Safety and Efficacy of KP1077 in a Phase 2, Double-blind, Randomized Trial in Patients With 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.
- The objectives of the study were to assess the safety (primary endpoint) and efficacy of KP1077 in patients with IH.
- The trial was not powered to show statistical significance for any endpoint.

Methods

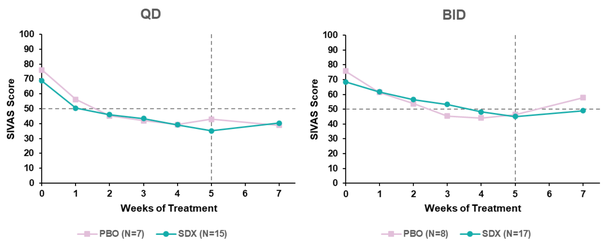
- Adult patients with IH were titrated to an optimal dose of KP1077 in a 5-week open-label (OL) titration period.
- Possible dose levels were 80, 160, 240, and 320 mg/day SDX.
- Patients were randomized to receive their daily dose either once per day (just before going to sleep) (QD), or twice per day (half the daily dose just before going to sleep and half shortly after awakening) (BID).
- After the titration period, patients in each dosing regimen cohort were randomized to placebo or continued KP1077 (optimized dose) during a 2-week double-blind (DB) withdrawal period.
- Assessments of safety were based on adverse events (AEs), physical examinations, clinical laboratory tests, vital signs, electrocardiograms, sleep quality, and suicidal ideation.
- Efficacy assessments included the Epworth Sleepiness Scale (ESS), the IH Severity Scale (IHSS), daily rating of difficulty of waking up in the morning with the Sleep Inertia Visual Analog Scale (SIVAS), and rating of brain fog symptoms with an exploratory Brain Fog Scale (BFS), with a 1-week look-back period for ESS, IHSS, and BFS.

Figure 1. Efficacy Endpoints (decrease=improvement) - All patients received active drug in Weeks 1-5

A. Epworth Sleepiness Scale (ESS)

B. Idiopathic Hypersomnia Severity Scale (IHSS)

C. Sleep Inertia Visual Analog Scale (SIVAS)



D. Brain Fog Symptom Scale (BFS)

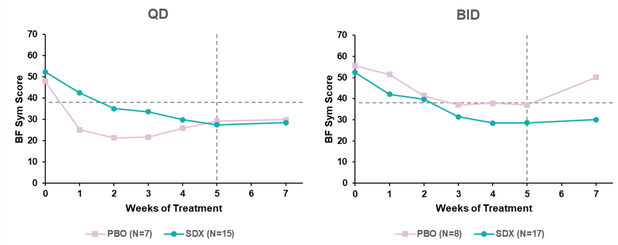


Table 1. Most Frequently Reported Adverse Events (≥5% overall) – Titration Period

Preferred Term	SDX QD (N=32) n (%)	SDX BID (N=34) n (%)	Total (N=66) n (%)
At least one TEAE	**19 (59.4)**	**21 (61.8)**	**40 (60.6)**
Insomnia (all types)	9 (28.1)	7 (20.6)	16 (24.2)
Headache	4 (12.5)	2 (5.9)	6 (9.1)
Anxiety	1 (3.1)	3 (8.8)	4 (6.1)
Decreased appetite	3 (9.4)	1 (2.9)	4 (6.1)
Nausea	1 (3.1)	3 (8.8)	4 (6.1)

TEAE = treatment-emergent adverse event.

Results

- KP1077 was well tolerated for both treatments, dosing regimens and all dose levels, with most frequent AEs of insomnia, headache, anxiety, decreased appetite, and nausea (**Table 1**).
- Most AEs occurred in the titration period, were mild, and did not lead to early discontinuation.
- AEs of insomnia occurred mainly during the first week of treatment, at the lowest dose, and the incidence did not appear dependent on dose or dosing regimen. AEs of insomnia were often transient, not leading to discontinuation, and allowed titration to higher doses. No insomnia AEs were reported in the DB withdrawal period.
- Clinically meaningful improvements in ESS, IHSS, SIVAS, and BFS scores were seen over the 5-week titration period for both treatment groups and were maintained in the 2-week DB withdrawal period (**Figure 1** and **Table 2**).
- Mean total ESS scores decreased by 9 points after 5 weeks of OL treatment.
- For the BID dosing regimen, an apparent separation from placebo was observed for the SDX treatment group at end of trial (Week 7) for all efficacy endpoints.
- For the QD dosing regimen, no separation between treatment groups was seen at the end of the 2-week DB period as the placebo group on average did not worsen. This may be due to variability in the small number of patients.

