The Orexin 2 Receptor Agonist ALKS 2680 in Patients With Narcolepsy or Idiopathic Hypersomnia: A Phase 1b Study

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INTRODUCTION

- Central disorders of hypersomnolence, which include narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH), are a group of disorders that share pathologic excessive daytime sleepiness (EDS)[1]
- NT1 is distinguished from NT2 by the presence of cataplexy and reduced or absent orexin levels[1]
- IH also features EDS without cataplexy and normal orexin levels, but is distinguished from NT2 by more pronounced sleep inertia and longer, unrefreshing daytime sleep periods[2]
- Orexin acts as a key regulator of wakefulness via activation of multiple downstream wake-promoting pathways.[3] Treatments that target the orexin system may address symptoms across hypersomnolence disorders with (NT1) or without (NT2 and IH) orexin deficiency[4]
- ALKS 2680 is a highly potent, oral, and selective orexin 2 receptor agonist being developed as a once-daily treatment for narcolepsy and IH
- Here we present the results from a phase 1b study of ALKS 2680 in patients with NT1, NT2, or IH

OBJECTIVES

- To assess the safety and tolerability of ALKS 2680 administered in single doses in patients with NT1, NT2, or IH
- To assess the effect of ALKS 2680 on increasing sleep latency and self-reported alertness in patients with NT1, NT2, or 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 NT1, NT2, or IH received single doses of ALKS 2680 or a placebo, with a 48-hour washout period between doses (**Figure 1**)
- Patients discontinued any medications prescribed for management of NT1, NT2, or IH symptoms for a ≥14-day washout period before baseline assessment
- Patients were housed onsite for the duration of the study

STUDY POPULATION

Key Inclusion Criteria for Each Cohort

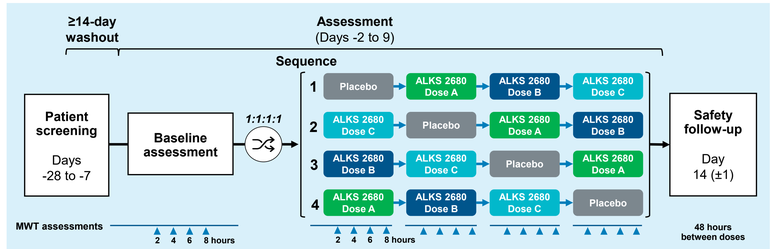
- Adults 18-65 years of age
- Patients had:
  - Diagnosis of NT1, NT2, or IH according to the *International Classification of Sleep Disorders, Third Edition* guidelines[5]
  - Residual EDS, defined as Epworth Sleepiness Scale (ESS) score >10 during the washout period
  - Body mass index ≥18 and ≤40 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 Each 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.

FIGURE 1: Study Design



Patient Population[a]	ALKS 2680 Dose A	ALKS 2680 Dose B	ALKS 2680 Dose C
NT1	8 mg	3 mg	1 mg
NT2	25 mg	12 mg	5 mg
IH	25 mg	12 mg	5 mg

[a]Patients with NT1 and patients with IH were recruited in Australia. Patients with NT2 were recruited in Australia and the USA.
IH = idiopathic hypersomnia; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

KEY STUDY ENDPOINTS FOR EACH COHORT

- **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 for all cohorts are shown in **Table 1**
- At baseline, patients in all cohorts exhibited EDS based on ESS >10. Narcolepsy symptoms were severe in patients with NT1 and moderate in patients with NT2 based on the Narcolepsy Severity Scale.[6] Patients with IH had severe IH symptoms based on the IH Severity Scale[7]

TABLE 1: Demographics and Baseline Characteristics for Patients With NT1, NT2, or IH

	NT1 (N = 10[a])	NT2 (N = 9)	IH (N = 8)
Age, mean (SD), years	25.6 (10.5)	36.0 (15.4)	35.3 (16.0)
Female, n (%)	6 (60.0)	5 (55.6)	7 (87.5)
Race, n (%)			
White	10 (100.0)	7 (77.8)	7 (87.5)
Asian	0	1 (11.1)	1 (12.5)
Other	0	1 (11.1)	0
BMI, mean (SD), kg/m^2	26.5 (4.8)	26.0 (6.2)	26.0 (3.2)
Baseline Disease Severity (post-washout),[b] mean (SD) [min, max]			
Narcolepsy Severity Scale[c]	40.6 (7.3) [28, 54]	24.4 (6.7) [12, 32]	N/A
IH Severity Scale[d]	N/A	N/A	37.5 (5.2) [27, 42]
Epworth Sleepiness Scale	15.9 (2.5) [12, 19]	15.9 (3.8) [11, 23]	14.8 (3.5) [11, 21]
Weekly cataplexy rate	32.0 (43.8) [0, 145]	N/A	N/A

[a]All 10 patients with NT1 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 or IH prior to ≥14-day washout leading into baseline assessment.
[c]On the Narcolepsy Severity Scale, scores of 0-14 = mild, 15-28 = moderate, 29-42 = severe, and 43-57 = very severe.[6]
[d]On the IH Severity Scale, scores of 26-38 = severe and 39-50 = very severe.[7]
BMI = body mass index; IH = idiopathic hypersomnia; N/A = not applicable; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

