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 to 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**)

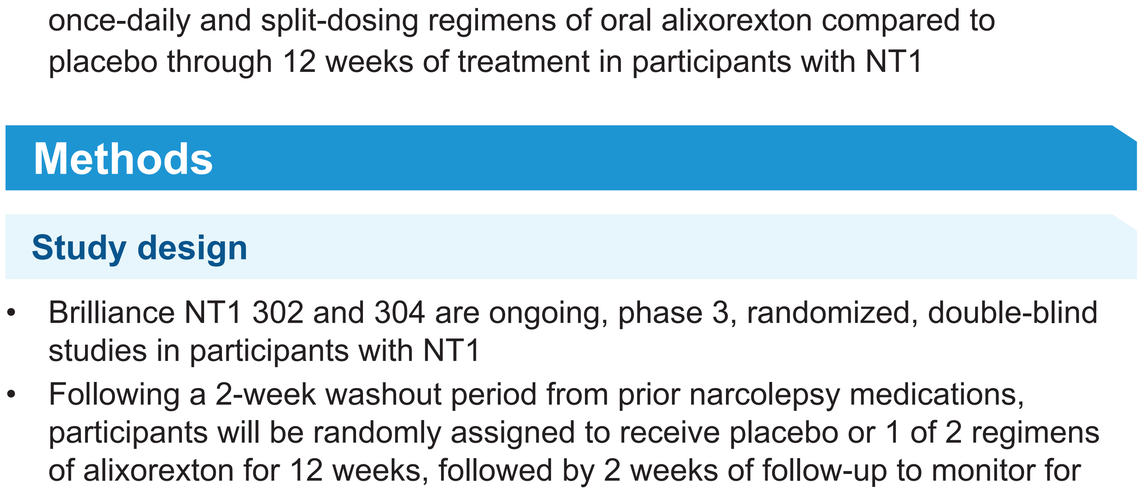
Study population

- 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

Acknowledgments

The authors would like to thank all participants and study staff in the Brilliance NT1 trials. These studies were funded by Alkermes, Inc. Medical writing support was provided by Caroline Leitschuh, PhD, of Oxford PharmaGenesis Inc., Wilmington, DE, USA, and was funded by Alkermes, Inc., Waltham, MA, USA.

Disclosures

GP received research funding from Bioprojet, Centessa, Idorsia, Jazz Pharmaceuticals, Orexia Therapeutics, and Takeda. **EM** received research funding from Avadel, Alkermes, Eisai, Jazz Pharmaceuticals, Takeda, and Vanda. **RKB** is a shareholder of Watermark Medical and Healthy Humming LLC. He serves on the Board of Directors for Watermark Medical, and has served as a consultant to Jazz Pharmaceuticals, Eisai, Harmony Biosciences, Takeda, Avadel, and Oventus. He has participated in industry-funded research for Avadel, Bayer, Bresotec, Alkermes, Harmony, Idorsia, Suven, Jazz Pharmaceuticals, Balance, Vanda, Merck, Eisai, Phillips, Fresca, Takeda, LivaNova, Roche, Sommetrics, NLS, Sanofi, and Apnimed. He has taken part in speakers bureaus for Jazz Pharmaceuticals, Eisai, Harmony, Axsome, and Idorsia. **RRG** received speaker fees from Eisai and SomnoMed; institutional funding from Alkermes, Lilly, Takeda, Novo Nordisk, and Vanda; participated on advisory boards for Apnimed and Lilly. **GJL** received consulting fees from Takeda, Bioprojet, Alkermes, and Daiichi Sankyo. **DTP** participated in advisory boards for Aditum Bio LLC, Alkermes, Centessa, Harmony Biosciences, Jazz Pharmaceuticals, Takeda, and Teva. **RdRV** participated in advisory boards for Alkermes, Takeda, and Bioprojet. **HC**, **JC**, **BR**, **CH**, **BK**, and **JH** are employees and shareholders of Alkermes. **YD** received institutional funding from Alkermes; participated on advisory boards for Avadel, Bioprojet, Centessa, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Pharmanovia, and Takeda.

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