SUPPORTING SCIENTIFIC INFORMATION FOR ALKERMES OREXIN PORTFOLIO STRATEGY REVIEW

OCTOBER 9, 2024

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Important Information About This Document

This document includes scientific information about ALKS 2680 that is intended for investors participating in the Alkermes Orexin Portfolio Strategy Review ("Strategy Review") and should be read in conjunction with the Strategy Review presentations. ALKS 2680 is investigational and has not been approved by the FDA or any other health authority, and its safety and efficacy have not been established.

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and the potential therapeutic and commercial value of ALKS 2680 for the treatment of central disorders of hypersomnolence with or without orexin deficiency, including narcolepsy and idiopathic hypersomnia. Such forward-looking statements are inherently uncertain and, although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, these statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether ALKS 2680 could be shown to be ineffective or unsafe; potential changes in the cost, scope and duration of the development program for ALKS 2680; whether initial clinical results will be predictive of results of future clinical studies or real-world results; whether future clinical trials or future stages of ongoing clinical trials for ALKS 2680 will be initiated or completed on time or at all; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2023 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this document. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this document.

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: 423

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)

OBJECTIVES

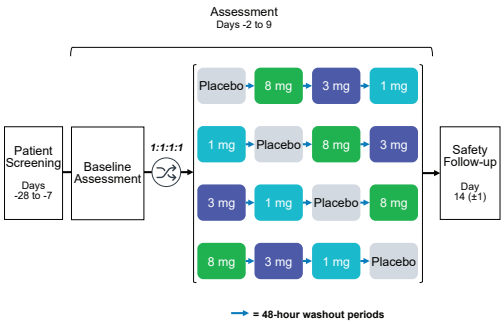
- To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with NT1
- To assess the effect of ALKS 2680 on increasing sleep latency and self-reported alertness in patients with NT1

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

FIGURE 1: Study Design



STUDY POPULATION

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

Select 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.

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)

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 (Centrally Acting),§ 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. †On Narcolepsy Severity Scale, score of 29–42 = severe and 43–54 = very severe. ‡On the Epworth Sleepiness Scale, score of >10 suggests excessive daytime sleepiness. §Medications used prior to washout by 2 patients include reboxetine, clomipramine, and fluoxetine. Medications used prior to washout by 1 patient include dexamphetamine sulfate, modafinil, aripiprazole, and baclofen.
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

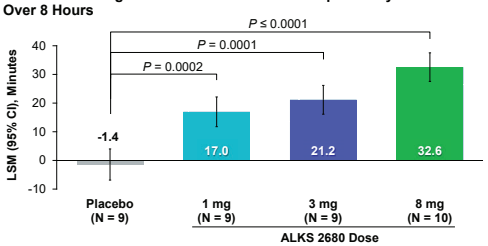
	Placebo	ALKS 2680			
TEAEs, n (%)	(N = 9)	1 mg (N = 9)	3 mg (N = 9)	8 mg (N = 10)	Total ALKS 2680 (N = 10)
Any TEAE	4 (44.4)	6 (66.7)	5 (55.6)	9 (90.0)	9 (90.0)
TEAEs by highest severity*					
Mild	4 (44.4)	6 (66.7)	5 (55.6)	8 (80.0)	8 (80.0)
Moderate	0	0	0	1 (10.0)†	1 (10.0)
Severe	0	0	0	0	0
TEAEs related 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 had multiple AEs, the highest severity is presented in summary by severity, and the closest relationship to study drug is presented in summary by relationship. Relationship assessment is per investigator determination. †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

- 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]

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



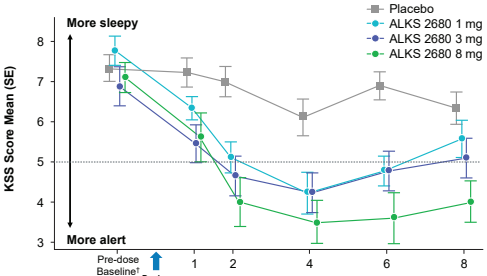
*Based on a mixed effect model of repeated measures with dose level and period as fixed factors; mean sleep latency on Day -1 was included as the baseline covariate. Mean sleep latency was calculated as the mean across the first 4 MWT sessions at 2, 4, 6, and 8 hours on Day -1 and at 2, 4, 6, and 8 hours post-dose on dosing days after a dosing time of approximately 9 AM.
LSM = least squares mean; MWT = Maintenance of Wakefulness Test.

- 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. Dashed line indicates *neither alert nor sleepy*. †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 (See Poster #462)

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.

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Disclosures

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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]

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Poster No: 200

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 (see Posters P797 and P5071)
- 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,[3] NT2, and IH (see Poster P5070)
- Here we present the results from this study of ALKS 2680 in patients with NT2

OBJECTIVES

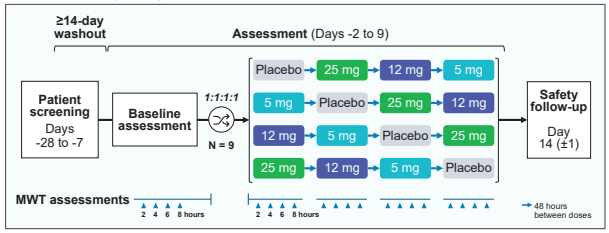
- To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with NT2
- To assess the effect of ALKS 2680 on sleep latency and self-reported alertness in patients with NT2

METHODS

STUDY DESIGN

- This was a randomised, 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

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[4]
  - 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.

