The Orexin 2 Receptor Agonist ALKS 2680 in Patients With Idiopathic Hypersomnia: An Initial Proof of Concept Phase 1b Study

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INTRODUCTION

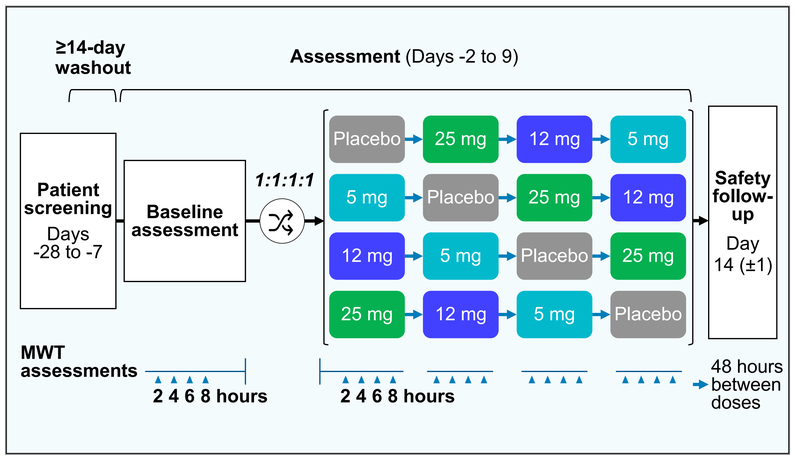
- Idiopathic hypersomnia (IH) is a central disorder of hypersomnolence characterized by excessive daytime sleepiness (EDS), with sleep inertia, long/unrefreshing naps, and prolonged nighttime sleep[1]
- Orexin acts as the master regulator of wakefulness via activation of multiple downstream wake-promoting pathways[2]
- Targeting the orexin system may address EDS across hypersomnolence disorders with orexin deficiency (narcolepsy type 1 [NT1]) and without orexin deficiency (eg, narcolepsy type 2 [NT2], IH)[3]
- ALKS 2680 is a highly potent and selective orexin 2 receptor agonist currently being evaluated in phase 2 studies as a once-daily oral treatment for narcolepsy and IH
- In a phase 1b study, ALKS 2680 was generally safe and well tolerated and achieved statistically significant, clinically meaningful improvements in mean sleep latency in patients with NT1,[4] NT2,[5] and IH
- Here we present the results from this study of ALKS 2680 in patients with IH
- The objectives of this study were:
  - To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with IH
  - To assess the effect of ALKS 2680 on sleep latency and self-reported alertness in patients with IH

METHODS

STUDY DESIGN

- This was a randomized, double-blind, placebo-controlled phase 1b study consisting of a 4-way crossover design with 4 periods (**Figure 1**). Patients with IH were recruited in Australia
- Patients with IH received single doses of 5, 12, and 25 mg of ALKS 2680 or a placebo, with a 48-hour washout period between doses (**Figure 1**)
- Patients discontinued any medications prescribed for management of IH symptoms for a ≥14-day washout period before baseline assessment
- Patients were housed onsite for the duration of the study

FIGURE 1: Study Design



MWT = Maintenance of Wakefulness Test.

STUDY POPULATION

Key Inclusion Criteria for the IH Cohort

- Adults 18 to 65 years of age
- Patients had:
  - Diagnosis of IH according to the International Classification of Sleep Disorders – Third Edition guidelines[6]
  - Residual EDS, defined as Epworth Sleepiness Scale score >10 during the washout period
  - Body mass index of ≥18 and ≤40 kg/m^2 at screening
- There was no limitation on baseline Maintenance of Wakefulness Test (MWT) for inclusion in the study

Key Exclusion Criteria for the IH Cohort

- Patients who had a history of or were diagnosed with:
  - Clinically significant disease or illness (other than IH) associated with excessive sleepiness
  - Substance use disorder[a]
  - Excessive consumption of caffeine, alcohol, nicotine, or cannabis (or derived products)

[a]According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* guidelines.

