Preliminary Results from a Phase 1 Study of ALKS 2680, an Orexin 2 Receptor Agonist, in Healthy Participants and Patients with Narcolepsy or Idiopathic Hypersomnia

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World Sleep Congress | October 23, 2023

Financial Relationship Disclosure

Ineligible companies are those whose primary business is producing, marketing, selling, re-selling, or distributing health care products used by, or on patients.

☐ **No**, I HAVE NOT had a financial relationship with an ineligible company in the past 24 months.
■ **Yes**, I HAVE had a financial relationship with an ineligible company in the past 24 months.

Relationship type	**Name of company**
Institutional funding	Alkermes (B. Yee, R. Grunstein, C. Argent); Lilly (B. Yee, R. Grunstein); Takeda (B. Yee, R. Grunstein); Vanda (B. Yee, R. Grunstein)
Employment	Alkermes (C. Hopkinson, J. Ramos, I. Landry, S. Yagoda, B. Rege)
Speaker fees	Eisai (R. Grunstein); GlaxoSmithKline (B. Yee); SomnoMed (B. Yee, R. Grunstein); TEVA (B. Yee)
Advisory Board	Apnimed (R. Grunstein); Lilly (R. Grunstein)

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

- ALKS 2680 is a highly potent, orally bioavailable, selective OX2R agonist
  - ≥10 fold more potent than orexin A[a]
  - >5,000-fold selectivity relative to OX1R[a]
- Designed to address underlying pathology of narcolepsy and achieve:
  - Improved wakefulness duration and quality, with a PK/PD profile that mirrors natural sleep/wake cycle
  - Cataplexy control
  - Low therapeutic dose with once-daily oral dosing
  - Acceptable safety profile with wide therapeutic window
- ALKS 2680 demonstrated dose-dependent improvements in wake duration and cataplexy control in a mouse model of narcolepsy[b]
- Initial data from the ongoing Phase 1 study, which includes innovative translational approaches, has shown:
  - ALKS 2680 is generally well tolerated
  - Proof of concept in patients with narcolepsy type 1

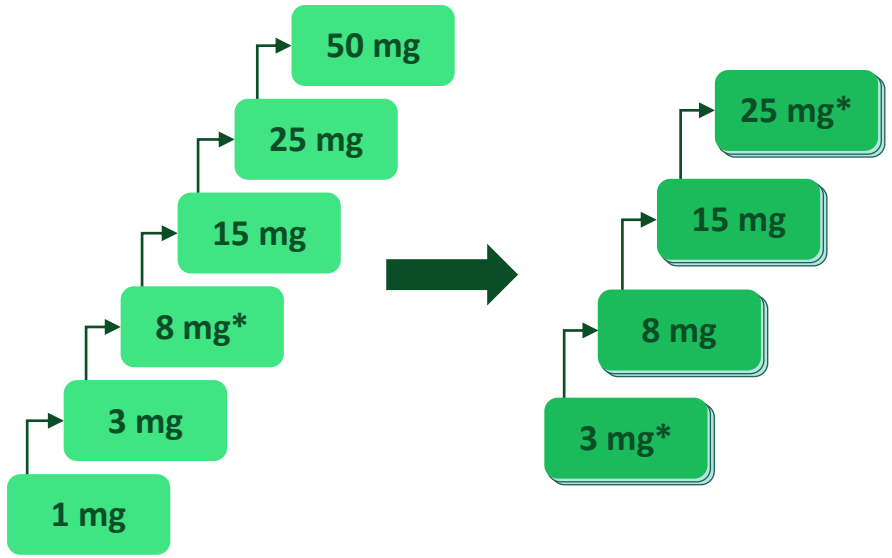
[a]Data from preclinical studies using CHO cells. [b]Orexin DTA mice

CHO: Chinese Hamster Ovary; DTA: diphtheria toxin subunit A; OX1R: orexin receptor type 1; OX2R: orexin receptor type 2; PD: pharmacodynamic; PK: pharmacokinetic

