Long-Term Safety, Tolerability, and Durability of Alixorexton: Interim Results From a Phase 2/3 Extension Study in Narcolepsy

Yves Dauvilliers, Emmanuel Mignot, Richard K. Bogan, Brendon J. Yee, Rafael del Río Villegas, Gert J. Lammers, Chad Ruoff, David T. Plante, Feng Miao, Derek Matthies, Sarah A. Chau, Michael J. Doane, Craig Hopkinson, Bhaskar Rege, Julie Himes, Giuseppe Plazzi

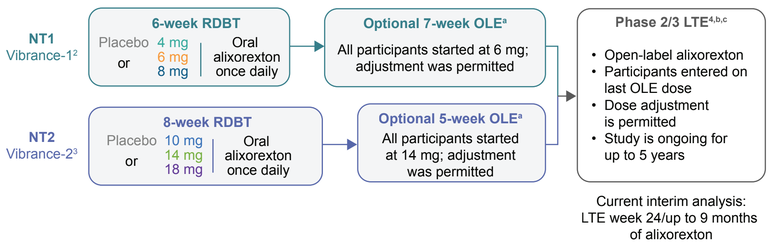
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Introduction

- This ongoing, open-label, phase 2/3 long-term extension (LTE) study is evaluating the long-term safety and efficacy of alixorexton, a highly potent, oral, selective orexin 2 receptor agonist, in rollover participants with narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia for up to 5 years[1,2]
  - Here, we present interim safety and efficacy results from participants with NT1 and NT2, with efficacy results representing up to 9 months of treatment with alixorexton

Study design

Figure 1. Phase 2 and long-term clinical evaluation of alixorexton in NT1 and NT2



[a]Dose adjustment was permitted for the first 2 weeks of the OLE. [b]Current analysis includes participants from Vibrance-1 and Vibrance-2. Participants from the Vibrance-3 phase 2 study in idiopathic hypersomnia and phase 3 Brilliance studies in NT1 and NT2 are also eligible to join the LTE upon completion of their respective studies. [c]Dose adjustment was permitted during the first 4 weeks of the LTE; participants may have received more than one dose level.
Data cutoff: May 12, 2026.

TEAEs during the LTE period (primary endpoint)

Table 1. Summary of TEAEs during the LTE period in participants with NT1

	Alixorexton once daily (by most frequent dose)			
n (%)	4 mg (n = 4)	6 mg (n = 24)	8 mg (n = 50)	Total (N = 78)
Any TEAE[a]	4 (100)	20 (83)	38 (76)	62 (79)
Mild	3 (75)	13 (54)	24 (48)	40 (51)
Moderate	1 (25)	6 (25)	13 (26)	20 (26)
Severe	0	1 (4)	1 (2)	2 (3)
TEAEs in ≥ 10% of all participants				
Headache	1 (25)	8 (33)	3 (6)	12 (15)
Micturition urgency	1 (25)	4 (17)	4 (8)	9 (12)
Pollakiuria	1 (25)	4 (17)	4 (8)	9 (12)
Nasopharyngitis	1 (25)	2 (8)	5 (10)	8 (10)
Drug-related TEAEs	2 (50)	10 (42)	16 (32)	28 (36)
TEAEs leading to study drug discontinuation	1 (25)	0	1 (2)	2 (3)

Table 2. Summary of TEAEs during the LTE period in participants with NT2

	Alixorexton once daily (by most frequent dose)			
n (%)	10 mg (n = 3)	14 mg (n = 25)	18 mg (n = 35)	Total (N = 63)
Any TEAE[a]	2 (67)	24 (96)	30 (86)	56 (89)
Mild	2 (67)	13 (52)	16 (46)	31 (49)
Moderate	0	9 (36)	14 (40)	23 (37)
Severe	0	2 (8)	0	2 (3)
TEAEs in ≥ 10% of all participants				
Insomnia	1 (33)	6 (24)	2 (6)	9 (14)
Headache	0	2 (8)	6 (17)	8 (13)
Pollakiuria	0	6 (24)	1 (3)	7 (11)
Upper respiratory tract infection	1 (33)	2 (8)	4 (11)	7 (11)
Drug-related TEAEs	0	16 (64)	10 (29)	26 (41)
TEAEs leading to study drug discontinuation	0	1 (4)	1 (3)	2 (3)

[a]Values denote the number of participants experiencing a TEAE that started during the LTE up to the May 12, 2026 data cutoff. If a participant had multiple TEAEs, the highest severity was counted. TEAE data from Vibrance-1 and Vibrance-2 are presented separately in an oral presentation at Sleep Europe 2026.