KEY STUDY ENDPOINTS

- **Primary:** Treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory assessments, and electrocardiograms
- **Secondary:** Change from baseline in the mean sleep latency post-dose across the first 4 sessions of the MWT
- **Exploratory:** Change from baseline in self-reported alertness on the Karolinska Sleepiness Scale (KSS)

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Patient demographics and baseline characteristics are shown in **Table 1**
- At baseline, patients exhibited severe to very severe IH symptoms[7] and EDS

TABLE 1: Demographics and Baseline Characteristics

Demographics	Total (N = 8)
Age, mean (SD), years	35.3 (16.0)
Female, n (%)	7 (87.5)
White race, n (%)	7 (87.5)
BMI, mean (SD), kg/m^2	26.0 (3.2)
Baseline Disease Severity (Post-washout)[a]	**Total (N = 8)**
Idiopathic Hypersomnia Severity Scale,[b] mean (SD) [min, max]	37.5 (5.2) [27, 42]
Epworth Sleepiness Scale,[c] mean (SD) [min, max]	14.8 (3.5) [11, 21]
Maintenance of Wakefulness Test, mean (SD) [min, max], minutes	22.6 (9.3) [5.5, 33.8]
Prior Medications, n (%) Used in >1 Patient	**Total (N = 8)**
Armodafinil	3 (37.5)
Paracetamol	3 (37.5)
Methylphenidate hydrochloride	2 (25.0)

[a]Patients had been receiving standard of care for narcolepsy prior to ≥14-day washout leading into baseline assessment. [b]On the Idiopathic Hypersomnia Severity Scale, score of 26-38 = severe and 39-50 = very severe.[7] [c]On the Epworth Sleepiness Scale, score of >10 suggests excessive daytime sleepiness. BMI = body mass index.

ADVERSE EVENTS

- All TEAEs were mild in severity except 1 moderate TEAE of pollakiuria at 25 mg
- All TEAEs related to the study drug resolved
- No clinically meaningful changes from baseline were identified in laboratory values
- No cardiovascular safety signals were identified in vital signs or electrocardiograms

TABLE 2: Adverse Events

	Placebo	ALKS 2680			
n (%)	(N = 8)	5 mg (N = 8)	12 mg (N = 8)	25 mg (N = 8)	Total ALKS 2680 (N = 8)
Any TEAE	4 (50.0)	6 (75.0)	5 (62.5)	7 (87.5)	8 (100)
TEAEs related to the study drug[a]	3 (37.5)	2 (25.0)	3 (37.5)	7 (87.5)	8 (100)
TEAEs related to study drug occurring in >1 patient[a]					
Pollakiuria	1 (12.5)	2 (25.0)	2 (25.0)	4 (50.0)	5 (62.5)
Insomnia[b]	0	1 (12.5)	1 (12.5)	3 (37.5)	4 (50.0)
Dizziness	0	0	0	2 (25.0)	2 (25.0)
TEAEs leading to study drug discontinuation	0	0	0	0	0
Any serious AE	0	0	0	0	0

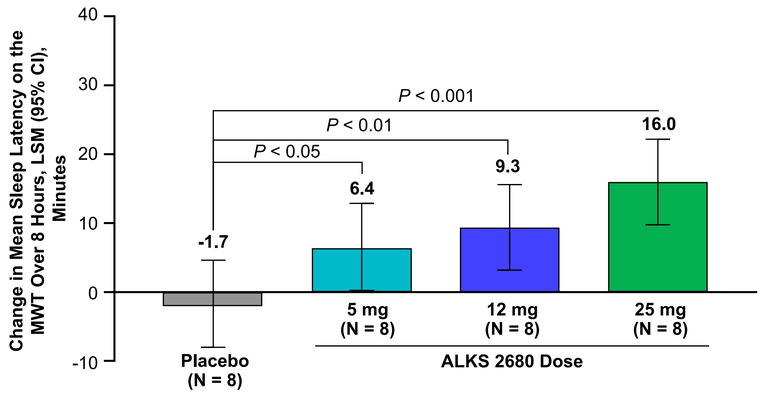
[a]If a patient experiences >1 AE in a category, the patient is counted only once in that category. If a patient experiences the same AE at multiple dose levels, the patient will be counted once per dose level and once in total. The relationship between study drug and AEs was determined by the investigator. [b]Insomnia includes TEAE terms of Insomnia and Middle insomnia.
AE = adverse event; TEAE = treatment-emergent adverse event.