Ongoing Randomized, Double-Blind, Placebo-Controlled First-in-Human Study of ALKS 2680

Healthy Volunteers

Double-Blind Placebo-Controlled Treatment



Single Ascending Dose (SAD)

Multiple Ascending Dose (MAD)[a]

- 6 active and 2 placebo healthy volunteers in each dose cohort

Narcolepsy Type 1 (NT1) Patients

Screening & Washout

Double-Blind Placebo-Controlled Treatment

PBO	8 mg	3 mg	1 mg
1 mg	PBO	8 mg	3 mg
3 mg	1 mg	PBO	8 mg
8 mg	3 mg	1 mg	PBO

→ = 48-hour washout between doses

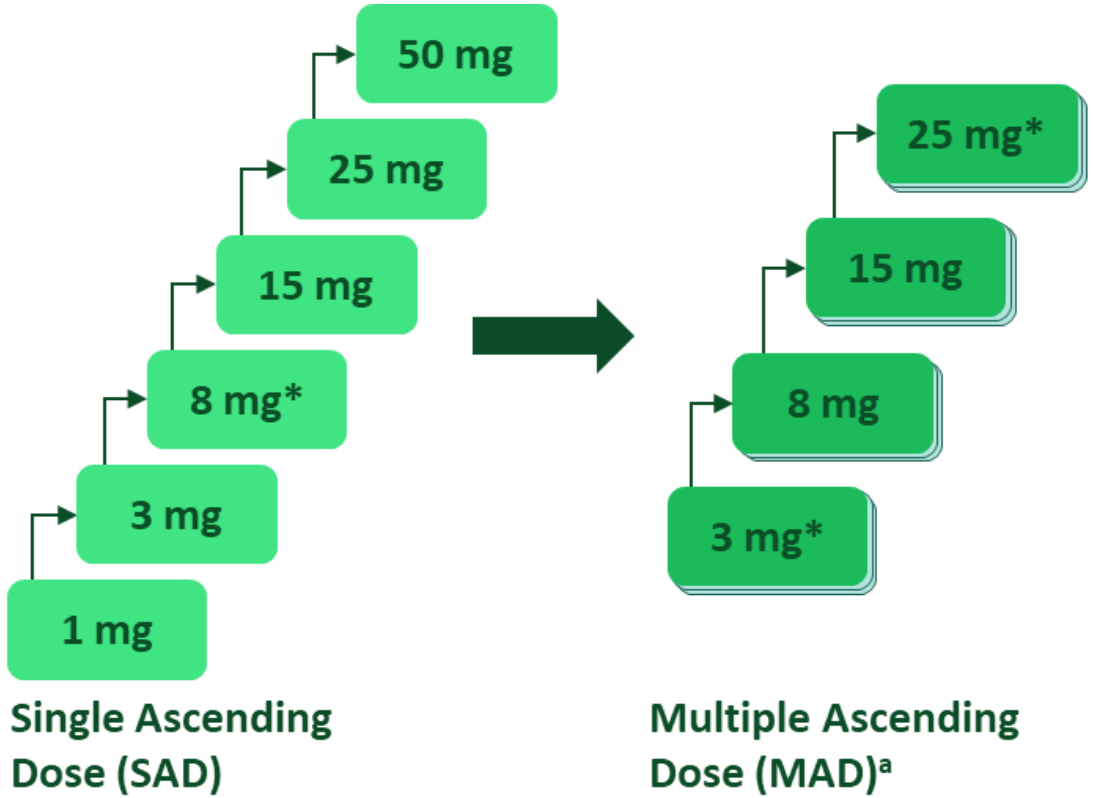
- 1:1:1:1 randomization in a 4-way crossover design
- NT2 and IH patient cohorts are currently being evaluated at higher doses

***Denotes dynamic decision points for triggering subsequent cohorts**
[a]In MAD, participants were dosed for 10 days once daily