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)

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

- Patient demographics and baseline characteristics are shown in **Table 1**
- At baseline, patients with NT2 exhibited moderate severity of narcolepsy symptoms and EDS

TABLE 1: Demographics and Baseline Characteristics

Characteristic	Total (N = 9)
Demographics	
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]	
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	
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.[4] [c]On the Epworth Sleepiness Scale, a score of >10 suggests excessive daytime sleepiness.

ADVERSE EVENTS

- 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

TABLE 2: Summary of Treatment-Emergent Adverse Events

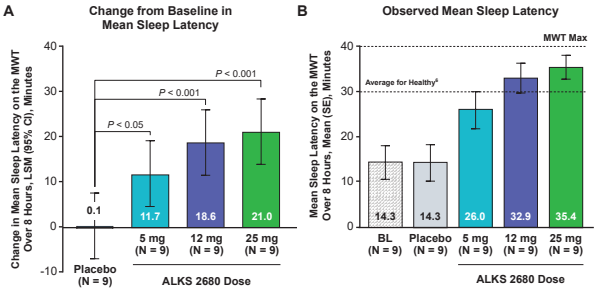
	Placebo	ALKS 2680			
TEAEs, n (%)	(N = 9)	5 mg (N = 9)	12 mg (N = 9)	25 mg (N = 9)	Total ALKS 2680 (N = 9)
Any TEAE	2 (22.2)	3 (33.3)	4 (44.4)	7 (77.8)	7 (77.8)
TEAEs related to the study drug[a]	2 (22.2)	1 (11.1)	1 (11.1)	6 (66.7)	6 (66.7)
TEAEs related to the study drug occurring in >1 patient[a]					
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.

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 (**Figure 2A**)
- Observed mean sleep latencies on the MWT were within the reported range for healthy individuals (average 30.4 ± SD 11.2 minutes[6]), and means for the 12 and 25 mg doses were above the 30.4 minute average (**Figure 2B**)

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

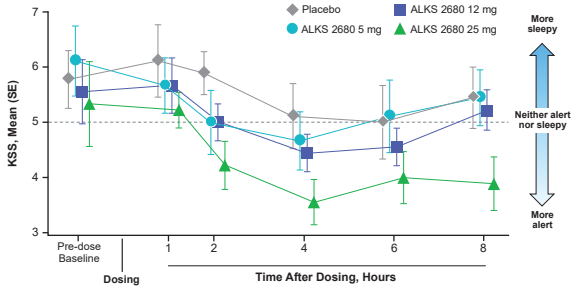


Mean sleep latency was calculated as the mean across MWT assessments at 2, 4, 6, and 8 hours at baseline and then post-dose (dose time: ~9 AM).
BL = baseline; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness Test; SE = standard error.

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)[6]
  - Improved self-reported alertness
- The results of this phase 1 study of patients with NT1,[3] NT2, and IH 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

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Acknowledgments

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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, GlaxoSmithKline, SomnoMed, Takeda, Teva Pharmaceuticals, and Vanda Pharmaceuticals. **JC** and **JET** have nothing to disclose. **SS** has received funding from SomnoMed, Teva Pharmaceuticals, and Vertex Pharmaceuticals. **CH**, **JR**, **SL**, **DS**, **SY**, and **BR** are employees and stockholders of Alkermes.

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

Brendon Yee,[1] Ron Grunstein,[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, MA, USA

Poster No: 5070

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 (see Posters P797 and P5071)
- 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 (see Poster P200), and IH
- Here we present the results from this study of ALKS 2680 in patients with IH

OBJECTIVES

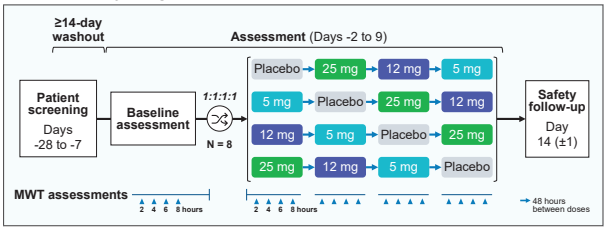
- To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with IH
- To assess the effect of ALKS 2680 on sleep latency and self-reported alertness in patients with IH

METHODS

STUDY DESIGN

- This was a randomised, 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[5]
  - 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 NT1, NT2, or 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[6] and EDS

TABLE 1: Demographics and Baseline Characteristics

Characteristic	Total (N = 8)
Demographics	
Age, mean (SD), years	35.3 (16.0)
Female, n (%)	7 (87.5)
White race, n (%)	7 (87.5)
Body mass index, mean (SD), kg/m^2	26.0 (3.2)
Baseline Disease Severity (Post-washout)[a]	
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	
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. [c]On the Epworth Sleepiness Scale, score of >10 suggests excessive daytime sleepiness.

