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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INTRODUCTION

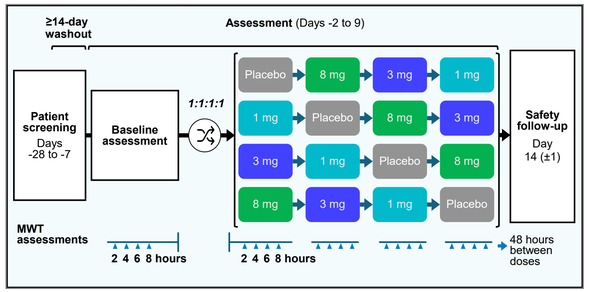
- ALKS 2680 is a highly potent, orally bioavailable, and selective orexin 2 receptor agonist being developed as a once-daily treatment for narcolepsy and idiopathic hypersomnia (IH)
- Narcolepsy type 1 (NT1) results from the selective loss of neurons that produce orexin (also known as hypocretin), a neurotransmitter that acts as the master regulator of wakefulness systems in the brain[1]
- 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 cohorts of patients with NT1, narcolepsy type 2 (NT2),[2] or IH[3] (see shaded box following Conclusions for more information)
- Here we present the results from this study of ALKS 2680 in patients with NT1
- The objectives of this 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 was a randomized, double-blind, placebo-controlled phase 1b study consisting of a 4-way crossover design with 4 periods (**Figure 1**). Patients with NT1 were recruited in Australia
- 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**)
- Patients discontinued any narcolepsy medications for a ≥14-day washout period prior to 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 NT1 Cohort

- Adults 18 to 65 years of age
- Patients had:
  - Diagnosis of NT1 according to the International Classification of Sleep Disorders – Third Edition guidelines[4]
  - 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 or illness (other than NT1) 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 testing of blood and urine, and electrocardiograms
- **Secondary:** Change from baseline in the mean sleep latency across the first 4 sessions of the Maintenance of Wakefulness Test
- **Exploratory:** Change from baseline in self-reported sleepiness on the Karolinska Sleepiness Scale (KSS)

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- 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

Demographics	Total (N = 10[a])
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 (Post-washout)[b]	**Total (N = 10[a])**
Narcolepsy Severity Scale, mean (SD)[c]	40.6 (7.3)
Epworth Sleepiness Scale, mean (SD)[d]	15.9 (2.5)
Weekly cataplexy rate, mean (SD)	32.0 (43.8)
Maintenance of Wakefulness Test, mean (SD) [min, max], minutes	6.4 (5.5) [0.6, 15.0]
Prior Medications, n (%) Used in ≥3 Patients	**Total (N = 10[a])**
Methylphenidate	6 (60.0)
Armodafinil	3 (30.0)
Methylphenidate hydrochloride	3 (30.0)
Venlafaxine	3 (30.0)
Sodium oxybate	3 (30.0)

[a]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. [b]Patients had been receiving standard of care for narcolepsy prior to ≥14-day washout leading into baseline assessment. [c]On Narcolepsy Severity Scale, score of 29-42 = severe and 43-57 = very severe.[5] [d]On the Epworth Sleepiness Scale, score of >10 suggests excessive daytime sleepiness.
BMI = body mass index.

ADVERSE EVENTS

- Most TEAEs were mild in severity (except 1 moderate TEAE of nausea at 8 mg, which resolved with food intake), transient, and resolved without medical intervention
- No 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 (%)	**(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 related to the study drug[a]	1 (11.1)	5 (55.6)	3 (33.3)	9 (90.0)	9 (90.0)
TEAEs related to the study drug occurring in >1 patient[a]					
Insomnia[b]	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

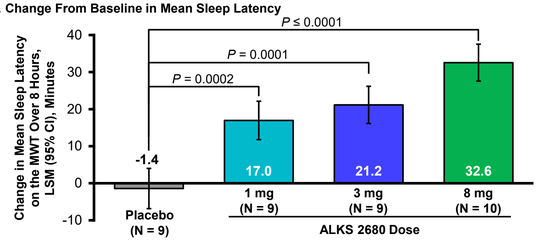
[a]If a patient experiences >1 AE in a category, the patient is counted only once in that category. If a patient experiences the same AE at multiple dose levels, the patient will be counted once per dose level and once in total. The relationship between study drug and AEs was determined by the investigator.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