CHANGE FROM BASELINE IN MEAN SLEEP LATENCY OVER 8 HOURS

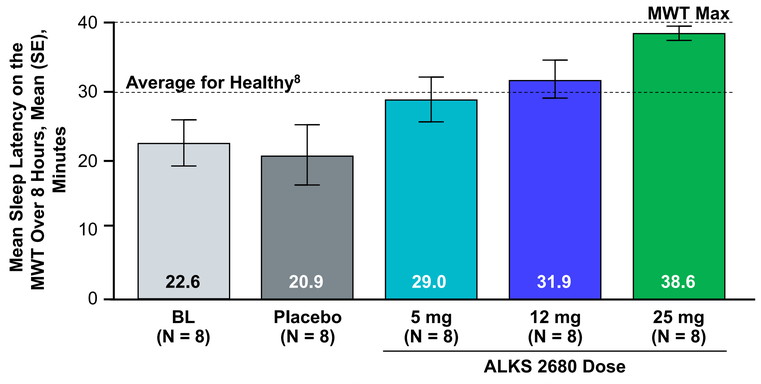
- ALKS 2680 showed clinically meaningful and statistically significant increases in mean sleep latency compared with placebo at all doses tested, with a clear dose response (**Figure 2A**)
- Mean sleep latency observed in the placebo group did not change significantly from baseline, indicating no carryover effects from previous narcolepsy medication or between crossover doses
- Observed mean sleep latencies on the MWT were within the reported range for healthy individuals (average 30.4 ± SD 11.2 minutes[8]), and means for 12 and 25 mg doses were above 30.4 minutes (**Figure 2B**)

FIGURE 2: Mean Sleep Latency on the MWT Over 8 Hours (N = 8)

A. Change From Baseline in Mean Sleep Latency



B. Observed Mean Sleep Latency

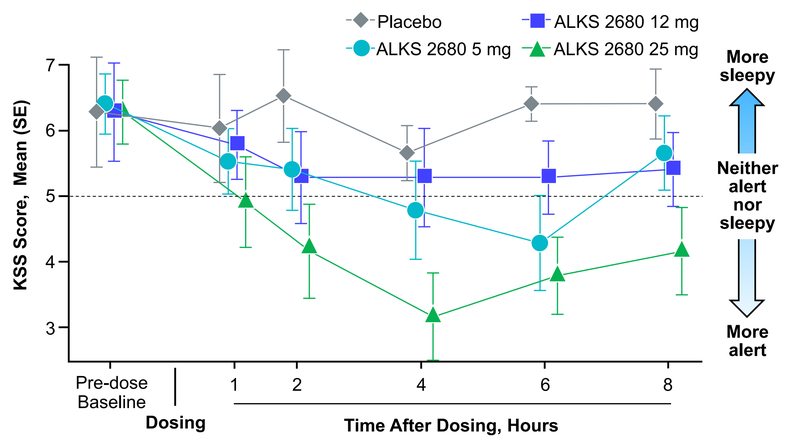


Mean sleep latency was calculated as the mean across the first 4 MWT sessions at 2, 4, 6, and 8 hours on Day -1 and at 2, 4, 6, and 8 hours post-dose on dosing days after a dosing time of approximately 9 AM.
BL = baseline; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness Test; SE = standard error.

SELF-REPORTED ALERTNESS BY KSS SCORE OVER TIME

- Patients who received ALKS 2680 demonstrated improvements in self-reported alertness (as demonstrated by decreases in mean KSS score) compared with placebo, with the greatest improvement seen with the 25 mg dose (**Figure 3**)

FIGURE 3: Subjective Alertness Assessed by KSS by Timepoint (N = 8)



KSS full range is 1-9. Baseline denotes 1 hour pre-dose; dosing occurred at approximately 9 AM local time.
KSS = Karolinska Sleepiness Scale; SE = standard error.

CONCLUSIONS

- In patients with IH, ALKS 2680:
  - Was generally safe and well tolerated at all doses
  - Demonstrated statistically significant, clinically meaningful improvements in mean sleep latency at all doses
    - The observed mean sleep latencies at doses of 12 and 25 mg of ALKS 2680 exceeded the average for healthy individuals (30.4 min)[8]
  - Improved self-reported alertness
- The results of this phase 1 study of patients with NT1,[4] NT2,[5] and IH demonstrate that ALKS 2680 may have benefit for central disorders of hypersomnolence with or without orexin deficiency
- These results informed dose selection for phase 2 study in patients with IH to begin in 2025

References

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