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: Summary of TEAEs

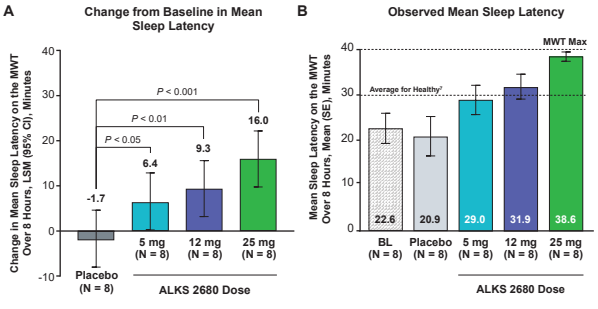
	Placebo	ALKS 2680			
TEAEs, n (%)	(N = 8)	5 mg (N = 8)	12 mg (N = 8)	25 mg (N = 8)	Total ALKS 2680 (N = 8)
Any TEAE	4 (50.0)	6 (75.0)	5 (62.5)	7 (87.5)	8 (100)
TEAEs related to the study drug[a]	3 (37.5)	2 (25.0)	3 (37.5)	7 (87.5)	8 (100)
TEAEs related to study drug occurring in >1 patient[a]					
Pollakiuria	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 adverse event	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[7]), 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)

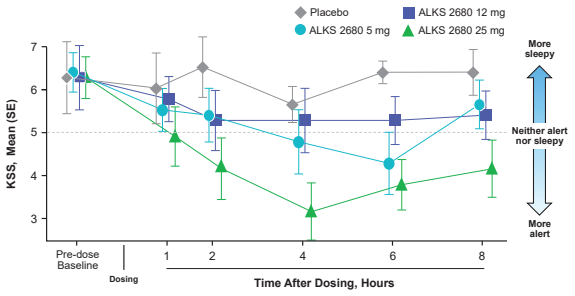


Mean sleep latency was calculated as the mean across the first 4 MWT sessions at 2, 4, 6, and 8 hours on Day -1 and at 2, 4, 6, and 8 hours post-dose on dosing days after a dosing time of approximately 9 AM.
BL = baseline; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness 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)[7]
  - Improved self-reported alertness
- The results of this phase 1 study of patients with NT1,[4] NT2, and IH 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

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1. Dauvilliers Y, et al. *Sleep Med Rev*. 2022;66:101709. **2.** Jászberényi M, et al. *Biomedicines*. 2024;12(2):448. **3.** Barateau L, Dauvilliers Y. *Ther Adv Neurol Disord*. 2019;12:1-12. **4.** Grunstein R, et al. Poster presented at SLEEP Congress 2024; June 1-5, 2024; Houston, TX, USA. **5.** Ruoff C, Rye D. *Curr Med Res Opin*. 2016;32(10):1611-1622. **6.** Rassu AL, et al. *J Clin Sleep Med*. 2022;18(2):617-629. **7.** Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498.

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Disclosures

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Vibrance-1: Study Design and Methods for a Phase 2, Randomised, Placebo-Controlled, Parallel Group Study Evaluating the Safety and Efficacy of ALKS 2680 in Patients With Narcolepsy Type 1

David Plante,[1] Ron Grunstein,[2] Giuseppe Plazzi,[3] Anne Marie Morse,[4] Jandira Ramos,[5] Shifang Liu,[5] Sergey Yagoda,[5] Bhaskar Rege[5]

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Poster No: 797

INTRODUCTION

- ALKS 2680 is a highly potent, orally bioavailable, and selective orexin 2 receptor (OX2R) 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]
- ALKS 2680 is designed to address the underlying pathology of narcolepsy by focusing on the following key objectives:
  - To improve the duration and quality of wakefulness, with a pharmacokinetic and pharmacodynamic profile that mirrors the natural sleep-wake cycle, allowing patients to stay awake during the day and sleep at night
  - To control cataplexy
  - To have a range of therapeutic doses with once-daily oral administration
  - To have an acceptable safety profile with a wide therapeutic window that can accommodate different doses needed for NT1 and narcolepsy type 2
- In a phase 1b study, single doses of ALKS 2680 were generally well tolerated among patients with NT1 and led to statistically significant, clinically meaningful improvements in sleep latency and patient-reported alertness[1,3]
  - These results informed the range of doses to be assessed in the phase 2 Vibrance-1 study

OBJECTIVES

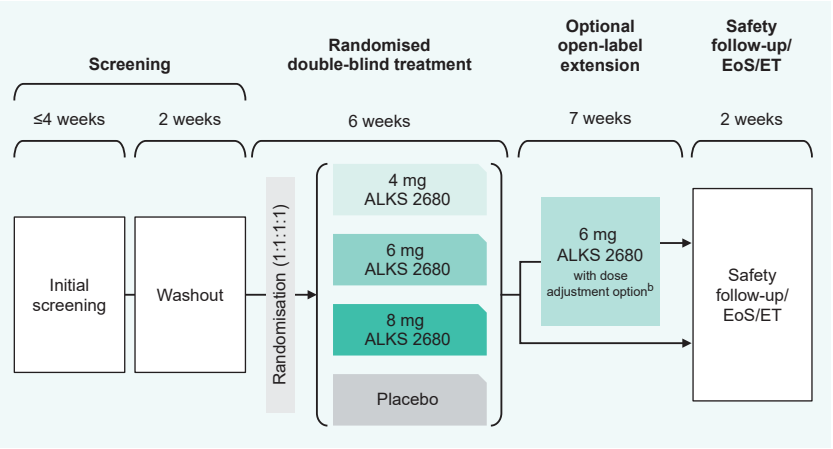
- The Vibrance-1 study (ClinicalTrials.gov identifier: NCT06358950) aims to assess the safety and efficacy of once-daily ALKS 2680 compared with placebo through 6 weeks of treatment in patients with NT1

