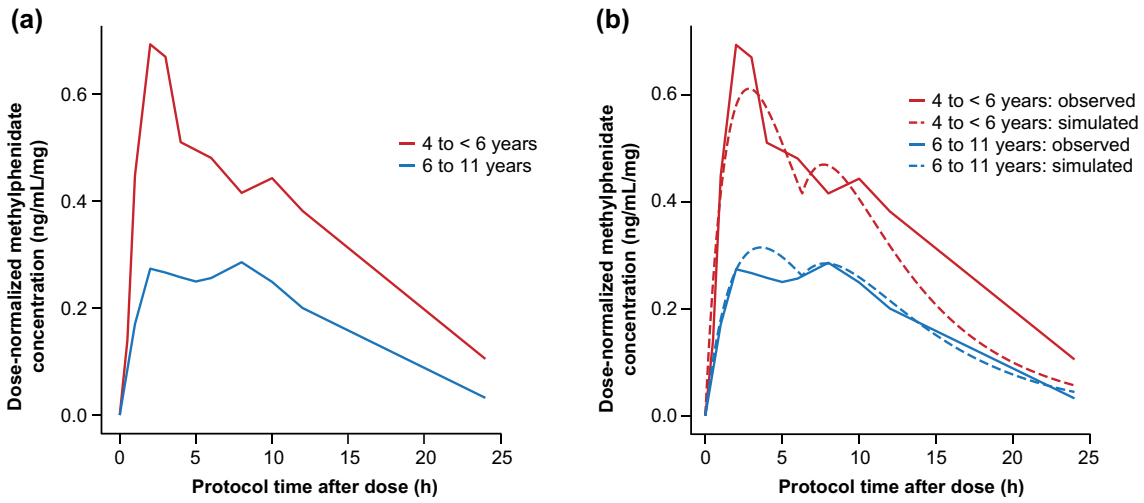


**Fig. 4** Dose-normalized mean methylphenidate concentration–time plot for **a** observed data and **b** observed and simulated data

(0.74–1.27). $AUC_{0-inf}$/dose was similar for the MPH 15-mg and 20-mg doses, and was lower after the 20-mg dose than after the 10-mg dose: geometric mean (90% CI) ratios for $AUC_{0-inf}$/dose were 0.90 (0.46–1.76) and 0.69 (0.36–1.35), respectively. The 95% CIs calculated for CL/*F*/kg fell within target CI range of 60–140% but the 95% CI for $V_d/F$/kg fell outside the target CI range of 60–140%. All children enrolled in the study completed the study and MPH-MLR was well tolerated, with no severe or serious AEs.

In a study of preschool children of similar mean age, drawn from the PATS study, Wigal et al. [7] found a significantly higher dose-normalized $C_{max}$ and slower CL in preschool children aged 4–5 years than in children aged 6–8 years, following a single dose of IR MPH. The CL/*F*/kg values obtained from the Wigal study (5.12 L/h/kg) compare favorably with results being reported in the current study, namely, 5.13 L/h/kg. Estimates of CL from our study also appear consistent with the CL of 5.47 L/h/kg from an earlier report in preschool children [25]. As expected, other values were different, most likely reflective of the formulation studied (IR vs ER). These differences likely contributed to the slightly higher rates of AEs reported in PATS compared with most trials in school-aged children [5, 7].

In this single-dose PK study conducted under fed conditions, the effect of food could not be evaluated. Previous studies of MPH-MLR in older children demonstrated that a high-fat meal could delay $C_{max}$ by 1 h compared with a standard meal, but the overall PK profile was similar [20].

In a previous model of MPH-MLR dosing in children aged 6–18 years, a relationship between body weight and $C_{max}$ was noted [21]. The present study expanded this model to include children aged 4 to < 6 years. A new relationship emerged from the analysis: the $V_d$ in the younger children (aged 4 to < 6 years) was lower than in children aged ≥ 6 years. All other PK parameters were similar across age groups. This suggests that lower doses of MPH-MLR can be used to achieve the same target MPH concentrations in children aged 4 to < 6 years. In fact, this finding is reflected in the range of doses used in children aged 6–11 years (MPH-MLR 20–80 mg) and the range of doses used in children aged 4 to < 6 years (MPH-MLR 10–20 mg). Although the doses were 50–75% lower in the younger children, MPH concentration values were similar for children aged 4–11 years.

