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

Ron Grunstein,[1] Brendon Yee,[1] Julia Chapman,[1] Jian Eu Tai,[1] Sheila Sivam,[1] Craig Hopkinson,[2] Jandira Ramos,[2] Shifang Liu,[2] Daniel Smith,[2] Sergey Yagoda,[2] Bhaskar Rege[2]

[1]Woolcock Institute of Medical Research, Sydney, Australia; [2]Alkermes, Inc., Waltham, Massachusetts

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INTRODUCTION

- Narcolepsy type 2 (NT2) is a central disorder of hypersomnolence characterized by excessive daytime sleepiness (EDS), but without the cataplexy associated with narcolepsy type 1 (NT1)[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 (NT1) and without orexin deficiency (eg, NT2; idiopathic hypersomnia [IH])[1]
- 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[3,4]
- 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,[5] NT2, and IH[6]
- Here we present the results from this study of ALKS 2680 in patients with NT2
- The objectives of this study were:
  - To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with NT2
  - To assess the effect of ALKS 2680 on sleep latency and self-reported alertness in patients with NT2

METHODS

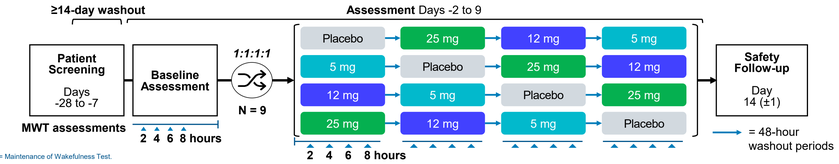
STUDY DESIGN

- 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 NT2 were recruited in Australia and the United States
- This design enables more precise dose selection for phase 2
- Patients with NT2 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 narcolepsy medications for a ≥14-day washout period before baseline assessment
- Patients were housed onsite for the duration of the study

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 sleepiness on the Karolinska Sleepiness Scale (KSS)

FIGURE 1: Study Design



MWT = Maintenance of Wakefulness Test.

STUDY POPULATION

Key Inclusion Criteria for the NT2 Cohort

- Adults 18 to 65 years of age
- Patients had:
  - Diagnosis of NT2 according to the International Classification of Sleep Disorders – Third Edition guidelines[7]
  - 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 NT2 Cohort

- Patients who had a history of or were diagnosed with:
  - Clinically significant disease or illness (other than NT1, NT2, 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.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- At baseline, patients with NT2 exhibited moderate severity of narcolepsy symptoms and EDS

TABLE 1: Demographics and Baseline Characteristics

Demographics	Total (N = 9)
Age, mean (SD), years	36.0 (15.4)
Female, n (%)	5 (55.6)
White race, n (%)	7 (77.8)
Body mass index, mean (SD), kg/m^2	26.0 (6.2)
Baseline Disease Severity (Post-washout)[a]	**Total (N = 9)**
Narcolepsy Severity Scale,[b] mean (SD) [min, max]	24.4 (6.7) [12, 32]
Epworth Sleepiness Scale,[c] mean (SD) [min, max]	15.9 (3.8) [11, 23]
Maintenance of Wakefulness Test, minutes, mean (SD) [min, max]	14.3 (11.2) [2.8, 32.9]
Prior Medications, n (%) Used in >1 patient	**Total (N = 9)**
Modafinil	5 (55.6)
Armodafinil	3 (33.3)
Dexamfetamine sulfate	2 (22.2)
Methylphenidate	2 (22.2)
Sodium oxybate	2 (22.2)

[a]Patients had been receiving standard of care for narcolepsy prior to ≥14-day washout leading into baseline assessment. [b]On the Narcolepsy Severity Scale, score of 15-28 = moderate severity, score of 29-42 = severe, and 43-57 = very severe.[5] [c]On the Epworth Sleepiness Scale, a score of >10 suggests excessive daytime sleepiness.