IH: idiopathic hypersomnia; NT2: narcolepsy type 2; PBO: placebo

Ongoing Randomized, Double-Blind, Placebo-Controlled First-in-Human Study of ALKS 2680: SAD and MAD

- Each dose cohort in both SAD and MAD included 8 new participants
  - 6 on ALKS 2680, 2 on placebo
- Objectives:
  - Safety and tolerability
  - Pharmacokinetics (PK) and pharmacodynamics (PD)



*Denotes dynamic decision points for triggering subsequent cohorts
[a]In MAD, participants were dosed for 10 days once daily

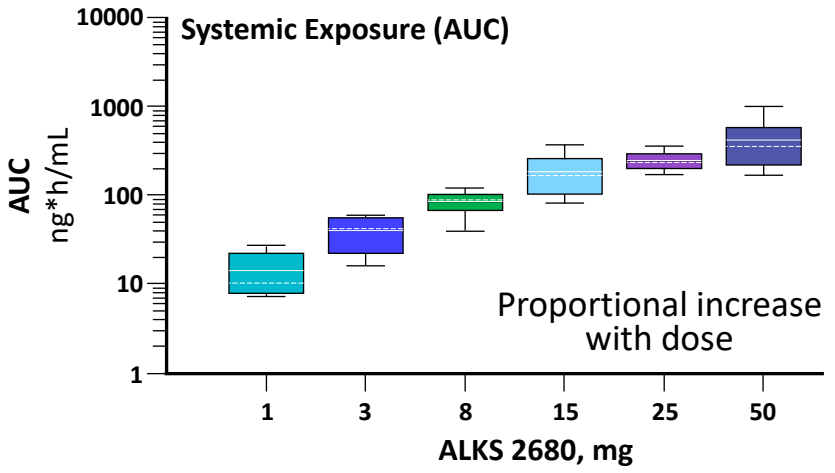
ALKS 2680 Was Generally Well Tolerated in Healthy Volunteers in Both SAD and MAD

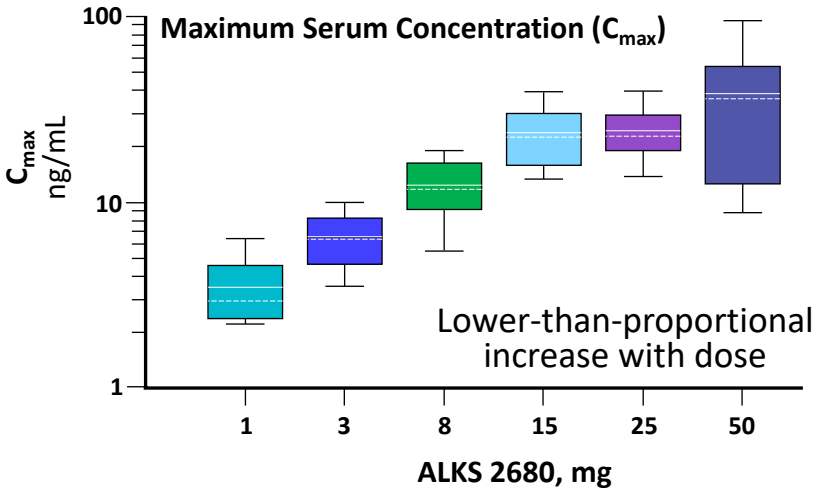
- Maximum tolerated dose not reached
- Most AEs were mild and observed at doses ≥15 mg (SAD) and ≥8 mg (MAD)
  - No severe AEs or serious adverse events (SAEs) were reported
  - Most AEs were transient and resolved without intervention or treatment interruption
  - AEs observed in >1 participant (>5%) and deemed related to study drug were:
    - SAD: dizziness, pollakiuria, nausea, and blurred vision
    - MAD: insomnia, dizziness, pollakiuria, and visual disturbance (described as blurred or distorted vision, increased light sensitivity)
- No safety signal identified in vital signs, laboratory parameters, or ECGs
- One participant in MAD discontinued after taking a single 25 mg dose due to transient, non-serious, non-severe AEs that resolved without treatment

