Safety and Pharmacodynamic Effects of the Orexin 2 Receptor Agonist ALKS 2680 in Patients With Narcolepsy Type 1: A First-in-Human Phase 1 Study

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Poster No: 23

INTRODUCTION

- ALKS 2680 is a highly potent, orally bioavailable, and selective orexin 2 receptor agonist being developed as a once-daily treatment for narcolepsy[1]
- Narcolepsy type 1 (NT1) results from the selective loss of neurons that produce orexin (also known as hypocretin), a neurotransmitter that acts as the master regulator of wakefulness systems in the brain[2]
- Initial results in patients with NT1 from this study have been previously presented[1]
  - In patients with NT1, single doses of ALKS 2680 demonstrated statistically significant, clinically meaningful, and dose-dependent improvements in sleep latency on the Maintenance of Wakefulness Test (MWT)
- The objectives of the study were:
  - To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with NT1
  - To assess the effect of ALKS 2680 on increasing sleep latency and self-reported alertness in patients with NT1

METHODS

STUDY DESIGN

- This phase 1b study conducted in Australia was a randomized, double-blind, placebo-controlled study with a 4-way crossover design with 4 periods, conducted in patients with NT1, narcolepsy type 2, or idiopathic hypersomnia (**Figure 1**)
  - Here, we report results in patients with NT1
- Patients with NT1 received single doses of 1, 3, and 8 mg of ALKS 2680 or a placebo, with a 48-hour washout period between doses (**Figure 1**)
  - Study patients discontinued any narcolepsy medications for a ≥14-day washout period prior to baseline assessment
  - Patients were housed on-site for the duration of the study

STUDY ENDPOINTS

- **Primary Endpoints:** Treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory testing of blood and urine, and electrocardiograms
- **Secondary Endpoint:** Change from baseline in the mean sleep latency across the first 4 sessions of the MWT
- **Exploratory Endpoint:** Change from baseline on the Karolinska Sleepiness Scale (KSS)

STUDY POPULATION

Key Inclusion Criteria for the NT1 Cohort

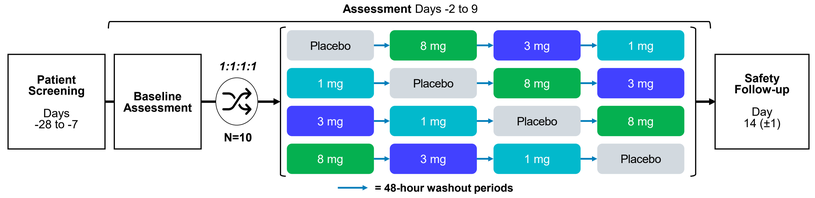
- The study included adults 18–65 years of age
- Study patients had:
  - Diagnosis of NT1 according to the International Classification of Sleep Disorders – Third Edition guidelines[3]
  - Residual excessive daytime sleepiness (EDS), defined as Epworth Sleepiness Scale score >10 during the washout period
  - Body mass index of ≥18 and ≤40 kg/m^2 at screening

Key Exclusion Criteria for the NT1 Cohort

- Patients who had a history of or were diagnosed with:
  - Clinically significant disease, illness, or abnormality (including cardiovascular, psychiatric, or other sleep disorders associated with excessive sleepiness)
  - Substance use disorder*
  - Excessive consumption of caffeine, alcohol, nicotine, or cannabis (or derived products)†

*According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* guidelines. †Consumption of over 400 mg of coffee, 20 g of alcohol, 1 cigarette, vaping or chewing tobacco, nicotine product, or gum per day, OR consumption of cannabis or derived products more than 3 times per month.

FIGURE 1: Study Design



RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Patient demographics and baseline characteristics are shown in **Table 1**
- Nine patients (90%) were positive for the HLA-DQB1*06:02 haplotype
- Patients exhibited EDS and severe narcolepsy symptoms at baseline (**Table 1**)

TABLE 1: Demographics and Baseline Characteristics

Characteristic	Total (N = 10*)
Age, mean (SD), years	25.6 (10.5)
Female, n (%)	6 (60.0)
White race, n (%)	10 (100.0)
BMI, mean (SD), kg/m^2	26.5 (4.8)
Baseline Disease Severity^	**Total (N = 10*)**
Narcolepsy Severity Scale, mean (SD)†	40.6 (7.3)
Epworth Sleepiness Scale, mean (SD)‡	15.9 (2.5)
Weekly cataplexy rate, mean (SD)	32.0 (43.8)
Prior Medications, n (%) Used in ≥3 patients	**Total (N = 10*)**
Methylphenidate	6 (60.0)
Armodafinil	3 (30.0)
Methylphenidate hydrochloride	3 (30.0)
Venlafaxine	3 (30.0)
Sodium oxybate	3 (30.0)

*All 10 patients underwent the washout period and received ≥1 dose of ALKS 2680. One patient discontinued the study after receiving the first dose (8 mg) due to poor venous access and inability to undergo further blood draws. †Patients had been receiving standard of care for narcolepsy prior to ≥14-day washout leading into baseline assessment. ‡On Narcolepsy Severity Scale, score of 29–42 = severe and 43–57 = very severe. ^On the Epworth Sleepiness Scale, score of >10 suggests excessive daytime sleepiness.
BMI = body mass index.