The double-peak in MPH concentration that is obvious in Fig. 4 is expected based on the known PK of MPH-MLR [18, 20]. Following oral administration, MPH-MLR releases an initial MPH bolus that results in a peak plasma concentration at approximately 2 h post-dose. A subsequent prolonged phase of MPH delivery results in a second peak concentration at approximately 8 h after dosing.

MPH-MLR was well tolerated in this study. A single dose was evaluated; therefore, this finding should be interpreted with caution. Although modeling offers a picture of expected response to administered doses, predicted concentrations may vary from actual concentrations; therapy should be guided not only by PK data, but also efficacy and tolerability of the administered product. Prospective studies should be conducted to confirm the findings of the model. This was a single-dose PK study and no long-term safety conclusions can be drawn from these data.

The small sample size in this study reflects the challenges of recruiting in this young population and was a limitation of the study. The study aimed to enroll 30 preschool-aged children, anticipating that there would be approximately 20 completers. Recruiting was left open for a 2-year period. During that time, we were unable to meet our original target number of children. In addition, our PK analysis was limited

by the number of blood draws permitted in this young population; for example, we were unable to fully characterize the elimination phase. Given these two primary limitations, the estimate of $AUC_{0\text{-inf}}$ and half-life must be interpreted cautiously. The interpretation of the data should include additional prospective safety and efficacy information, when available, for this population.

Profiles of MPH exposure suggest that the biphasic release of MPH-MLR is similar in the younger (4 to < 6 years of age) and older (6–11 years of age) children. The younger children did have exposure to MPH that was approximately twofold higher than that observed in the older children, likely due to differences in MPH CL in the two populations, and although the number of subjects in the study is small, exposures and partial AUCs from results should provide meaningful information to clinicians and regulators on in vivo PK of MPH-MLR in preschool children with ADHD.

## 5 Conclusion

In preschool children aged 4 to < 6 years, MPH-MLR 10–20 mg provides MPH PK profiles concordant with MPH-MLR 10–60 mg in children aged 6–11 years. Preschool-aged children enrolled in this study had a lower $V_d$ and relatively higher systemic MPH levels than has been observed in older children. Dose-normalized maximum and total MPH exposure, as measured by $C_{max}$/dose and $AUC_{0-t}$/dose, were similar across dose groups. Further, this study may be the first reporting of MPH partial AUCs in children with ADHD 4 to < 6 years of age. MPH-MLR was well tolerated at all doses, including some MPH doses that were higher than previously studied in preschool-aged children.

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### Declarations

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**Conflict of interest** Akwete L. Adjei and Inder Chaudhary are employees of Rhodes Pharmaceuticals L.P. Scott H. Kollins receives research support and/or consulting fees from Aevi Genomic Medicine, Akili, Alcobra, Bose, Ironshore, Jazz, KemPharm, NLS, Purdue Canada, Rhodes Pharmaceuticals L.P., Shire, SK Life Science, and Sunovion. Americo Padilla has nothing to disclose.

**Ethics** The study was undertaken in compliance with the Good Clinical Practice Guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. The protocol (WIRB No. 20150806) was reviewed and approved by the Western Institutional Review Board® (Puyallup, WA, USA).

**Consent to participate** All participants/guardians provided consent to participate in the study.

**Consent for publication** Not applicable.

**Availability of data and material** Raw data presented in this analysis are available by request at www.rhodespharma.com.

**Code availability** Not applicable.

**Author contributions** Analyses were conducted by Inder Chaudhary and data interpretation was provided by all authors. Akwete L. Adjei wrote the first draft and all authors provided input into revising the article and approved the final version for publication.



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