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

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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 stimulate the OX2R and address the underlying pathology of narcolepsy by achieving 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 low therapeutic dose that can be effective 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
  - The phase 1b study results are presented in Poster #423 at SLEEP 2024[3]

OBJECTIVES

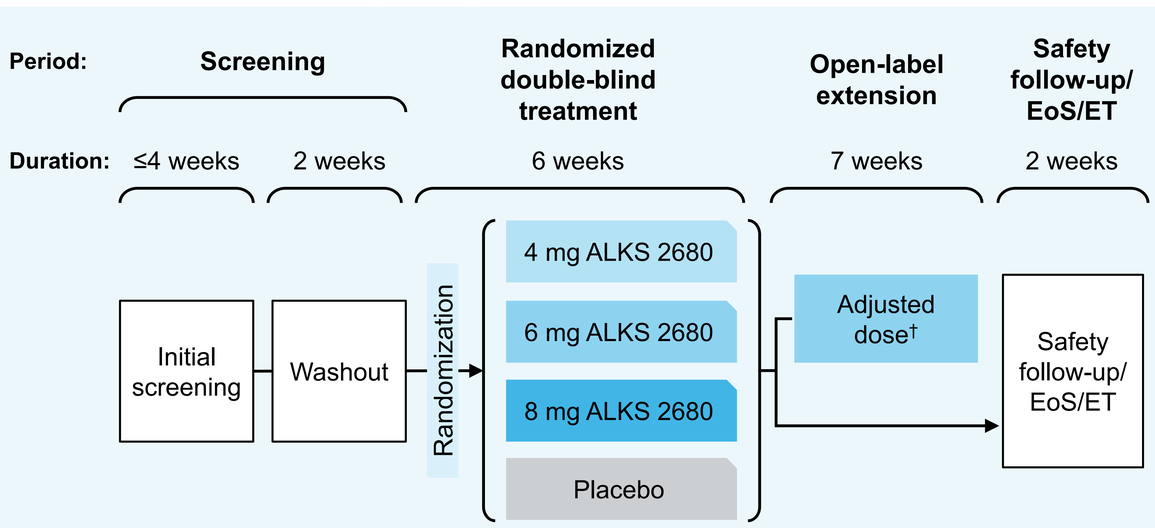
- The Vibrance-1 study (ClinicalTrials.gov identifier: NCT06358950) aims to assess the efficacy and safety of once-daily ALKS 2680 compared with placebo through 6 weeks of treatment in patients with NT1

METHODS

STUDY DESIGN

- Vibrance-1 is an ongoing, phase 2, placebo-controlled, parallel-group, dose-ranging study with a randomized 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*



*The study is being conducted in the United States, Australia, and Europe. †All patients will start the open-label extension period with 6 mg of ALKS 2680.
EoS = end of study; ET = early termination.

STUDY POPULATION

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

FIGURE 2: Key Inclusion and Exclusion Criteria

Inclusion Criteria[4]*

- Adults ≤70 years of age
- 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† and cataplexy‡
- Willing and able to discontinue any medications prescribed for the management of narcolepsy symptoms for at least 14 days

Exclusion Criteria[4]*

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

*Additional criteria apply. Eligibility will be determined on an individual basis by the study investigator. †Epworth Sleepiness Scale score >10 at Visit 1. ‡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 summarized in **Figure 3**

FIGURE 3: Study Endpoints

Primary Endpoint[4]

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

Secondary Endpoints[4]

- Change in Epworth Sleepiness Scale from baseline to Week 6 by dose level
- Mean weekly cataplexy rate as derived by patient cataplexy (measured in diary over Weeks 5 and 6 by dose level)
- Treatment-emergent adverse events by study period

Exploratory Endpoints

- Sleep stages as measured by EEG power spectra
- Patient-reported outcomes, including:
  - Karolinska Sleepiness Scale
  - Narcolepsy Severity Scale
  - Clinical Global Impressions Scale
  - Patient Global Impression of Severity

EEG = electroencephalogram.

SUMMARY

- Vibrance-1 is evaluating once-daily ALKS 2680 over six 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

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.** Grunstein R, et al. Poster at SLEEP 2024 Meeting; June 1-5, 2024; Houston, TX. **4.** Alkermes, Inc. A Study to Evaluate the Safety and Effectiveness of ALKS 2680 in Subjects With Narcolepsy Type 1 (Vibrance-1). NCT06358950. Accessed April 30, 2024. https://clinicaltrials.gov/study/NCT06358950. **5.** Ruoff C, Rye D. *Curr Med Res Opin.* 2016;32(10):1611-1622.

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