AE: adverse event; ECG: electrocardiogram; MAD: multiple ascending dose; SAD: single ascending dose

ALKS 2680 Achieved Desired Pharmacokinetic Profile With Once-Daily Dosing

- Overall PK profile supports once-daily dosing
  - Mimics natural sleep/wake cycle
  - Half life = 8-10 hours
- Wide safety margin
  - ~100-fold safety multiples for planned therapeutic doses relative to toxicology studies[a]
- 2 metabolites measured
  - Consistent with preclinical studies
  - Neither contribute to pharmacologic activity
  - No reactive metabolites have been identified



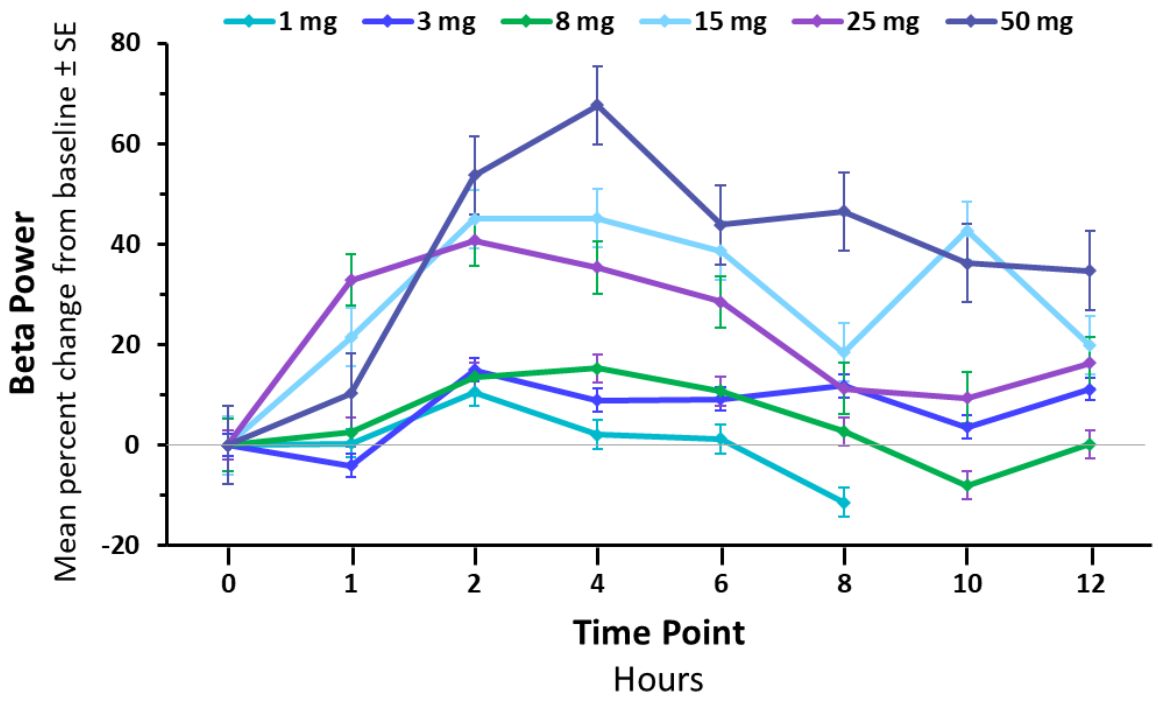


[a]Toxicology studies in mice up to 28 days of dosing completed
AUC: area under the curve; PK: pharmacokinetics