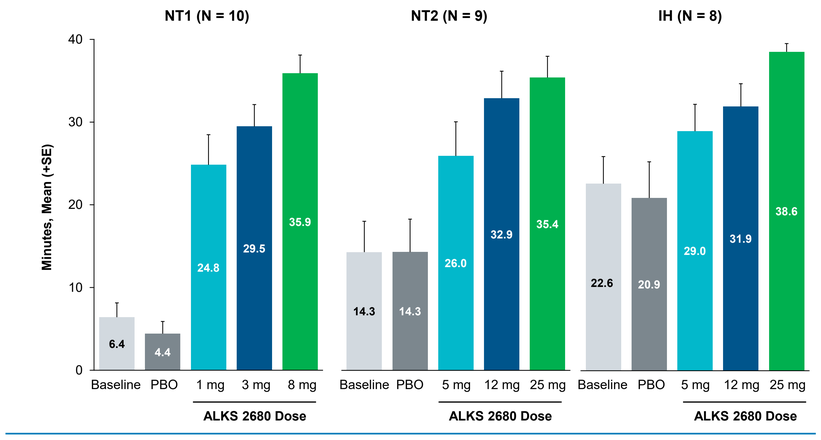
CHANGE FROM BASELINE IN MEAN SLEEP LATENCY OVER 8 HOURS

- In all cohorts, 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 (**Figure 2**)
- Across cohorts, the observed mean sleep latency over 8 hours for each dose exceeded the normal threshold reported for healthy individuals[8,9] (**Figure 2**)

ADVERSE EVENTS

- A summary of TEAEs for each cohort is provided in **Table 2**
- Across all cohorts:
  - No serious or severe TEAEs were reported, and no patients discontinued due to a TEAE
  - Most TEAEs were mild in severity and resolved without medical intervention
    - Across all cohorts, 3 moderate TEAEs were reported; 1 moderate TEAE of nausea occurred at 8 mg in the NT1 cohort (resolved with food intake) and 1 moderate TEAE of pollakiuria occurred at 25 mg in each of the NT2 and IH cohorts (resolved in 2 to 3 days)
  - No clinically meaningful changes from baseline were identified in laboratory values
  - No cardiovascular safety signals were identified in vital signs or electrocardiograms

FIGURE 2: Mean Sleep Latency on the MWT Over 8 Hours



	NT1			NT2			IH		
	PBO	1 mg	3 mg	8 mg	PBO	5 mg	12 mg	25 mg	PBO	5 mg	12 mg	25 mg
LSM	-1.4	17.0	21.2	32.6	0.1	11.7	18.6	21.0	-1.7	6.4	9.3	16.0
95% CI of LSM	-6.9 to 4.0	11.8-22.1	16.1-26.2	27.6-37.5	-7.2 to 7.4	4.4-19.0	11.3-25.9	13.7-28.3	-8.0 to 4.6	0.1-12.6	3.1-15.6	9.7-22.2
LSM difference vs PBO		18.4	22.6	34.0		11.6	18.6	21.0		8.1	11.1	17.7
95% CI of LSM difference		11.0-25.8	15.6-29.6	26.7-41.2		2.2-21.0	9.2-27.9	11.6-30.3		0.1-16.1	3.0-19.1	9.7-25.7
***P* value**		**< 0.001**	**< 0.001**	**< 0.0001**		**< 0.05**	**< 0.001**	**< 0.001**		**< 0.05**	**< 0.01**	**< 0.001**

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 ~9 AM.
LSM (95% CI), LSM difference vs PBO (95% CI), and *P* values are based on a mixed effect model of repeated measures with the mean sleep latency change from baseline as the dependent variable, and dose level and period as fixed factors; mean sleep latency on Day -1 was included as the baseline covariate.
IH = idiopathic hypersomnia; LSM = least squares mean; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; PBO = placebo.

TABLE 2: Treatment-Emergent Adverse Events, Number of Patients (%)

