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Dose-Proportionality and Steady-State Pharmacokinetics of KP415, an Investigational ADHD Product Containing Serdexmethylphenidate (SDX), a Novel Prodrug of d-Methylphenidate

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BACKGROUND

- KP415 is an investigational ADHD product containing serdexmethylphenidate (SDX), a novel prodrug of d-methylphenidate (d-MPH), co-formulated with d-MPH HCl in a fixed molar dose ratio of 70% SDX:30% d-MPH HCl
- KP415 has been designed as a once-daily, oral product that provides both early exposure to d-MPH and sustained exposure throughout the day
- Following a single KP415 dose, initial d-MPH exposure during the first few hours is governed by d-MPH HCl and subsequent sustained d-MPH exposure primarily by SDX conversion to d-MPH
- Determining the predictability of d-MPH exposure across the clinical dose range is critical for initial dose titration in patients with ADHD and for implementing dose adjustments over time

OBJECTIVE

- To assess the pharmacokinetics (PK) and dose-proportionality of single oral KP415 doses, as well as the steady-state PK after multiple-dose administration of the highest clinical daily dose

METHODS

Subjects and Study Design

- Eligible subjects were healthy males and non-pregnant, non-breastfeeding females 18-55 years of age
- This was a Phase 1, open-label, randomized, single-dose, 3-treatment, 3-period crossover study evaluating KP415 doses of:
  - 28 mg SDX/6 mg d-MPH HCl (“28/6 mg”, equimolar to 20 mg d-MPH HCl)
  - 42 mg SDX/9 mg d-MPH HCl (“42/9 mg”, equimolar to 30 mg d-MPH HCl),
  - 56 mg SDX/12 mg d-MPH HCl (“56/12 mg”, equimolar to 40 mg d-MPH HCl)
- All treatments (separated by a minimum 96-hour washout period) were administered orally under fasted conditions
- During the single-dose phase, pharmacokinetic sampling was conducted pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, 24, 36, 48, 60 and 72 hours post-dose
- Following washout after the single-dose crossover phase, all subjects received 4 doses of 56/12 mg KP415 once daily for 4 days to evaluate the steady-state PK
- On Day 1 of the multiple-dose phase, PK sampling was conducted pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, and 24 hours post-dose. The 24-hr postdose PK sample was taken before administration of the 2nd dose of study drug.
- On Days 2-3, PK sampling was conducted at 2, 8, and 24 hours postdose. The 24-hr post-dose PK samples were taken before administration of the 3rd and 4th doses of study drug
- On Day 4, PK sampling was conducted at 0.5, 1, 1.5, 2, 2.5, 3, 5, 7, 9, 12, 13, 24, 36, 48, 60 and 72 hours ±5 minutes post-dose
- Safety assessments were performed throughout the study

Statistical Analyses

- The following were among the pharmacokinetic parameters derived for d-MPH from the plasma concentration-time data under single- and multiple-dose conditions: C_{max}, C_{min} (at 24 hours post-dose), T_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-24h}}$, and $T_{1/2}$
- Evaluation of dose-proportionality and dose-linearity of C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-24hr}}$, and $AUC_{0\text{-inf}}$ for d-MPH was assessed using a power analysis with mixed effects (Smith 2000)
- A statistical comparison of the d-MPH PK parameters of exposure between the 1st and last (4th) dose was performed using an ANOVA model for the paired data after ln-transformation
- The least squares geometric means (LSGM) of the PK parameters for each dosing day (1st and 4th dose) were calculated, as well as point estimates and 90% Confidence Intervals (CI) for the Test to Reference ratios of geometric means

RESULTS

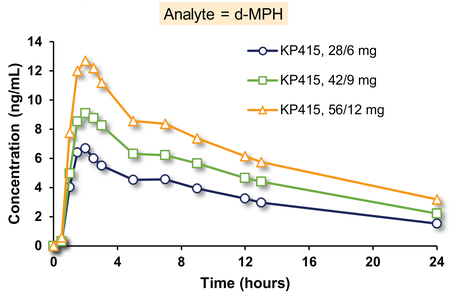
Subject Disposition

- A total of 24 subjects participated in the study and 23 completed both the single- and multiple-dose phases

Single-dose Phase

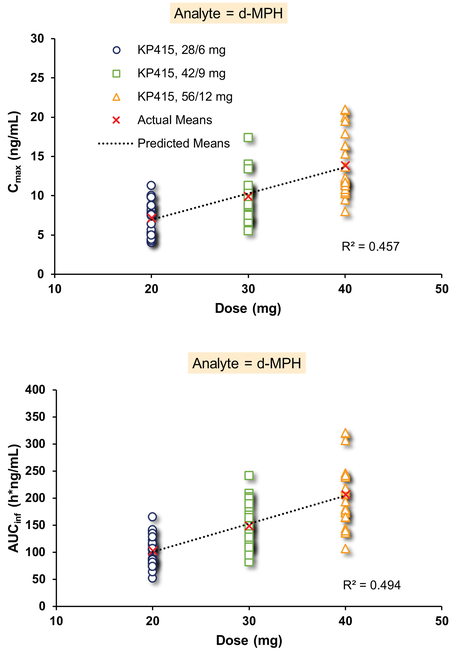
- After single-dose KP415 administration (**Figure 1**), d-MPH plasma concentrations increased rapidly for all dosage strengths, with peak concentrations (C_{max}) of 7.15, 9.88, and 13.85 ng/mL for the 28/6 mg, 42/9 mg, and 56/12 mg doses, respectively
- Median T_{max} occurred at 2.0 hours postdose for all 3 treatments
- Plasma d-MPH concentrations decreased gradually after C_{max}, with appreciable concentrations still apparent at 13 h post-dose.