ADVERSE EVENTS

TABLE 2: Summary of Treatment-Emergent Adverse Events

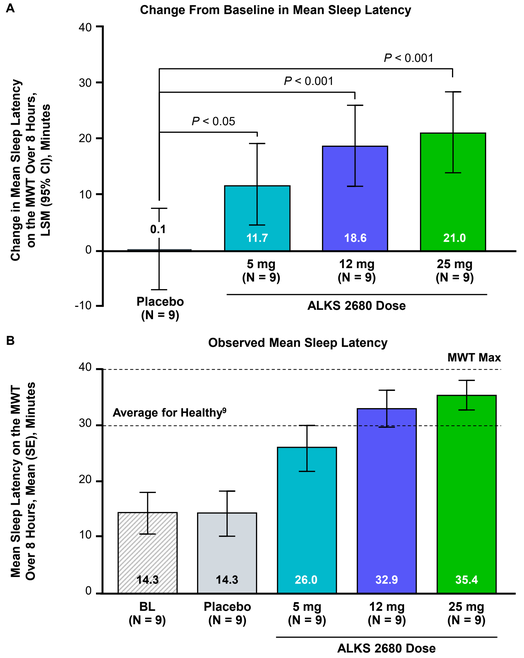
	Placebo	ALKS 2680			
	(N = 9)	5 mg (N = 9)	12 mg (N = 9)	25 mg (N = 9)	Total ALKS 2680 (N = 9)
Any TEAE	2 (22.2)	3 (33.3)	4 (44.4)	7 (77.8)	7 (77.8)
TEAEs related to the study drug[a]	2 (22.2)	1 (11.1)	1 (11.1)	6 (66.7)	6 (66.7)
TEAEs related to the study drug occurring in >1 patient[a]					
Pollakiuria	0	0	1 (11.1)	3 (33.3)	3 (33.3)
Insomnia[b]	1 (11.1)	1 (11.1)	0	2 (22.2)	3 (33.3)
Dizziness[c]	0	0	0	3 (33.3)	3 (33.3)
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 Initial insomnia. [c]Dizziness includes TEAE terms of Dizziness and Dizziness postural.
AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

- All TEAEs were mild in severity except 1 moderate TEAE of pollakiuria at 25 mg
- All TEAEs related to study drug resolved without medical intervention
- No clinically meaningful changes from baseline were identified in laboratory values
- No cardiovascular safety signals were identified in vital signs or electrocardiograms

CHANGE FROM BASELINE IN MEAN SLEEP LATENCY OVER 8 HOURS

FIGURE 2: Mean Sleep Latency on the MWT Over 8 Hours (N = 9)



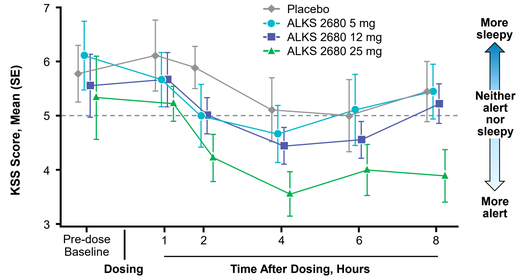
Mean sleep latency was calculated as the mean across MWT assessments at 2, 4, 6, and 8 hours at baseline and then post-dose (dose time: ~9 AM).
BL = baseline; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness Test; SE = standard error.

- 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 (**Figure 2A**)
- Observed mean sleep latencies on the MWT were within the reported range for healthy individuals (average 30.4 ± SD 11.2 minutes[9]), and means for the 12 and 25 mg doses were above the 30.4 minute average (**Figure 2B**)

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 = 9)



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 NT2, 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 all doses of ALKS 2680 were within the range for healthy individuals, with the 12 and 25 mg doses at or above the average for healthy individuals (30.4 min)[9]
  - Improved self-reported alertness
- The results of this phase 1 study of patients with NT1,[5] NT2, and IH[6] demonstrate that ALKS 2680 may have benefit for central disorders of hypersomnolence with or without orexin deficiency and inform dose selection for phase 2 development

References

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