METHODS

STUDY DESIGN

- Vibrance-1 is an ongoing, phase 2, placebo-controlled, parallel-group, dose-ranging study with a randomised double-blind treatment period and an open-label extension period (**Figure 1**)
- Following a 2-week washout period from prior narcolepsy medications, patients will be randomized 1:1:1:1 to receive placebo or ALKS 2680 once daily at doses of 4, 6, or 8 mg for 6 weeks
- The double-blind treatment period will be followed by an optional open-label extension period of up to 7 weeks

FIGURE 1: Vibrance-1 Study Design[a]



[a]The study is being conducted in the United States, Australia, and Europe. [b]Dose adjustment possible (up or down) during the first 2 weeks of the optional open-label extension period.
EoS = end of study; ET = early termination.

STUDY POPULATION

- Planned enrolment is approximately 80 patients with NT1
- Key inclusion and exclusion criteria are described in **Figure 2**

FIGURE 2: Key Inclusion and Exclusion Criteria[4a]

Inclusion Criteria

- Age 18 to ≤70 years
- BMI ≥18 and ≤35 kg/m^2
- Meets the diagnostic criteria of NT1 according to ICSD-3-TR guidelines[5] and:
  - Is HLA-DQB1*06:02-positive OR hypocretin-1 CSF levels ≤110 pg/mL
  - Has residual excessive daytime sleepiness[b] and cataplexy[c]
- Willing and able to discontinue any medications prescribed for the management of narcolepsy symptoms for at least 14 days

Exclusion Criteria

Presence of other significant comorbid medical conditions, including other sleep, cardiovascular, and psychiatric disorders

[a]Additional criteria apply. Eligibility will be determined on an individual basis by the study investigator. [b]Epworth Sleepiness Scale score >10 at Visit 1. [c]Average of >4 weekly cataplexy events during the last 2 weeks of the washout period.
BMI = body mass index; CSF = cerebrospinal fluid; ICSD-3-TR = International Classification of Sleep Disorders – Third Edition, Text Revision; NT1 = narcolepsy type 1.

STUDY ENDPOINTS

- Primary, secondary, and exploratory endpoints are summarised in **Figure 3**

FIGURE 3: Study Endpoints[4]

Primary Endpoint

Change in mean sleep latency on the Maintenance of Wakefulness Test (MWT) from baseline to Week 6 by dose level

Secondary Endpoints

Change in Epworth Sleepiness Scale (ESS) from baseline to Week 6 by dose level

Mean weekly cataplexy rate as derived from the patient cataplexy diary over Weeks 5 and 6 by dose level

Treatment-emergent adverse events and other safety parameters by study period

Exploratory Endpoints

Sleep stages as measured by EEG power spectra

Patient- and clinician-reported outcomes, including:

- Karolinska Sleepiness Scale
- Narcolepsy Severity Scale
- Patient Global Impression of Severity
- Clinical Global Impression of Severity

EEG = electroencephalogram.

SUMMARY

- ALKS 2680 is currently the only OX2R agonist in phase 2 clinical development for both narcolepsy subtypes
- Vibrance-1 is evaluating once-daily ALKS 2680 over 6 weeks in patients with NT1, followed by open-label treatment
- To learn about participation or patient referrals, please visit vibrancestudies.com or clinicaltrials.gov/study/NCT06358950

Visit vibrancestudies.com

Visit Vibrance-1 at ClinicalTrials.gov

References

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2. Bassetti CLA, et al. *Nat Rev Neurol*. 2019;15(9):519-539.
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5. Ruoff C, Rye D. *Curr Med Res Opin*. 2016;32(10):1611-1622.

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Disclosures

DP received funding from Aditum Bio, Alkermes, Harmony Biosciences, Jazz Pharmaceuticals, Takeda, and Teva Australia. **RG** received funding from Alkermes, Apnimed, Eisai, Eli Lilly & Company, SomnoMed, Takeda, and Vanda Pharmaceuticals. **GP** received funding from Biogroject, Centessa Pharmaceuticals, Idorsia, Jazz Pharmaceuticals, Orexia Therapeutics, and Takeda. **AMM** received funding from Alkermes, Avadel, Geisinger Health Plan, Harmony Biosciences, Jazz Pharmaceuticals, NIH, and Takeda; and is the CEO of DAMM Good Sleep, LLC. **JR**, **SL**, **SY**, and **BR** are employees and stockholders of Alkermes.