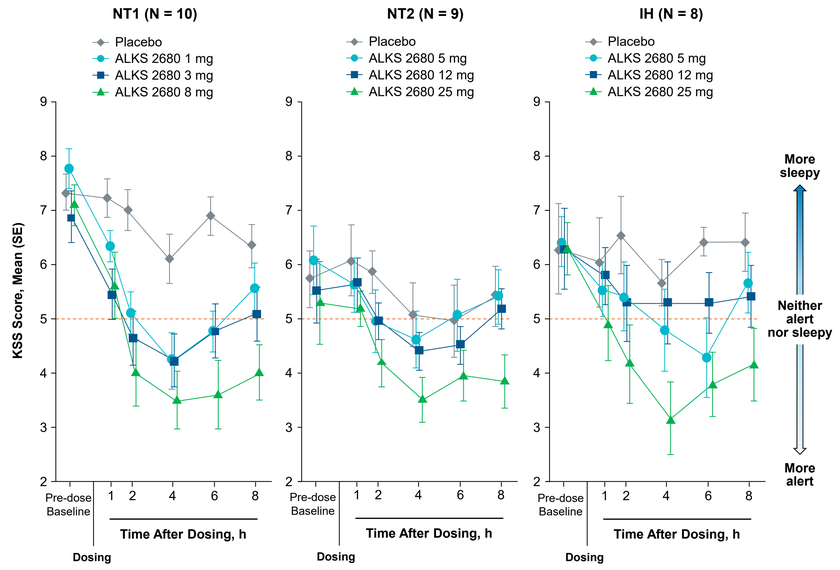
	NT1					NT2					IH				
		ALKS 2680					ALKS 2680					ALKS 2680			
	PBO (N = 9)	1 mg (N = 9)	3 mg (N = 9)	8 mg (N = 10)	Total ALKS 2680 (N = 10)	PBO (N = 9)	5 mg (N = 9)	12 mg (N = 9)	25 mg (N = 9)	Total ALKS 2680 (N = 9)	PBO (N = 8)	5 mg (N = 8)	12 mg (N = 8)	25 mg (N = 8)	Total ALKS 2680 (N = 8)
Any TEAE	4 (44.4)	6 (66.7)	5 (55.6)	9 (90.0)	9 (90.0)	2 (22.2)	3 (33.3)	4 (44.4)	7 (77.8)	7 (77.8)	4 (50.0)	6 (75.0)	5 (62.5)	7 (87.5)	8 (100)
Any SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TEAEs leading to study drug discontinuation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TEAEs related to study drug[a]	1 (11.1)	5 (55.6)	3 (33.3)	9 (90.0)	9 (90.0)	2 (22.2)	1 (11.1)	1 (11.1)	6 (66.7)	6 (66.7)	3 (37.5)	2 (25.0)	3 (37.5)	7 (87.5)	8 (100)
TEAEs related to study drug occurring in >1 patient per cohort[a]															
Insomnia[b]	0	0	1 (11.1)	6 (60.0)	6 (60.0)	1 (11.1)	1 (11.1)	0	2 (22.2)	3 (33.3)	0	1 (12.5)	1 (12.5)	3 (37.5)	4 (50.0)
Pollakiuria	0	0	2 (22.2)	4 (40.0)	4 (40.0)	0	0	1 (11.1)	3 (33.3)	3 (33.3)	1 (12.5)	2 (25.0)	2 (25.0)	4 (50.0)	5 (62.5)
Dizziness[c]	0	1 (11.1)	0	2 (20.0)	2 (20.0)	0	0	0	3 (33.3)	3 (33.3)	0	0	0	2 (25.0)	2 (25.0)
Salivary hypersecretion	1 (11.1)	1 (11.1)	1 (11.1)	3 (30.0)	3 (30.0)	0	0	0	0	0	0	0	0	0	0
Decreased appetite	0	1 (11.1)	0	1 (10.0)	2 (20.0)	0	0	0	0	0	0	0	0	0	0
Nausea	0	2 (22.2)	0	2 (20.0)	2 (20.0)	0	0	0	0	0	0	0	0	0	0

[a]If a patient experienced >1 AE in a category, the patient was counted only once in that category. If a patient experienced the same AE at multiple dose levels, the patient was counted once per dose level and once in total. The relationship between study drug and AEs was determined by the investigator.
[b]Insomnia includes the preferred terms of insomnia, initial insomnia, and middle insomnia (difficulty maintaining sleep).
[c]Dizziness includes the preferred terms of dizziness and dizziness postural.
AE = adverse event; IH = idiopathic hypersomnia; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; PBO = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

SELF-REPORTED ALERTNESS BY KSS SCORE OVER TIME

- Across all cohorts, 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 improvements seen with the highest respective doses for each cohort (**Figure 3**)

FIGURE 3: Subjective Alertness Assessed by KSS by Time Point



KSS full range is 1-9. Baseline denotes 1 hour pre-dose; dosing occurred at ~9 AM local time.
IH = idiopathic hypersomnia; KSS = Karolinska Sleepiness Scale; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

CONCLUSIONS

- In patients with NT1, NT2, or IH, treatment with ALKS 2680:
  - Was generally well tolerated at all doses tested, with all TEAEs mild or moderate in severity
  - Demonstrated statistically significant, clinically meaningful improvements in mean sleep latency at all doses
  - Demonstrated observed mean sleep latencies over 8 hours for each dose that exceeded the normal threshold reported for healthy individuals[8,9]
  - Showed clinically meaningful, dose-dependent improvements in self-reported alertness
- In this phase 1b study, ALKS 2680 is the first oral orexin 2 receptor agonist to have demonstrated efficacy across NT1, NT2, and IH
- Phase 2 evaluation of ALKS 2680 is ongoing in NT1 (Vibrance-1; NCT06358950), NT2 (Vibrance-2; NCT06555783), and IH (Vibrance-3; NCT06843590)

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