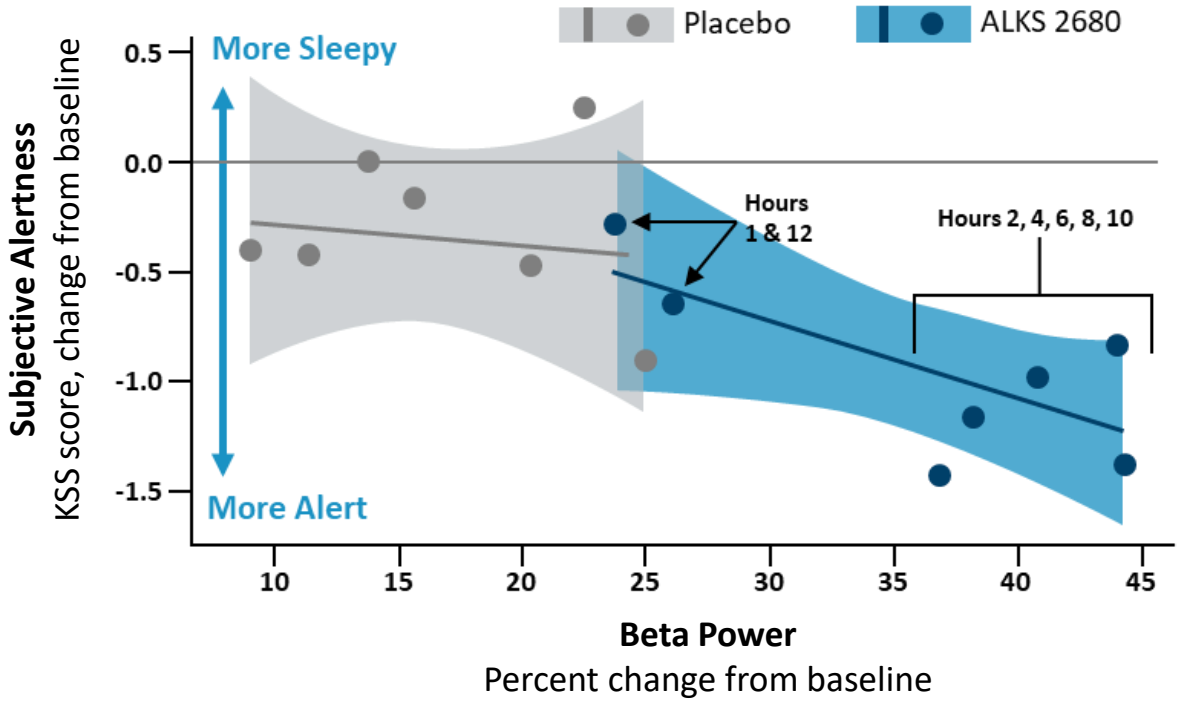
ALKS 2680 Exhibited CNS Activity in Non-Sleep Deprived Healthy Volunteers

Dose-Dependent Increase in Frontal Cortex Beta Power

Placebo-corrected percent change from pretreatment baseline



Correlation Between Beta Power (Objective Measure) and Karolinska Sleepiness Scale (Subjective Measure)