CHANGE FROM BASELINE IN MEAN SLEEP LATENCY OVER 8 HOURS

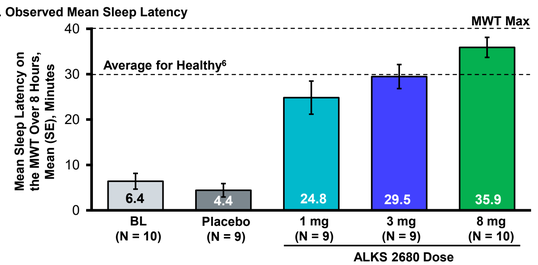
- ALKS 2680 showed clinically meaningful and statistically significant increases in mean sleep latency compared with placebo at all doses tested, with a clear dose response (**Figure 2A**)
- Mean sleep latency following placebo treatment did not change significantly from baseline, indicating no carryover effects from previous narcolepsy medication or between crossovers (**Figure 2A**)
- Observed mean sleep latencies over 8 hours at the 3 and 8 mg doses were within the reported normal range for healthy individuals[6] (**Figure 2B**)

FIGURE 2: Mean Sleep Latency on the MWT Over 8 Hours (N = 10)

A. Change From Baseline in Mean Sleep Latency



B. Observed Mean Sleep Latency

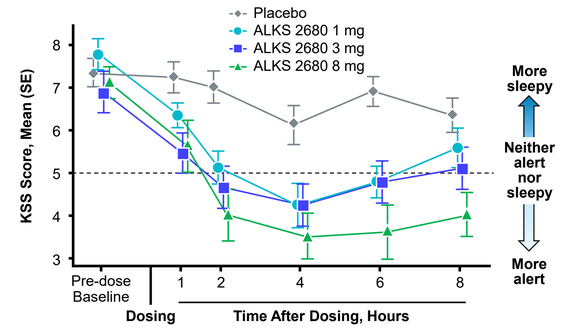


Mean sleep latency was calculated as the mean across the first 4 MWT sessions at 2, 4, 6, and 8 hours on Day -1 and at 2, 4, 6, and 8 hours post-dose on dosing days after a dosing time of approximately 9 AM.
BL = baseline; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness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

SELF-REPORTED ALERTNESS BY KSS SCORE OVER TIME

- Patients who received 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; SE = standard error.

CONCLUSIONS

- In patients with NT1, ALKS 2680:
  - Was generally well tolerated at all doses tested
  - 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 (average [SD] of 30.4 [11.2] min)[6]
  - Showed clinically meaningful, dose-dependent improvements in self-reported alertness
- The results of this phase 1 study of patients with NT1, NT2,[2] and IH[3] demonstrate that ALKS 2680 may have benefit for central disorders of hypersomnolence with or without orexin deficiency
- The results of this phase 1 study informed the dose range of 4 to 8 mg daily being used in the phase 2 Vibrance-1 study (ClinicalTrials.gov identifier: NCT06358950)

SUMMARY OF RESULTS IN PATIENTS WITH NT2 OR IH

- ALKS 2680 was also assessed in cohorts of patients with NT2 (N = 9) or IH (N = 8) with single doses of 5, 12, and 25 mg[2,3]
- In both patient cohorts, ALKS 2680 was well tolerated, with no serious or severe TEAEs and no TEAEs leading to discontinuation
  - The most common drug-related TEAEs in both cohorts were pollakiuria, insomnia, and dizziness
- ALKS 2680 led to statistically significant, dose-dependent, and clinically meaningful improvements on the Maintenance of Wakefulness Test at all doses tested in patients with NT2 and IH
  - At 12 mg and 25 mg in both cohorts, ALKS 2680 exceeded the average mean sleep latency established for healthy individuals (30.4 minutes)[6]
- Phase 2 evaluation of ALKS 2680 is ongoing in NT2 (Vibrance-2; NCT06555783) and planned in IH (Vibrance-3; NCT06843590)

References

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