Results

Figure 2. Alixorexton once-daily treatment effects for up to 9 months of continuous treatment (through LTE week 24) in participants with NT1: A, MWT (secondary); B, ESS (secondary); C, WCR (secondary); D, BC-CCI (exploratory); E, PROMIS-Fatigue (exploratory)

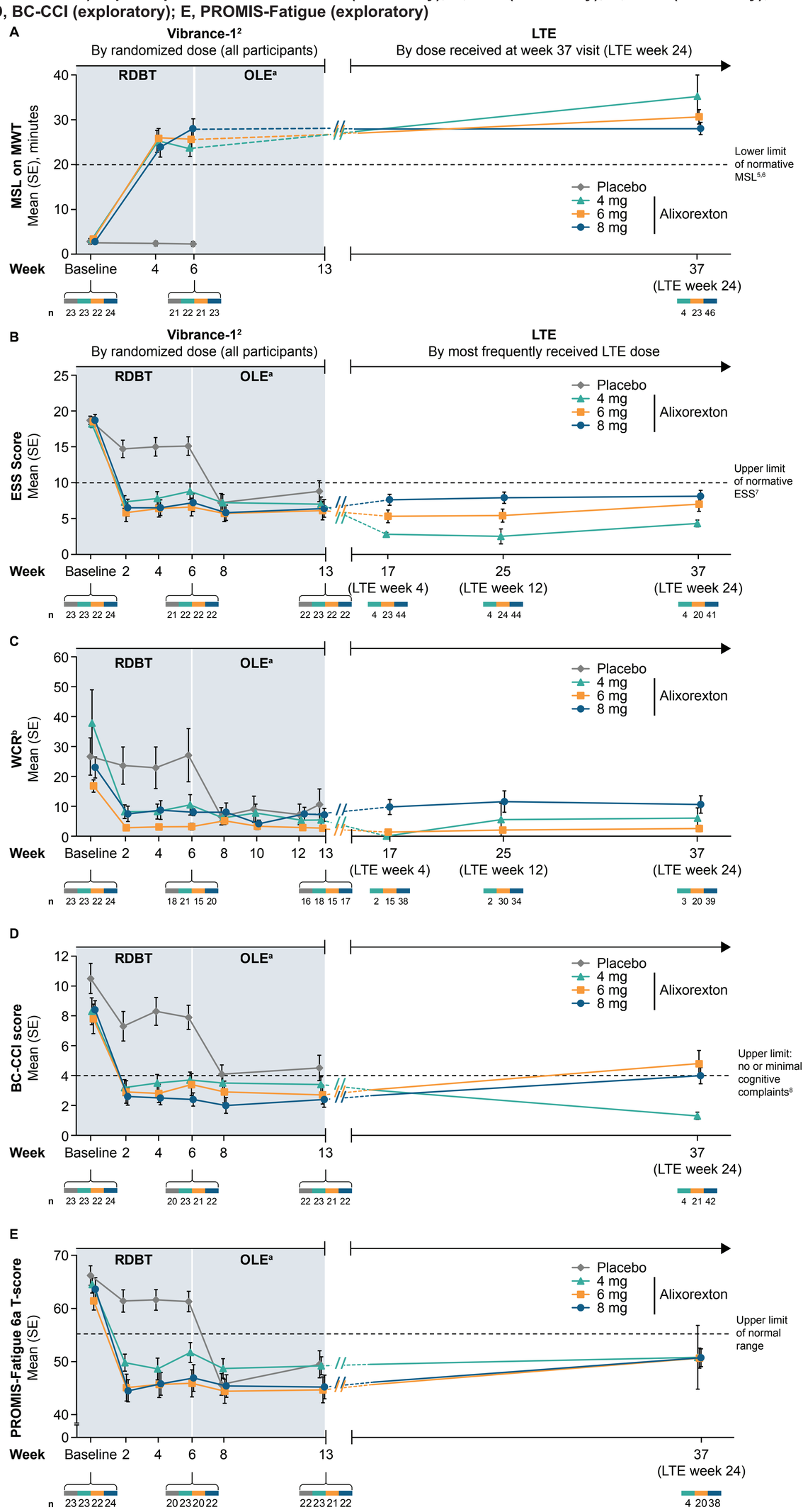
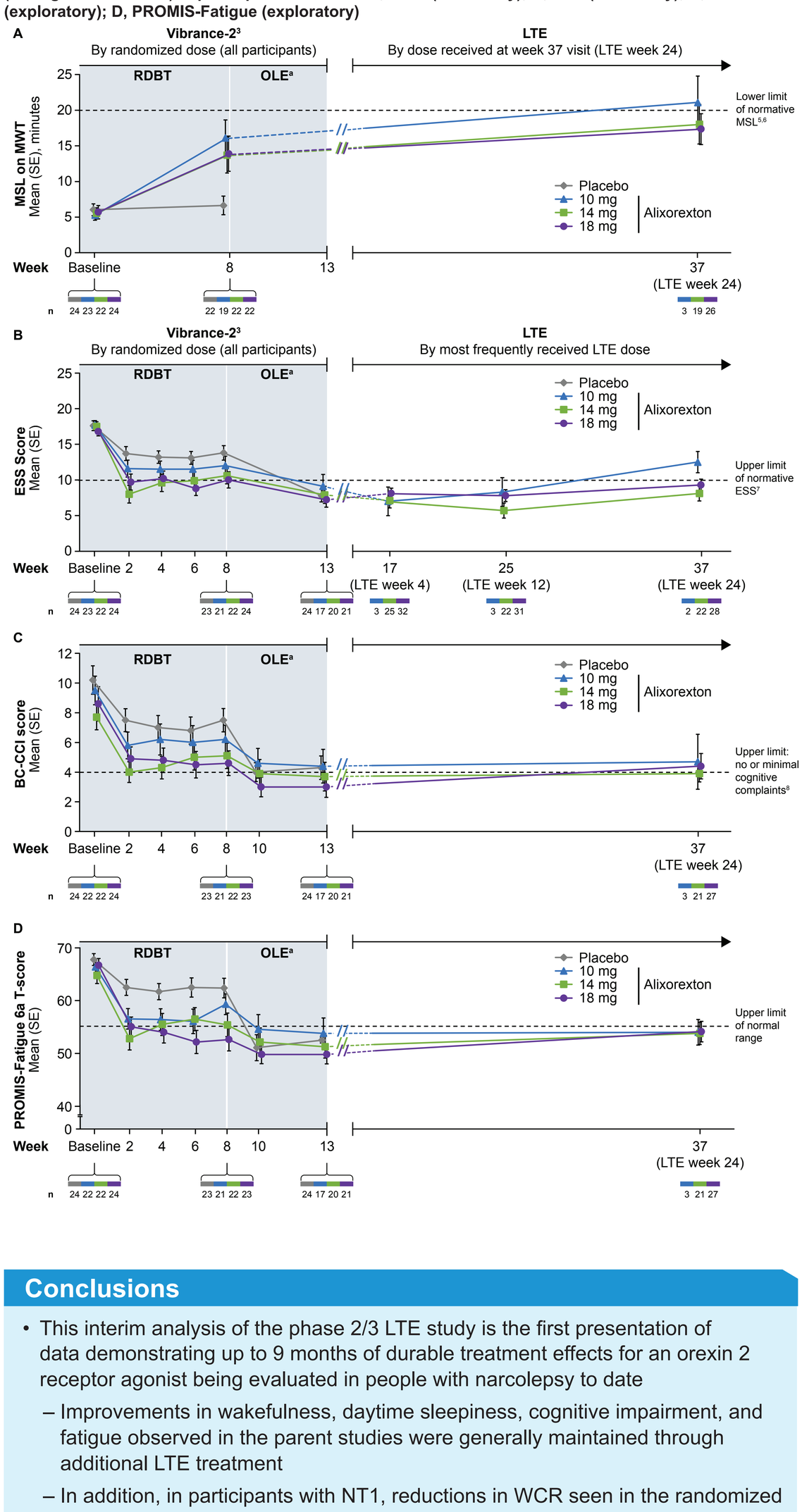


