Pharmacokinetics of Morning and Nighttime Doses of KP1077, an Investigational Treatment for Idiopathic Hypersomnia

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Introduction

- KP1077 is under development as an oral medication for the treatment of rare sleep disorders with excessive daytime sleepiness (EDS), including idiopathic hypersomnia (IH).
- The active ingredient in KP1077 is serdexmethylphenidate (SDX), a prodrug of d-methylphenidate (d-MPH).
- SDX is converted to d-MPH in the lower intestinal tract resulting in a product with a unique pharmacokinetic (PK) profile defined by a delayed onset and extended duration kinetics.
- The objectives of the study were to assess the PK and safety after single morning and nighttime doses in healthy volunteers.

Methods

- Healthy adult subjects received single oral doses of 240 mg SDX, either in the morning or at night, just before bedtime, in a randomized crossover fashion with a washout of 6 days between treatments.
- Subjects went to bed and nighttime conditions were maintained after administration of the evening dose.
- Multiple blood PK samples and safety parameters were collected after each administration.
- d-MPH was measured with a validated LC/MS-MS method.

Results

- A total of 15 subjects (9 males/6 females) were randomized, with 14 completing both treatments.
- After the morning dose, d-MPH exposure was characterized by little or no d-MPH exposure for the first 4 hours followed by a gradual rise to ~7 hours post-dose (T_{max}), followed by a gradual decline (**Figure 1, Table 1**).
- An even more gradual rise in d-MPH concentrations was seen after the nighttime dose, with substantial levels reached around 10 hours postdose and a statistically significant longer T_{max} of 15 hours (**Figure 1, Table 1,** and **Table 2**).
- Mean d-MPH peak concentrations were lower after the evening dose (22.0 ng/mL) compared to the morning dose (26.8 ng/mL), while total exposures (AUC_{inf}) were similar (594 and 557 h*ng/mL, respectively) (**Table 1** and **Figure 2**).
- Both treatments were well tolerated with adverse events typical for d-MPH (**Table 3**).

Table 1. Plasma d-MPH PK Parameters by Treatment

Treatment Statistic	C_{max} (ng/mL)	T_{max} (h)	T_{lag} (h)	$T_{½}$ (h)	AUC_{0-24h} (h × ng/mL)	AUC_{inf} (h × ng/mL)
SDX 240 mg single dose in the morning						
n	14	14	14	14	14	14
Mean (SD)	26.8 (13.9)	6.9 (1.7)	0.9 (0.5)	8.22 (3.07)	342 (139)	557 (266)
Median (min, max)	-	6.5 (5.0, 12.0)	-	-	-	-
SDX 240 mg single dose in the evening						
n	15	15	15	13	15	13
Mean (SD)	22.0 (9.44)	15.1 (5.3)	1.4 (0.4)	7.90 (2.49)	340 (145)	594 (223)
Median (min, max)	-	16.0 (9.0, 24.0)	-	-	-	-

Table 2. Wilcoxon Signed Rank Test of Plasma d-MPH T_{max}

Parameter (Unit)	SDX 240 mg Single Dose in the Morning (R)		SDX 240 mg Single Dose in the Evening (T)		Median Difference (T-R)	90% CI of Median Differences	p-value
	n	Median	n	Median			
T_{max} (h)	14	6.50	14	16.00	9.00	4.00, 10.00	0.0001

Note: A Wilcoxon signed rank test was performed on the untransformed T_{max}. The exact p-value was calculated with small sample size (n<20). 90% CI was estimated using the Hodges-Lehmann method. R = reference; T = test.