Figure 1. Plasma d-MPH concentration-time profiles following single-dose administrations of KP415



- As shown in **Figure 2**, after single dose administrations of 28/6 mg, 42/9 mg, and 56/12 mg KP415, d-MPH C_{max} and $AUC_{0\text{-inf}}$ values appeared to increase proportionally with an increase in KP415 dose

Figure 2. Regression analysis of plasma d-MPH C_{max} (top panel) and $AUC_{0\text{-inf}}$ (bottom panel) versus dose



- **Table 1** shows results from the power analysis assessing dose-proportionality across the 3 doses administered
- The slope (β_1) for all parameters was close to 1 and the 90% confidence intervals estimated for the slope were contained within the lower and upper critical regions of 0.6781 and 1.3219, respectively, indicative of dose-proportionality
- Rho1 predicts a large theoretical range of dose proportionality, (approximately 6.5-fold [C_{max}] to 82.7-fold [$AUC_{0\text{-inf}}$]), suggesting that d-MPH increases proportionally with an increase in dose over the entire dose range administered for this study and beyond

Table 1. Assessment of dose-proportionality across KP415 doses of 28/6 mg, 42/9 mg, and 56/12 mg

Dependent Variable	Model Variable	Estimate (β_1)	90% CI Lower	90% CI Upper	Rho1[a]
ln(C_{max})	ln(Dose)	0.9625	0.8807	1.0444	6.4861
ln($AUC_{0\text{-24hr}}$)	ln(Dose)	0.9421	0.8921	0.9921	7.9077
ln($AUC_{0\text{-last}}$)	ln(Dose)	1.0403	0.9878	1.0928	11.0605
ln($AUC_{0\text{-inf}}$)	ln(Dose)	1.0021	0.9537	1.0505	82.7245

Power Model: $\ln(PK)=\ln(\beta_0)+\beta_1*\ln(Dose)+\varepsilon$, where PK is the pharmacokinetic parameter tested, $\ln(\beta_0)$ is the y intercept, β_1 is the slope, and ε is an error term

[a] Maximal dose ratio for definitive proportionality. Rho1 was calculated as: $Rho1=\theta_1\text{^}(1/\max(1\text{-lower, upper-1}))$, in which θ_1=1.25.

Multiple-dose Phase

- **Figure 3** shows plasma d-MPH concentrations following single (Day 1) and multiple (Day 4) doses of KP415, 56/12 mg
- Mean maximum (C_{max}), minimum (C_{min}), and overall ($AUC_{0\text{-24h}}$) d-MPH exposure were approximately 35%, 12%, and 36% higher, respectively, after multiple doses (Dose 4) of KP415, 56/12 mg, relative to a single dose (Dose 1), as expressed by the least square geometric mean ratios of the respective parameters values (**Table 2**)
- Steady-state plasma concentrations, as assessed by trough concentrations of d-MPH, were achieved prior to the third dose (i.e., between the second and the third day of multiple dosing)
- There was no accumulation of the intact prodrug, SDX, during once-daily dosing

Figure 3. Mean plasma d-MPH concentration-time profiles after single- (Day 1) and multiple-dose (Day 4) administrations of KP415, 56/12 mg

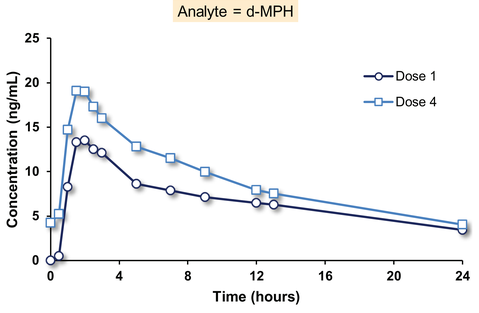


Table 2. Statistical analysis of natural log transformed systemic exposure of d-MPH comparing Dose 4 of KP415, 56/12 mg (Test) vs. Dose 1 of KP415, 56/12 mg (Reference)

Dependent Variable	GeoMean[a] Test	GeoMean[a] Ref	Ratio (%)[b] (Test/Ref)	90% CI Lower	90% CI Upper
ln(C_{max})	19.49	14.43	**134.99**	127.52	142.90
ln(C_{min})	3.61	3.22	**111.94**	102.23	122.58
ln($AUC_{0\text{-24hr}}$)	209.83	154.62	**135.71**	130.25	141.40

[a] Geometric Mean based on Least Squares Mean of log transformed parameter values
[b] Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref)
CI – Confidence Interval

Safety and Tolerability

- The most frequently reported adverse events (AEs) were dizziness, tachycardia, and feeling jittery, each reported by 3 (12.5%) subjects
- There were no serious AEs

CONCLUSIONS

- **KP415 demonstrated proportionality across the tested dose range with respect to rate and extent of d-MPH exposure. A power model predicted significant additional dose proportionality beyond the test range**
- **Following once-daily KP415 dosing, steady-state plasma concentrations of d-MPH were achieved prior to the third dose**
- **KP415 has the potential to provide a rapid onset and extended duration of therapeutic benefit, with predictable d-MPH exposure during titration and maintenance**

Disclosures

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References

Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000; 17: 1278–1283.