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Vibrance-2: Study Design and Methods for a Phase 2, Randomised, Placebo-Controlled, Parallel Group Study Evaluating the Safety and Efficacy of ALKS 2680 in Patients With Narcolepsy Type 2

David Plante,[1] Ron Grunstein,[2] Giuseppe Plazzi,[3] Chad Ruoff,[4] Jandira Ramos,[5] Shifang Liu,[5] Sergey Yagoda,[5] Bhaskar Rege[5]

[1]University of Wisconsin School of Medicine and Public Health, UW Department of Psychiatry, Madison, WI, USA; [2]Woolcock Institute of Medical Research, Macquarie Park, Sydney, Australia; [3]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; [4]Mayo Clinic Hospital, Division of Pulmonary Medicine, Phoenix, AZ, USA; [5]Alkermes, Inc., Waltham, MA, USA

Poster No: 5071

INTRODUCTION

- ALKS 2680 is a highly potent, orally bioavailable, and selective orexin 2 receptor (OX2R) agonist being developed as a once-daily treatment for narcolepsy[1]
- Targeting the orexin (also known as hypocretin) system may address daytime sleepiness across hypersomnolence disorders with orexin deficiency (narcolepsy type 1 [NT1]) and without orexin deficiency (eg, narcolepsy type 2 [NT2] and idiopathic hypersomnia [IH])[2]
- In a phase 1b study, single doses of ALKS 2680 were generally well tolerated among patients with NT1[3] (1, 3, and 8 mg), NT2 (5, 12, and 25 mg), or IH (5, 12, and 25 mg), and led to statistically significant, clinically meaningful improvements in sleep latency and improved patient-reported alertness
  - Phase 1b results in patients with NT2 are presented in Poster P200
  - Phase 1b results in patients with IH are presented in Poster P5070
  - These results demonstrate that a potent OX2R agonist can be effective in patients with or without orexin deficiency
- Results from the phase 1b study of patients with NT2 informed the range of doses to be assessed in the phase 2 Vibrance-2 study

OBJECTIVES

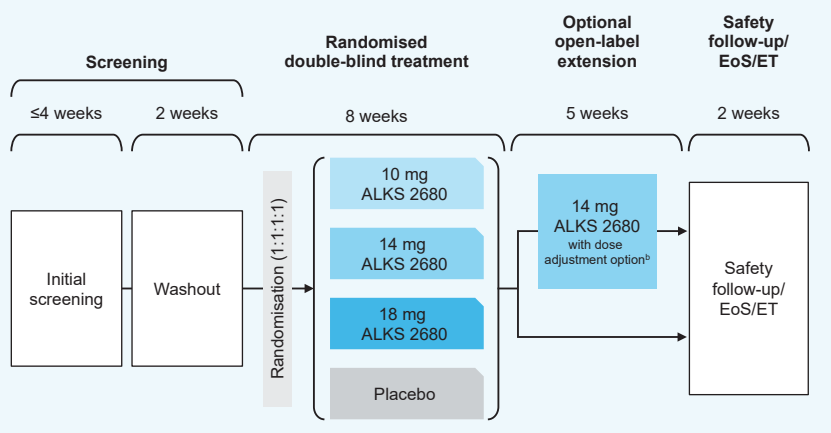
- The Vibrance-2 study (ClinicalTrials.gov identifier: NCT06555783) aims to assess the safety and efficacy of once-daily ALKS 2680 compared with placebo through 8 weeks of treatment in patients with NT2

METHODS

STUDY DESIGN

- Vibrance-2 is an ongoing, phase 2, placebo-controlled, parallel-group, dose-ranging study with a randomised double-blind treatment period and an open-label extension period (**Figure 1**)
- Following a 2-week washout period from prior narcolepsy medications, patients will be randomized 1:1:1:1 to receive placebo or ALKS 2680 once daily at doses of 10, 14, or 18 mg for 8 weeks
- The double-blind treatment period will be followed by an optional open-label extension period of 5 weeks

FIGURE 1: Vibrance-2 Study Design[a]



[a]The study is being conducted in the United States, Australia, and Europe. [b]Dose adjustments possible (up or down) during the first 2 weeks of the optional open-label extension period.
EoS = end of study; ET = early termination.

STUDY POPULATION

- Planned enrolment is approximately 80 patients with NT2
- Key inclusion and exclusion criteria are described in **Figure 2**

FIGURE 2: Key Inclusion and Exclusion Criteria[4a]

Inclusion Criteria	• Age 18 to ≤70 years
	• BMI ≥18 and ≤35 kg/m^2
	• Meets the diagnostic criteria of NT2 according to ICSD-3-TR guidelines[5] and:
	  ○ Has residual excessive daytime sleepiness[b]
	  ○ Has a mean sleep latency of ≤15 minutes across the 4 Maintenance of Wakefulness Test trials during screening
	• Willing and able to discontinue any medications prescribed for the management of narcolepsy symptoms for at least 14 days

Exclusion Criteria	**Presence of other significant comorbid medical conditions, including other sleep, cardiovascular, and psychiatric disorders**

[a]Additional criteria apply. Eligibility will be determined on an individual basis by the study investigator. [b]Epworth Sleepiness Scale score >12 at Visit 4.
BMI = body mass index; ICSD-3-TR = International Classification of Sleep Disorders – Third Edition, Text Revision; NT2 = narcolepsy type 2.

STUDY ENDPOINTS

- Primary, secondary, and exploratory endpoints are summarised in **Figure 3**

FIGURE 3: Study Endpoints[4]

Primary Endpoint
Change in mean sleep latency on the Maintenance of Wakefulness Test (MWT) from baseline to Week 8 by dose level

Secondary Endpoints
Change in Epworth Sleepiness Scale (ESS) from baseline to Week 8 by dose level

Treatment-emergent adverse events and other safety parameters by study period

Exploratory Endpoints
Sleep stages as measured by EEG power spectra

Patient- or clinician-reported outcomes, including:
- Karolinska Sleepiness Scale
- Narcolepsy Severity Scale
- Patient Global Impression of Severity
- Clinical Global Impression of Severity

EEG = electroencephalogram.