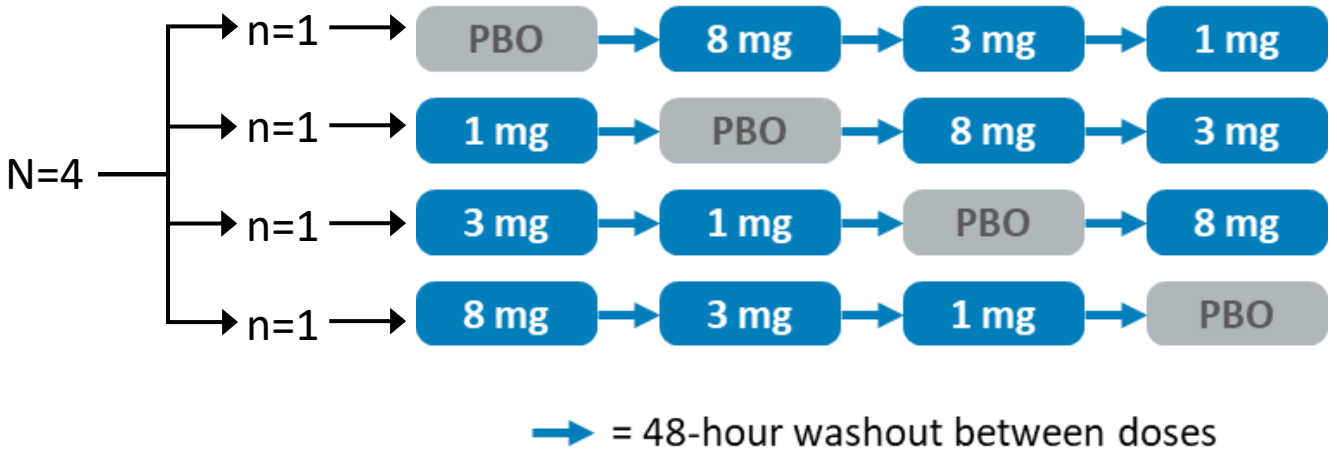


CNS: central nervous system; KSS: Karolinska Sleepiness Scale

Shaded areas indicate 95% confidence intervals

Ongoing Randomized, Double-Blind, Placebo-Controlled First-in-Human Study of ALKS 2680 in Patients With NT1

- 1:1:1:1 randomization in a 4-way cross-over design
- Up to 8 patients per cohort
  - First 4 patients in the NT1 cohort completed
- Objectives:
  - Safety and tolerability
  - Sleep latency (MWT) at each cross-over



NT2 and IH patient cohorts are currently being evaluated at higher doses

IH: idiopathic hypersomnia; NT1: narcolepsy type 1; NT2: narcolepsy type 2; PBO: placebo; MWT: Maintenance of Wakefulness Test

Demographics and Baseline Characteristics

Demographic Characteristic	Total (N=4)
Age, years, mean (SD)	23.5 (6.40)
Female, n (%)	1 (25)
White Race, n (%)	4 (100)
Body Mass Index, kg/m^2, mean (SD)	30.5 (5.45)

Baseline Disease Severity	Total (N=4)
Narcolepsy Severity Scale, mean (SD) Severe 29-42, very severe 43-54	39.8 (3.50)
Epworth Sleepiness Scale, mean (SD) Score >10 suggests excessive daytime sleepiness	16.0 (2.83)
Weekly Cataplexy Rate, mean (SD)	9.0 (10.61)