Figure 1. Mean Plasma d-MPH Concentrations by Treatment

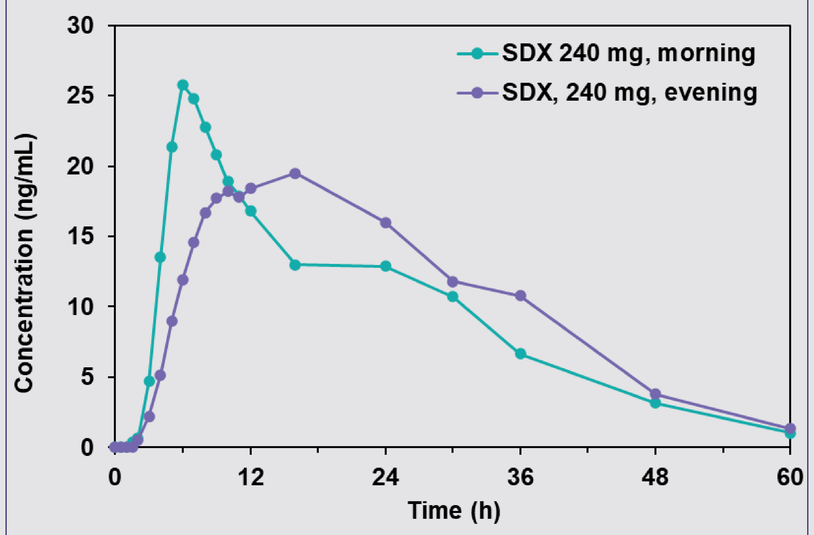
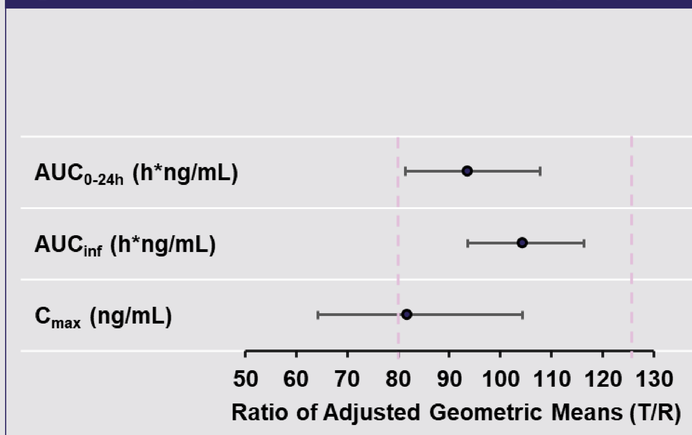


Figure 2. Analysis of Relative Bioavailability of Plasma d-MPH PK Parameters



	SDX 240 mg Single Dose in the Morning (R) n	SDX 240 mg Single Dose in the Morning (R) AGM	SDX 240 mg Single Dose in the Evening (T) n	SDX 240 mg Single Dose in the Evening (T) AGM	Ratio of AGM (T/R) [90% CI]
AUC_{0-24h} (h*ng/mL)	14	314	14	294	93.6 [81.3, 107.8]
AUC_{inf} (h*ng/mL)	13	536	13	560	104.3 [93.5, 116.4]
C_{max} (ng/mL)	14	23.5	14	19.2	81.8 [64.3, 104.3]

Table 3. Most Frequently Reported (≥2 Subjects Overall) TEAEs

Preferred Term	SDX 240 mg Single Dose in the Morning (N=14) n (%)	SDX 240 mg Single Dose in the Evening (N=15) n (%)	Total (N=15) n (%)
Most frequent TEAEs	7 (50.0)	8 (53.3)	10 (66.7)
Insomnia	5 (35.7)	8 (53.3)	9 (60.0)
Headache	1 (7.1)	1 (6.7)	2 (13.3)
Energy increased	1 (7.1)	1 (6.7)	2 (13.3)

% = 100 × n/N. TEAEs were defined as adverse events that started after the first dose of the study drug. Subjects reporting more than 1 event for a given MedDRA preferred term were counted only once for that term. Adverse events were coded using the MedDRA version 26.0. MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Conclusions

- Peak exposure of SDX-derived d-MPH after a nighttime dose of SDX occurs during the next morning leading to higher exposure at awakening compared to a morning dose.
- The delay in exposure after a nighttime dose is likely due to a longer intestinal transit time and lower intestinal activity during the nighttime sleeping hours.
- The delay in exposure supports nighttime dosing of SDX in patients with IH who suffer from EDS and sleep inertia (difficulty waking up in the morning).
- SDX was well tolerated with adverse events typical for MPH.

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Disclosures: KP1077 is an experimental medication, not approved by any regulatory agency.
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