Brilliance NT1: Study Design and Methods for Two Phase 3, Randomized, Double-Blind, Placebo-Controlled Studies Evaluating Alixorexton in Patients With Narcolepsy Type 1

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Introduction

- Narcolepsy type 1 (NT1) is a rare, chronic, neurological disorder characterized by excessive daytime sleepiness and cataplexy[1–3]
  - Additional key symptoms of NT1 include disrupted nighttime sleep, sleep paralysis, hypnagogic/hypnopompic hallucinations, cognitive impairment, and fatigue[1,3]
- The pathophysiology of NT1 involves loss of orexin neurons, which project to brain regions that affect wakefulness, arousal, and cognition[4]
- The orexin system initiates and regulates the cascade of neurologic interactions that stabilize the sleep/wake cycle and modulate diverse neuronal functions beyond wakefulness, such as fatigue, cognition, and mood[5–7]
- Alixorexton (ALKS 2680) is a highly potent, oral, and selective orexin 2 receptor (OX2R) agonist being developed for the treatment of narcolepsy and idiopathic hypersomnia[8]
- In the phase 2 Vibrance-1 study (NCT06358950) in participants with NT1, alixorexton:[9]
  - Provided statistically significant, clinically meaningful improvements from baseline compared with placebo in objective measures of wakefulness and participant-reported outcomes related to sleepiness at week 6 at all doses tested
  - Led to clinically meaningful improvement from baseline compared with placebo in cataplexy (statistically significant improvement at week 6 at the 6 mg dose). Improvements were maintained through the 7-week open-label extension (week 13)
  - Demonstrated statistically significant (unadjusted for multiplicity) and clinically meaningful improvements from baseline compared with placebo on established measures evaluating severity of participant-reported narcolepsy symptoms, cognitive impairment, fatigue, and quality of life
  - Was generally well tolerated
- Results from Vibrance-1 led to dose selection for two large, global, pivotal phase 3 studies of alixorexton in participants with NT1: Brilliance NT1 302 and 304

Objective

- The phase 3 Brilliance NT1 302 and 304 studies (NCT07455383, NCT07540897) aim to evaluate the efficacy, safety, and tolerability of once-daily and split-dosing regimens of oral alixorexton compared with placebo through 12 weeks of treatment in participants with NT1

Methods

Study design

- Brilliance NT1 302 and 304 are ongoing, phase 3, randomized, double-blind studies in participants with NT1
- Following a 2-week washout period from prior narcolepsy medications, participants will be randomly assigned to receive placebo or 1 of 2 regimens of alixorexton for 12 weeks, followed by 2 weeks of follow-up to monitor for treatment-emergent adverse events (**Figure 1**)

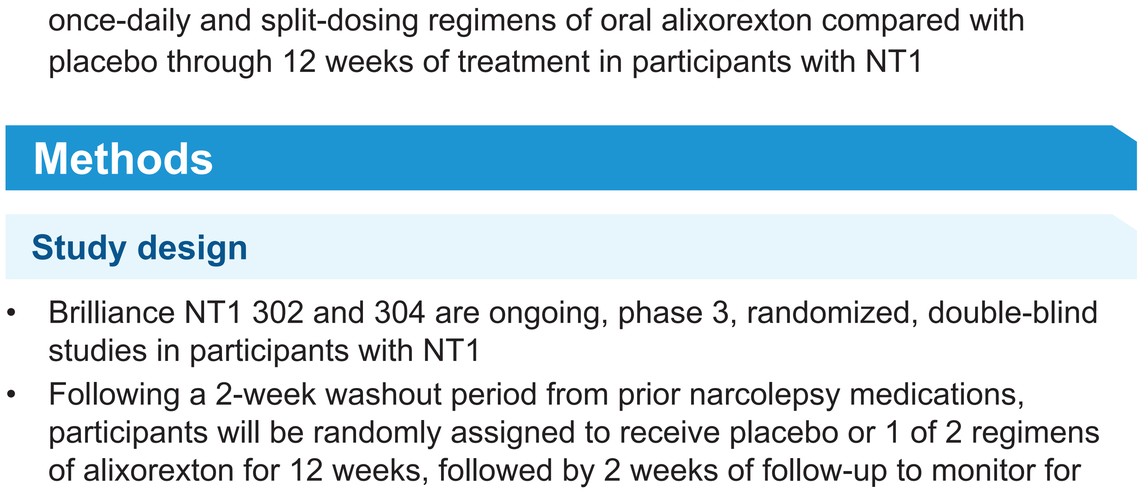
Study population

- Planned enrollment is approximately 150 participants with NT1 in each study
- Key inclusion and exclusion criteria are described in **Figure 2**

Study endpoints

- Primary and secondary endpoints are summarized in **Figure 3**

Figure 1. Study design for Brilliance NT1 302 and 304



NT1, narcolepsy type 1.

Methods (continued)

Figure 2. Key inclusion and exclusion criteria[a]

Inclusion criteria

- Participants with NT1 (ICSD-3-TR), confirmed by diagnostic evaluations (either PSG/MSLT or CSF hypocretin-1 level)
- Age 18 to ≤ 70 years

Exclusion criteria

- Has another comorbid sleep disorder or condition that may influence the sleep/wake cycle
- Has a history or presence of other clinically significant illness, disease, abnormality, or surgical procedure that might compromise safety, study assessment, or ability to complete the trial

[a]Additional criteria apply.

CSF, cerebrospinal fluid; ICSD-3-TR, International Classification of Sleep Disorders, Third Edition, Text Revision; MSLT, Multiple Sleep Latency Test; NT1, narcolepsy type 1; PSG, polysomnography.

Figure 3. Study endpoints

Primary endpoint

- Change in mean sleep latency on the Maintenance of Wakefulness Test from baseline to week 12 by dose level

Secondary endpoints

- Change in Epworth Sleepiness Scale from baseline to week 12 by dose level
- Weekly cataplexy rate at week 12 by dose level
- TEAEs and other safety parameters up to 14 weeks
- Change in outcomes for cognitive impairment and fatigue from baseline to week 12, including:
  - Patient Global Impression of Severity
  - British Columbia Cognitive Complaints Inventory
  - Psychomotor Vigilance Task
  - Patient-Reported Outcomes Measurement Information System® Item Bank v1.0 - Fatigue - Short Form 6a
  - Clinical Global Impression of Severity
  - Narcolepsy Severity Scale for Clinical Trials

TEAE, treatment-emergent adverse event.

Summary

- The phase 3 Brilliance NT1 302 and 304 studies will confirm the efficacy and safety profile of alixorexton in NT1 that was preliminarily established in the phase 2 Vibrance-1 study
- To learn about participation or participant referrals, please scan the QR code or visit brilliancestudies.com or clinicaltrials.gov/study/NCT07455383 and clinicaltrials.gov/study/NCT07540897

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