SUMMARY

- ALKS 2680 is currently the only OX2R agonist in phase 2 clinical development for both narcolepsy subtypes
- Vibrance-2 is evaluating once-daily ALKS 2680 over 8 weeks in patients with NT2, followed by optional open-label treatment
- To learn about participation or patient referrals, please visit vibrancestudies.com or clinicaltrials.gov/study/NCT06555783

Visit vibrancestudies.com

Visit Vibrance-2 at ClinicalTrials.gov

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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, MA, USA

SLEEP EUROPE 2024 | September 24-27, 2024

Financial Relationship Disclosure

- Ron Grunstein: Alkermes, ApniMed, Eisai, Eli Lilly & Company, SomnoMed, Takeda, and Vanda Pharmaceuticals
- Brendon Yee: Alkermes, Eli Lilly & Company, GlaxoSmithKline, SomnoMed, Takeda, Teva Pharmaceuticals, and Vanda Pharmaceuticals
- Julia Chapman and Jian Eu Tai: Nothing to disclose
- Sheila Sivam: SomnoMed, Teva Pharmaceuticals, and Vertex Pharmaceuticals
- Craig Hopkinson, Jandira Ramos, Shifang Liu, Daniel Smith, Sergey Yagoda, and Bhaskar Rege: Employees and stockholders of Alkermes

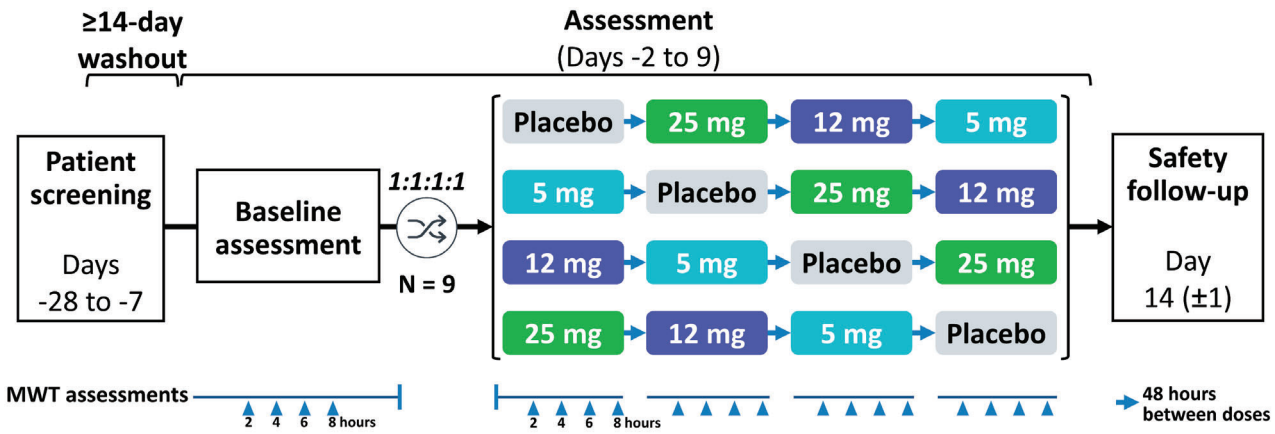
ALKS 2680 Is an Investigational Oral Orexin 2 Receptor Agonist for the Treatment of Narcolepsy and Idiopathic Hypersomnia

- Orexin acts as the master regulator of wakefulness[1]
- Targeting the orexin system may address daytime sleepiness across hypersomnolence disorders[2]
  - With orexin deficiency (narcolepsy type 1 [NT1]), and
  - Without orexin deficiency (eg, narcolepsy type 2 [NT2], idiopathic hypersomnia [IH])
- ALKS 2680 is a once-daily, highly potent, orally bioavailable, and selective orexin 2 receptor agonist
  - 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,[3] NT2, and IH (Poster P5070)
  - ALKS 2680 is currently being evaluated in phase 2 studies as a once-daily treatment for NT1[a] and NT2[b]
- Here we present the results from the phase 1b study of ALKS 2680 in patients with NT2

[a]Poster No. 797. [b]Poster No. 5071.

1. Jászberényi M, et al. *Biomedicines*. 2024;12(2):448. **2.** Barateau L, Dauvilliers Y. *Ther Adv Neurol Disord*. 2019;12:1756286419875622.
3. Grunstein R, et al. Poster presented at SLEEP Congress 2024; June 1-5, 2024; Houston, TX, USA.

Randomised, Double-Blind, Placebo-Controlled Phase 1b Study of ALKS 2680 in Patients With NT2



- Had a confirmed diagnosis of NT2
- No criteria on baseline Maintenance of Wakefulness Test (MWT) for inclusion
- Design enables more precise dose selection for phase 2

- Key objectives:
  - Safety and tolerability
  - Sleep latency on the MWT over 8 hours at each crossover

NT2 = narcolepsy type 2.