SAFETY

- Most TEAEs were mild in severity, transient, and resolved without medical intervention
- No one discontinued treatment or study participation because of any TEAE (**Table 2**)
- No serious or severe adverse events were reported (**Table 2**)
- The majority of TEAEs related to study drug were observed with 8 mg (**Table 2**)
- No drug-related, treatment-emergent, clinically meaningful changes from baseline were identified in laboratory values
- No cardiovascular safety signals were identified in vital signs or electrocardiograms

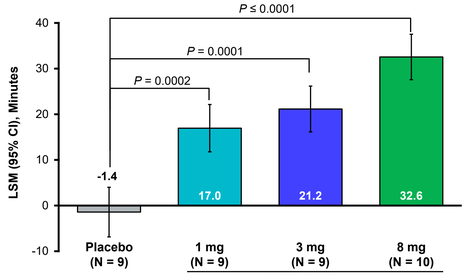
TABLE 2: Adverse Events

	Placebo	ALKS 2680			
	(N = 9)	1 mg (N = 9)	3 mg (N = 9)	8 mg (N = 10)	Total ALKS 2680 (N = 10)
Any TEAE	4 (44.4)	6 (66.7)	5 (55.6)	9 (90.0)	9 (90.0)
TEAEs by highest severity*					
Mild	4 (44.4)	6 (66.7)	5 (55.6)	8 (80.0)	8 (80.0)
Moderate	0	0	0	1 (10.0)†	1 (10.0)
Severe	0	0	0	0	0
TEAEs related to the study drug Occurring in >1 patient*	1 (11.1)	5 (55.6)	3 (33.3)	9 (90.0)	9 (90.0)
Insomnia‡	0	0	1 (11.1)	6 (60.0)	6 (60.0)
Pollakiuria	0	0	2 (22.2)	4 (40.0)	4 (40.0)
Salivary hypersecretion	1 (11.1)	1 (11.1)	1 (11.1)	3 (30.0)	3 (30.0)
Decreased appetite	0	1 (11.1)	0	1 (10.0)	2 (20.0)
Dizziness	0	1 (11.1)	0	2 (20.0)	2 (20.0)
Nausea	0	2 (22.2)	0	2 (20.0)	2 (20.0)
TEAEs leading to study drug discontinuation	0	0	0	0	0
Any SAEs	0	0	0	0	0

*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. †One moderate case of nausea which resolved with food intake. ‡Insomnia includes TEAE terms of insomnia and middle insomnia (ie, difficulty maintaining sleep).
AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

MEAN SLEEP LATENCY OVER 8 HOURS

FIGURE 2: Change From Baseline in Mean Sleep Latency on the MWT Over 8 Hours



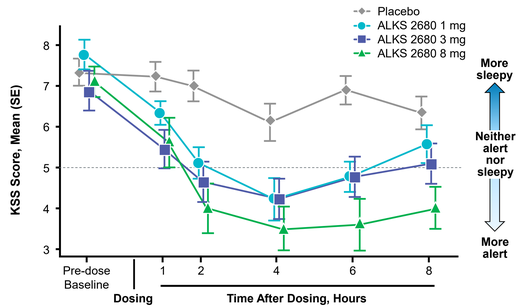
Mean sleep latency was calculated as the mean across the first 4 MWT sessions at 2, 4, 6, and 8 hours on Day -1 and at 2, 4, 6, and 8 hours post-dose on dosing days after a dosing time of approximately 9 AM.
LSM = least squares mean; MWT = Maintenance of Wakefulness Test.

- At baseline (Day -1), mean (SD) sleep latency on the MWT was 6.4 (5.5) minutes
- 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 2**)
- Mean sleep latency following placebo treatment did not change significantly from baseline, indicating no carryover effects from previous narcolepsy medication or between crossovers
- Observed mean sleep latencies over 8 hours at the 3 and 8 mg doses were within the reported normal range for healthy individuals[4]
- Placebo-corrected changes from baseline in mean sleep latency over 8 hours were 18.4 minutes (1 mg), 22.6 minutes (3 mg), and 34.0 minutes (8 mg)

SELF-REPORTED ALERTNESS

- Patients who received once-daily ALKS 2680 demonstrated dose-dependent improvements in self-reported alertness (as demonstrated by decreases in mean KSS score) compared with placebo, with the greatest improvement seen with the 8 mg dose (**Figure 3**)

FIGURE 3: Subjective Alertness Assessed by KSS by Timepoint (N = 10)



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

CONCLUSIONS

- ALKS 2680 was generally well tolerated at all doses tested
- ALKS 2680 demonstrated statistically significant, clinically meaningful improvements in mean sleep latency at all doses
  - Mean sleep latencies observed at the 3 and 8 mg doses were similar to those observed in healthy individuals[4]
- ALKS 2680 showed clinically meaningful, dose-dependent improvements in self-reported alertness
- The pharmacodynamic profile of ALKS 2680 is supportive of once-daily administration
- The results of this phase 1 study inform a phase 2 dose range of 4 to 8 mg daily

References

1. Yee B, et al. Presentation at World Sleep Congress 2023; October 20-25, 2023; Rio de Janeiro, Brazil. **2.** Bassetti CLA, et al. *Nat Rev Neurol*. 2019;15(9):519-539. **3.** Ruoff C, Rye D. *Curr Med Res Opin*. 2016;32(10):1611-1622. **4.** Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498.

Acknowledgments

The study was supported by Alkermes, Inc. Medical writing support was provided by Aparna Rao, PhD, at Envision Pharma Group, and was funded by Alkermes, Inc. This poster was developed in accordance with Good Publication Practice (GPP4) guidelines. Authors had full control of the content and made the final decision on all aspects of this poster.

Disclosures

RG has received funding from Alkermes, Apnimed, Eisai, Eli Lilly & Company, SomnoMed, Takeda, and Vanda Pharmaceuticals. **BY** has received funding from Alkermes, Eli Lilly & Company, GSK, SomnoMed, Takeda, Teva Pharmaceuticals, and Vanda Pharmaceuticals. **JC** and **AD** have nothing to disclose. **CH**, **JR**, **DS**, **SY**, and **BR** are employees and shareholders of Alkermes.