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

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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 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

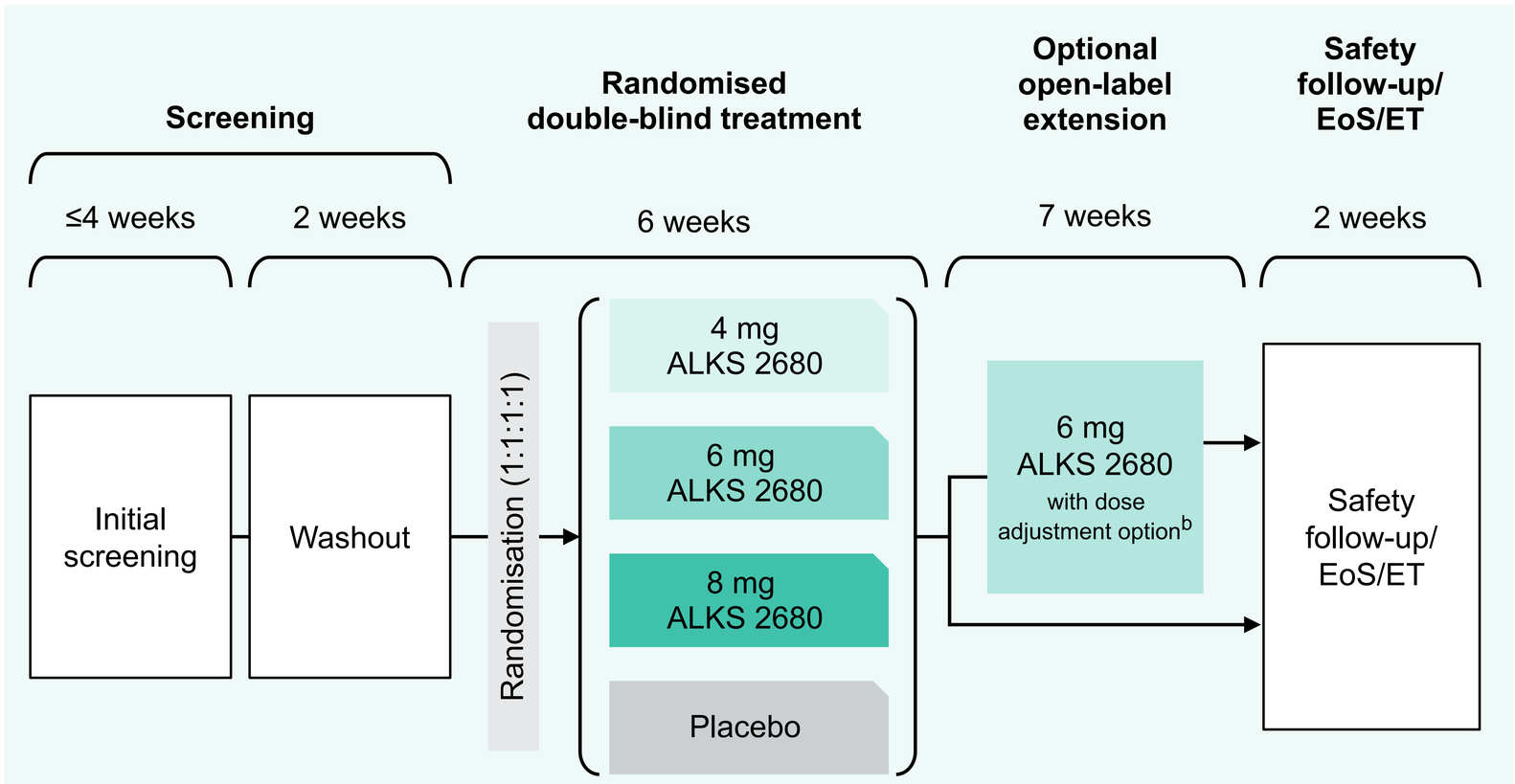
- The Vibrance-1 study (ClinicalTrials.gov identifier: NCT06358950) aims to assess the safety and efficacy of once-daily ALKS 2680 compared with placebo through 6 weeks of treatment in patients with NT1

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

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