NT2 Baseline Characteristics Consistent With Moderate to Severe Baseline Disease

Baseline Characteristics	Total (N=9)
Demographics	
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]	
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, mean (SD) [min, max], minutes	14.3 (11.2) [2.8, 32.9]

At baseline, patients with NT2 exhibited moderate severity of narcolepsy symptoms and excessive daytime sleepiness

[a]Patients had been receiving standard of care for narcolepsy prior to ≥14-day washout leading into baseline assessment. [b]On Narcolepsy Severity Scale, score of 15-28 = moderate, 29-42 = severe, and 43-57 = very severe. [c]On the Epworth Sleepiness Scale, score of >10 suggests excessive daytime sleepiness.
NT2 = narcolepsy type 2; SD = standard deviation.

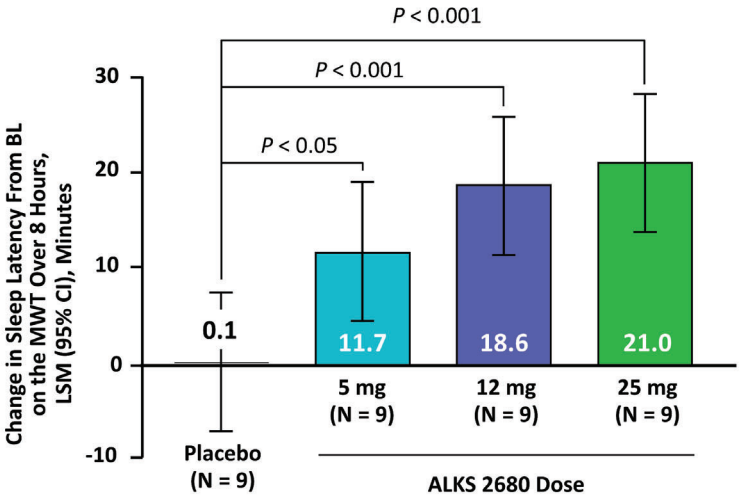
ALKS 2680 Was Generally Safe and Well Tolerated in Patients With NT2

- All treatment-emergent adverse events (TEAEs) were mild in severity except 1 moderate TEAE of pollakiuria at 25 mg
- All TEAEs related to the 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

	Placebo	ALKS 2680			
TEAEs, n (%)	**(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 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; NT2 = narcolepsy type 2; SAE = serious adverse event.

ALKS 2680 Improved Mean Sleep Latency in Patients With NT2

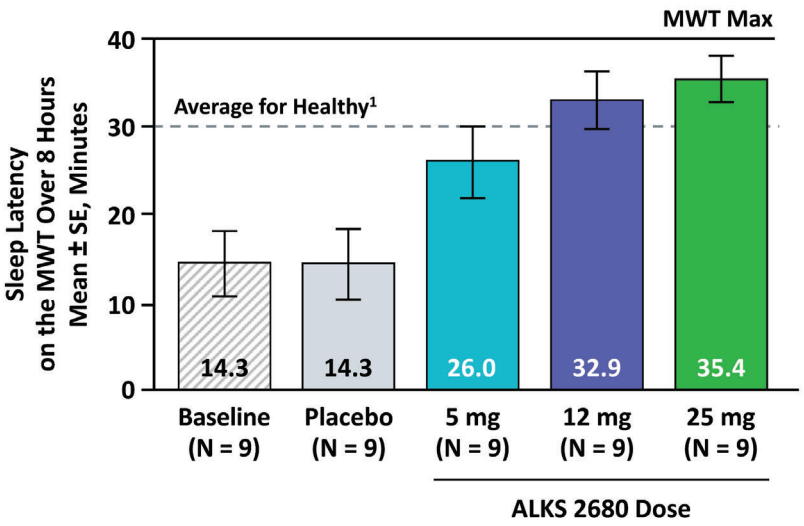


- ALKS 2680 resulted in improved mean sleep latency compared with placebo
- Improvements were statistically significant and clinically meaningful at all doses
- A clear dose response was observed

BL = baseline; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness Test; NT2 = narcolepsy type 2.