Conclusions

- KP1077 was well tolerated in patients with IH, with AEs typical for a central nervous system stimulant.
- Meaningful clinical improvements of EDS, sleep inertia, and brain fog were observed after 5 weeks of OL KP1077 and were maintained during the 2-week DB withdrawal period. Results were similar for BID and QD dosing.
- The results provide valuable information for the design of a potential Phase 3 study.

Table 2. Summary Results of ESS, IHSS, SIVAS and BFS

Endpoint	Regimen: QD PBO (N=7)	Regimen: QD SDX (N=15)	Regimen: BID PBO (N=8)	Regimen: BID SDX (N=17)
ESS, Mean (SD)				
Titration Baseline	18.3 (3.50)	16.9 (2.36)	16.5 (3.30)	16.5 (2.72)
Randomization Baseline (Week 5)	10.9 (3.98)	7.5 (3.78)	6.9 (5.51)	7.5 (3.84)
End of Withdrawal Period (Week 7)	9.6 (7.35)	7.5 (5.17)	12.8 (5.75)	7.6 (4.37)
Change from Randomization Baseline to Week 7	*-1.3 (3.95)*	*0.0 (4.17)*	*5.9 (4.26)*	*0.1 (4.87)*
Difference in LS Mean (SE)[a]	0.5 (2.07)		-5.6 (1.88)	
p-value[a]	0.818		0.005	
IHSS, Mean (SD)				
Titration Baseline	33.4 (10.26)	35.4 (4.22)	36.6 (5.78)	34.3 (6.42)
Randomization Baseline (Week 5)	20.9 (8.91)	18.6 (10.87)	21.5 (10.18)	21.3 (9.58)
End of Withdrawal Period (Week 7)	20.1 (12.20)	19.3 (12.37)	30.8 (11.08)	21.6 (9.60)
Change from Randomization Baseline to Week 7	*-0.7 (8.69)*	*0.7 (6.86)*	*9.3 (11.65)*	*0.3 (7.61)*
Difference in LS Mean (SE)[a]	0.9 (3.73)		-9.0 (3.48)	
p-value[a]	0.802		0.013	
SIVAS, Mean (SD)				
Titration Baseline	76.0 (15.08)	68.8 (17.29)	75.8 (10.11)	68.5 (18.82)
Randomization Baseline (Week 5)	42.9 (20.84)	35.1 (20.20)	46.4 (20.94)	45.0 (22.86)
End of Withdrawal Period (Week 7)	38.9 (14.89)	40.4 (21.23)	57.8 (21.44)	49.0 (23.56)
Change from Randomization Baseline to Week 7	*-4.0 (21.08)*	*5.9 (15.13)*	*11.4 (13.69)*	*1.1 (7.35)*
Difference in LS Mean (SE)[a]	8.2 (6.39)		-10.0 (5.98)	
p-value[a]	0.208		0.104	
Brain Fog Symptom Scale, Mean (SD)				
Titration Baseline	47.9 (12.64)	52.3 (16.88)	55.6 (10.90)	52.4 (17.44)
Randomization Baseline (Week 5)	29.3 (22.42)	27.5 (24.86)	36.9 (24.26)	28.6 (22.95)
End of Withdrawal Period (Week 7)	29.9 (23.83)	28.5 (26.12)	50.1 (23.01)	30.1 (23.58)
Change from Randomization Baseline to Week 7	*0.6 (9.80)*	*0.9 (20.79)*	*13.3 (12.66)*	*1.5 (17.34)*
Difference in LS Mean (SE)[a]	0.0 (7.50)		-13.7 (7.07)	
p-value[a]	0.995		0.060	

[a] ANCOVA with terms for randomization baseline score, treatment (active or placebo), regimen (BID or QD), and treatment by regimen as covariates.

Zevra Therapeutics thanks the participants and investigators who made this trial possible.

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