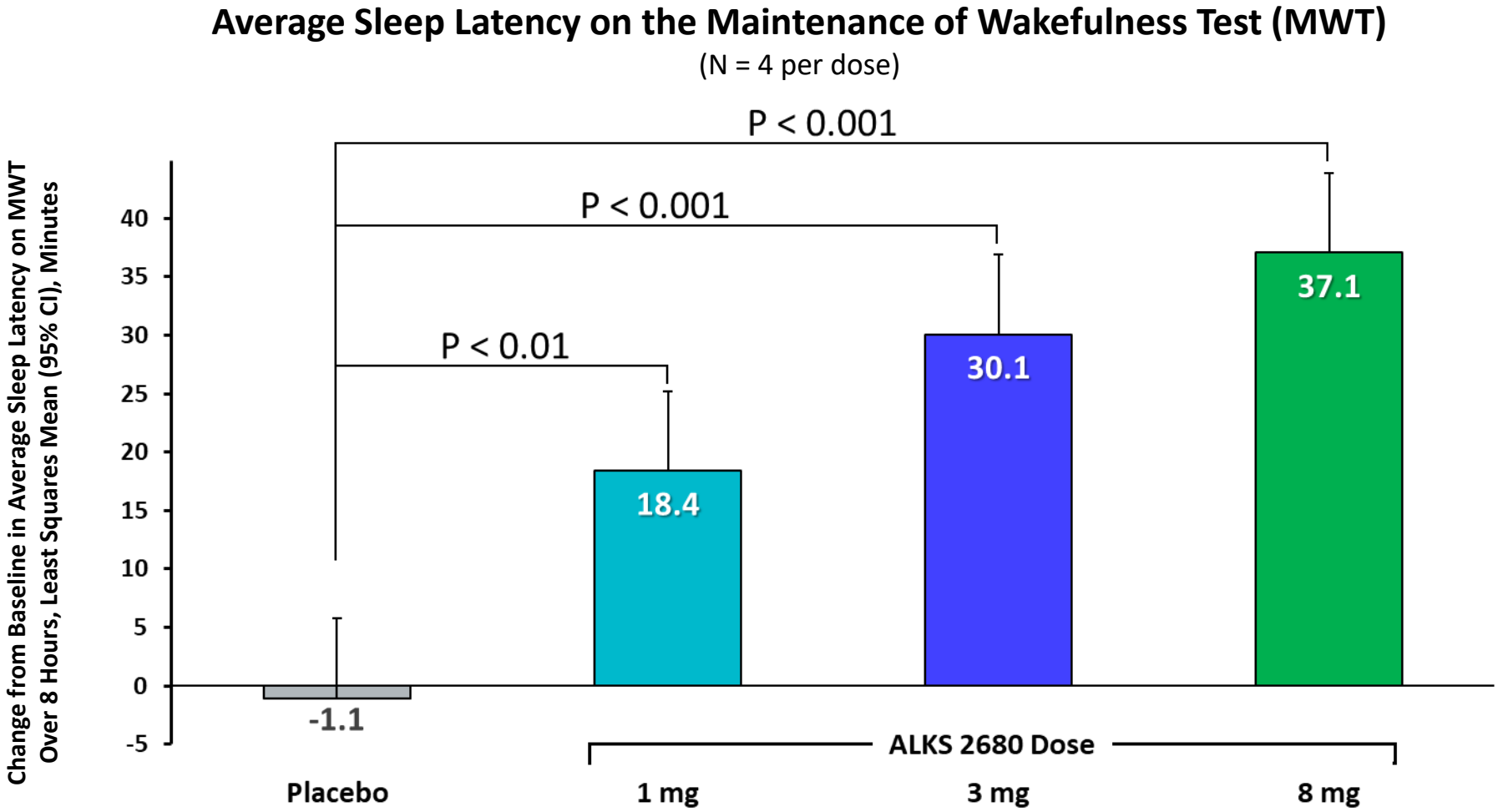
Single Doses of ALKS 2680 Were Generally Well Tolerated

	Placebo	ALKS 2680		
	n=4	1 mg n=4	3 mg n=4	8 mg n=4
Adverse events (AEs) reported as related to study drug, n (%)	0	0	0	4 (100)
Insomnia	0	0	0	3 (75)
Pollakiuria	0	0	0	2 (50)
Salivary hypersecretion	0	0	0	2 (50)
Blood pressure increased	0	0	0	1 (25)
Bruxism	0	0	0	1 (25)
Dizziness	0	0	0	1 (25)
Hyperhidrosis	0	0	0	1 (25)