ALKS 2680 Improved Mean Sleep Latency in Patients With NT2

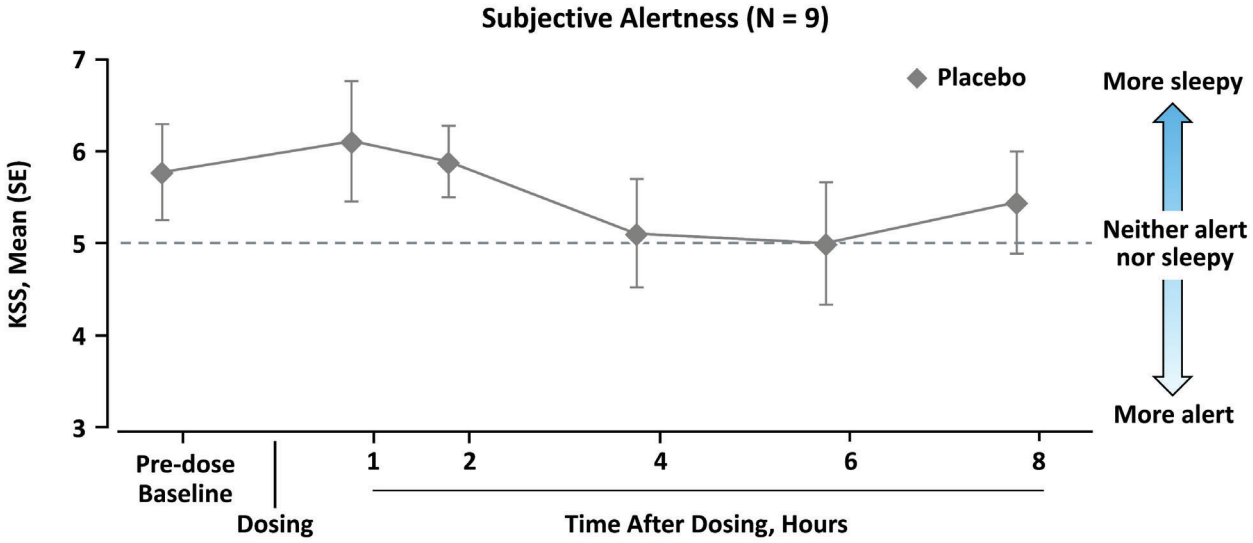
- ALKS 2680 resulted in observed mean sleep latencies within the range for healthy individuals (average 30.4 ± SD 11.2 minutes[1])
- ALKS 2680 doses of 12 and 25 mg resulted in mean sleep latency times above 30.4 minutes



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).
MWT = Maintenance of Wakefulness Test; NT2 = narcolepsy type 2; SD = standard deviation; SE = standard error.

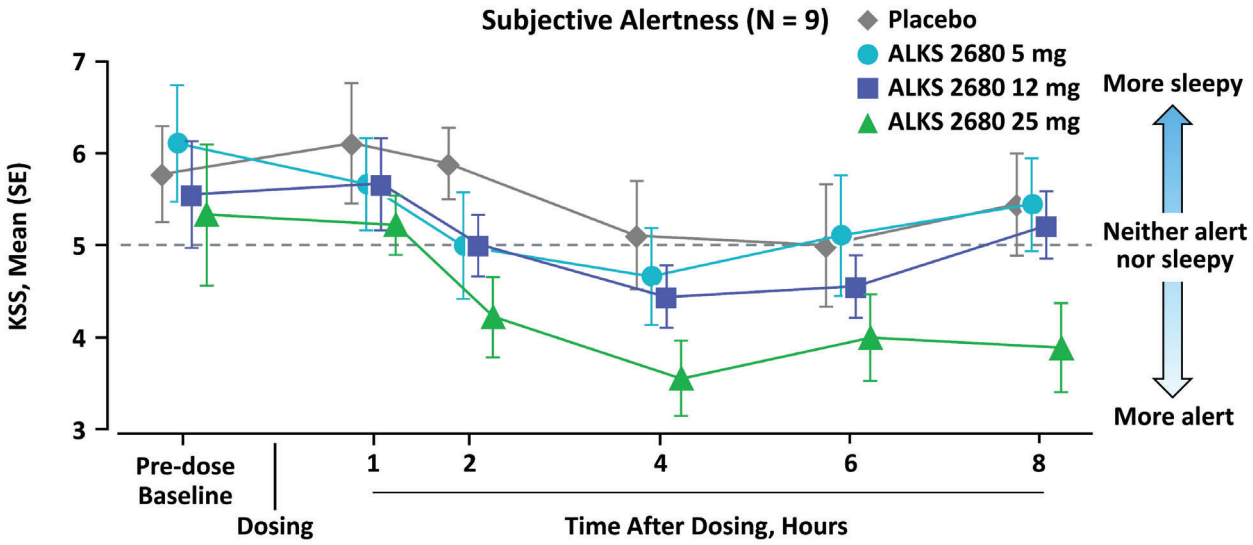
1. Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498.

ALKS 2680 Improved Self-Reported Alertness in Patients With NT2



KSS full range is 1-9. Pre-dose baseline measured the same day.
KSS = Karolinska Sleepiness Scale; NT2 = narcolepsy type 2; SE = standard error.

ALKS 2680 Improved Self-Reported Alertness in Patients With NT2



KSS full range is 1-9. Pre-dose baseline measured the same day.
KSS = Karolinska Sleepiness Scale; NT2 = narcolepsy type 2; 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 on the MWT at all doses
  - Achieved observed mean sleep latencies within the range for healthy individuals at all doses
  - ALKS 2680 12 and 25 mg doses exceeded the average mean sleep latency established for healthy individuals (30.4 minutes)[1]
- Improved self-reported alertness

Results of this phase 1b study of patients with NT1, NT2, and IH[a] 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

[a]Poster No. 5070.
IH = idiopathic hypersomnia; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.
1. Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498.

ALKS 2680 Is Currently the Only OX2R Agonist in Phase 2 for Both Narcolepsy Subtypes

Vibrance-1 Study

Phase 2: Once-daily ALKS 2680 in patients with **NT1**

- Now enrolling in Australia and the United States (NCT06358950)
- Study sites planned for Europe
- See Poster P797

Vibrance-2 Study

Phase 2: Once-daily ALKS 2680 in patients with **NT2**

- Now enrolling in the United States (NCT06358950)
- Study sites planned for Australia and Europe
- See Poster P5071

NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; OX2R = orexin 2 receptor .

Acknowledgements

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Thank you to the investigators and researchers

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