Brilliance NT2: Study Design and Methods for a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Alixorexton in Patients With Narcolepsy Type 2

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Introduction

- 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[1–3]
  - The orexin 2 receptor (OX2R) is the main receptor mediating the wake-stabilizing effect[4]
- Sleep/wake stabilization is an unmet need in diseases associated with excessive daytime sleepiness, such as narcolepsy type 2 (NT2)[5–9]
- Individuals with NT2 retain underlying orexin tone and demonstrate a large degree of symptom heterogeneity[6,7,9]
- OX2R agonism offers an opportunity to modulate an intact orexin system in NT2 to improve excessive daytime sleepiness and potentially address broader symptoms[3,10,11]
- Alixorexton (ALKS 2680) is a highly potent, oral, selective OX2R agonist being developed for the treatment of narcolepsy and idiopathic hypersomnia[10]
- In the phase 2 Vibrance-2 study in participants with NT2, alixorexton:
  - Demonstrated clinically meaningful improvements from baseline compared with placebo in daytime sleepiness on the Epworth Sleepiness Scale, with statistically significant improvement at week 8 at the 18 mg dose; improvements were maintained through the open-label extension (week 13)
  - Led to clinically meaningful improvements from baseline compared with placebo in wakefulness on the Maintenance of Wakefulness Test, with statistically significant improvements at week 8 at the 14 mg and 18 mg doses
  - Led to clinically meaningful improvements from baseline compared with placebo in cognition and fatigue at week 8 that were maintained through week 13
  - Most treatment-emergent adverse events (TEAEs) were mild to moderate in severity; no serious TEAEs or safety signals in hepatic or renal parameters, vital signs, or electrocardiograms were observed. There were no treatment-related clinically meaningful changes on ophthalmic exams
- These results led to dose selection for this large, global, pivotal phase 3 study of alixorexton in individuals with NT2, Brilliance NT2 303

Objective

- The Brilliance NT2 303 study (NCT07502443) aims to assess the efficacy and safety of once-daily and split-dosing regimens of oral alixorexton compared with placebo in participants with NT2

Methods

Study design

- Brilliance NT2 303 is an ongoing, phase 3, randomized, double-blind, placebo-controlled study in participants with NT2 (**Figure 1**)
- Following a 2-week washout period from prior narcolepsy medications, participants will be randomly assigned to receive placebo or 1 of 3 regimens of alixorexton for 12 weeks, followed by 2 weeks of follow-up to monitor for TEAEs

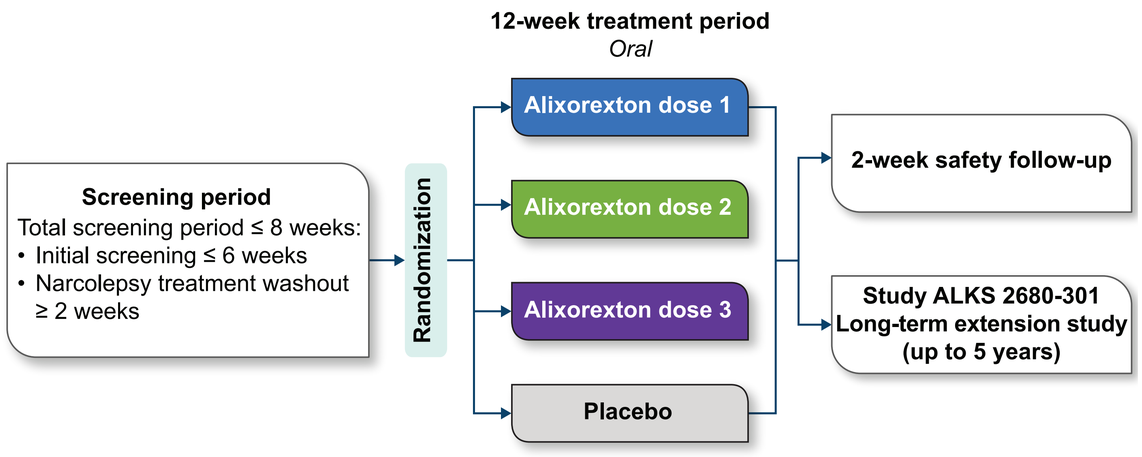
Study population

- Planned enrollment for Brilliance NT2 303 is approximately 176 participants
- Key inclusion and exclusion criteria are described in **Figure 2**

Study endpoints

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

Figure 1. Brilliance NT2 303 study design



NT2, narcolepsy type 2.

Methods (continued)

Figure 2. Key inclusion and exclusion criteria[a]

Inclusion criteria

- Participants with NT2 (ICSD-3-TR), confirmed by diagnostic evaluations (either PSG or MSLT)
- 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.

ICSD-3-TR, International Classification of Sleep Disorders, Third Edition, Text Revision; MSLT, Multiple Sleep Latency Test; NT2, narcolepsy type 2; 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

Incidence of TEAEs, laboratory assessments, ECG, and C-SSRS

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

C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; TEAE, treatment-emergent adverse event.

Summary

- The phase 3 Brilliance NT2 303 study will confirm the efficacy and safety profile of alixorexton in NT2 that was preliminarily established in the phase 2 Vibrance-2 study
- To learn about participation or participant referrals, please scan the QR code or visit brilliancestudies.com or clinicaltrials.gov/study/NCT07502443

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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. **EM** received research funding from Avadel, Alkermes, Eisai, Jazz Pharmaceuticals, Takeda Pharmaceuticals, and Vanda. **YD** received institutional funding from Alkermes; participated on advisory boards for Avadel, Bioprojet, Centessa, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Pharmanovia, and Takeda. **RRG** received funding from Apnimed and Eli Lilly & Company, and his department has received funding from Alkermes, Eisai, Eli Lilly & Company, Takeda, and Vanda. **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. **FM**, **JC**, **BR**, **CH**, **BK**, and **JH** are employees and shareholders of Alkermes. **GP** received research funding from Bioprojet, Centessa, Idorsia, Jazz Pharmaceuticals, Orexia Therapeutics, and Takeda.

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