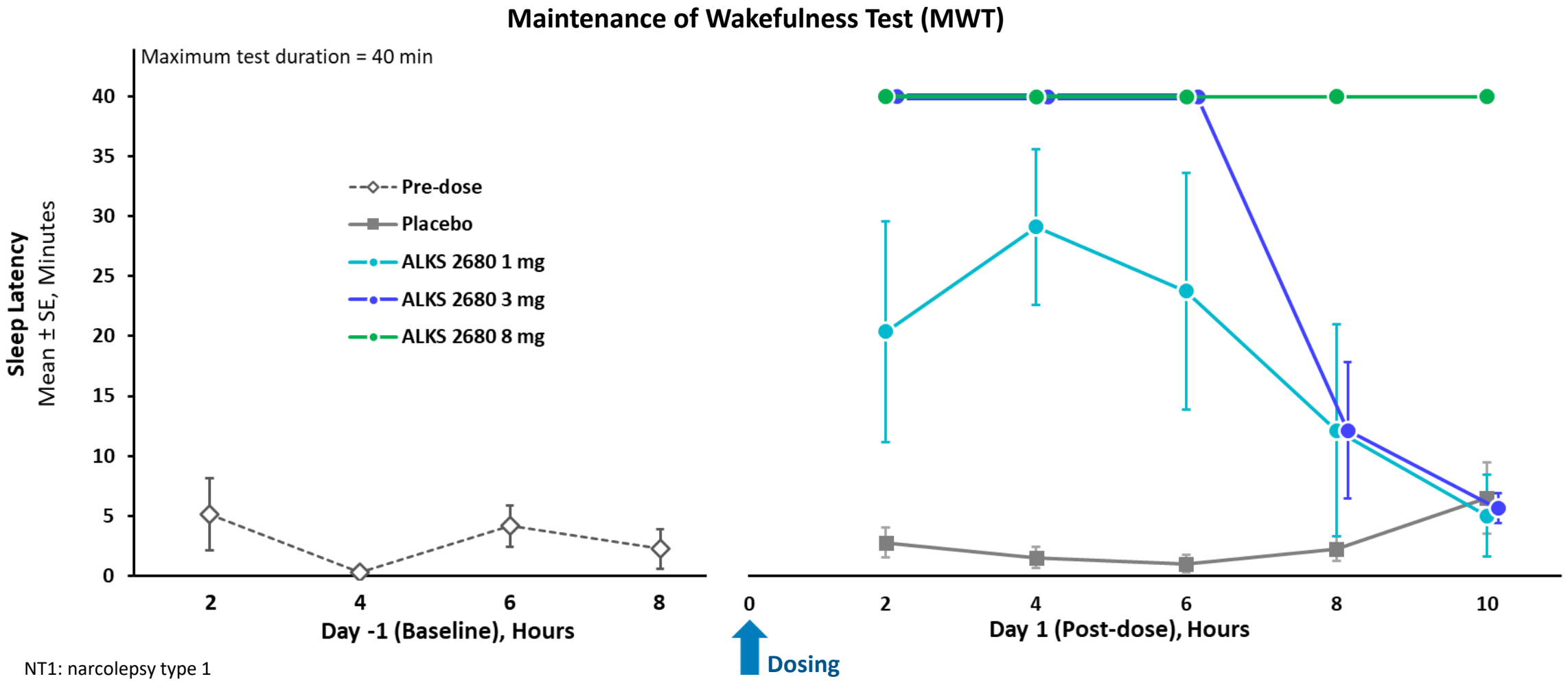
- All AEs were mild in severity; no serious AEs or AEs leading to discontinuation were reported
- No treatment-emergent, clinically meaningful changes in laboratory parameters or ECGs at any dose

AE: adverse event; ECG: electrocardiogram

ALKS 2680 Significantly Improved Sleep Latency With a Clear Dose Response



ALKS 2680 Single Dose Time Course Suggests a Therapeutic Dose Between 3 mg and 8 mg in NT1



NT1: narcolepsy type 1

Conclusions

Initial benefit/risk profile supports continued clinical evaluation of ALKS 2680

ALKS 2680 in Healthy Volunteers (N = 80)

- Generally well tolerated up to doses of 50 mg
- Increased objective and subjective measures of alertness
- PK/PD profile supports once-daily oral dosing

ALKS 2680 in NT1 Patients (N = 4)

- Generally well tolerated at all doses tested; drug-related adverse events only observed at highest dose (8 mg)
- Statistically significant, clinically meaningful, and durable improvement of sleep latency
- Profile supportive of once-daily administration
- Improvement in sleep latency observed at a low therapeutic dose targeted between 3 and 8 mg in narcolepsy type 1

Next Steps

- Additional data to be presented at upcoming conferences
- Phase 1b study ongoing in patients with narcolepsy and patients with idiopathic hypersomnia
- Phase 2 study planned for first half of 2024

Acknowledgments

- The authors would like to thank:
  - The volunteers and patients who are participating in this study and their families
  - The investigators and research staff
- This study is sponsored by Alkermes, Inc.