Figure 3. Alixorexton once-daily treatment effects for up to 9 months of continuous treatment (through LTE week 24) in participants with NT2: A, MWT (secondary); B, ESS (secondary); C, BC-CCI (exploratory); D, PROMIS-Fatigue (exploratory)



[a]All participants with NT1 in Vibrance-1 who entered the OLE started alixorexton 6 mg; participants with NT2 in Vibrance-2 who entered the OLE started alixorexton 14 mg. Dose adjustment was permitted during the first 2 weeks of the OLE for both studies. Participants are shown throughout the OLE according to their original RDBT-period randomized groups. [b]WCR was derived from participants' cataplexy diaries biweekly from baseline up to week 12. At all other timepoints, cataplexy rate was derived weekly.

Dashed lines mark the transition to the LTE; connectors do not represent observed data. For MWT, LTE dose was defined as the dose received at the week 37 visit (LTE week 24). For ESS, WCR, BC-CCI, and PROMIS-Fatigue, LTE dose was defined as the most frequently received LTE dose. LTE dose groups do not correspond to the respective parent-study randomized groups. Data cutoff: May 12, 2026.

Abbreviations: BC-CCI, British Columbia Cognitive Complaints Inventory; ESS, Epworth Sleepiness Scale; LTE, long-term extension; MSL, mean sleep latency; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OLE, open-label extension; PROMIS-Fatigue, Patient-Reported Outcomes Measurement Information System® Item Bank v1.0-Fatigue-Short Form 6a; RDBT, randomized double-blind treatment; SE, standard error; TEAE, treatment-emergent adverse event; WCR, weekly cataplexy rate.

Conclusions

- This interim analysis of the phase 2/3 LTE study is the first presentation of data demonstrating up to 9 months of durable treatment effects for an orexin 2 receptor agonist being evaluated in people with narcolepsy to date
  - Improvements in wakefulness, daytime sleepiness, cognitive impairment, and fatigue observed in the parent studies were generally maintained through additional LTE treatment
  - In addition, in participants with NT1, reductions in WCR seen in the randomized trial were maintained through the LTE
- Alixorexton continued to be generally well tolerated through the interim analysis[2,3]
- These findings support the long-term durability of alixorexton treatment effects and its continued clinical evaluation in the global, pivotal phase 3 Brilliance NT1 and NT2 studies, including once-daily and split-dose regimens

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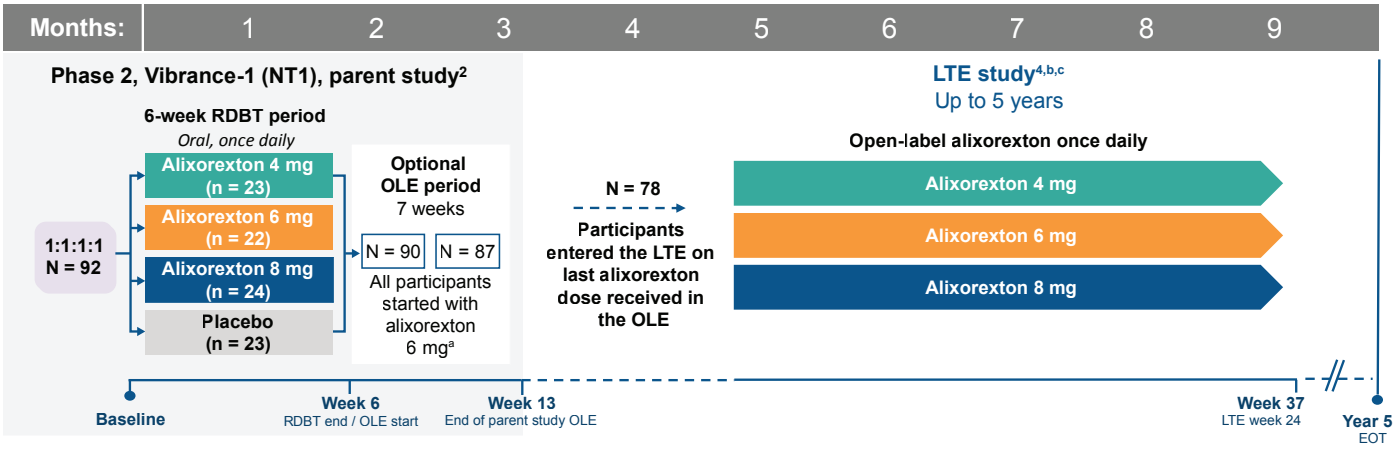
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Supplemental Methods

- Vibrance-1 and Vibrance-2 were phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging studies with 6- and 8-week randomized double-blind treatment periods, followed by optional 7- and 5-week open-label extensions, respectively
  - Participants were eligible to enter the ongoing phase 2/3 long-term extension study, in which the primary endpoint was the incidence of treatment-emergent adverse events (TEAEs)
- The British Columbia Cognitive Complaints Inventory (BC-CCI) is a 6-item screening tool that assesses cognitive impairment as perceived by the patient over 7 days
- The British Columbia Cognitive Complaints Inventory-Expanded (BC-CCI-E) includes 3 additional items that assess the impact of participant-reported cognitive impairment on quality of life
- The Patient-Reported Outcomes Measurement Information System® Item Bank v1.0-Fatigue-Short Form 6a (PROMIS-Fatigue) is a 6-item questionnaire designed to assess a patient's fatigue over the past 7 days

Supplemental Figure 1. Phase 2 and long-term clinical evaluation of alixorexton in NT1



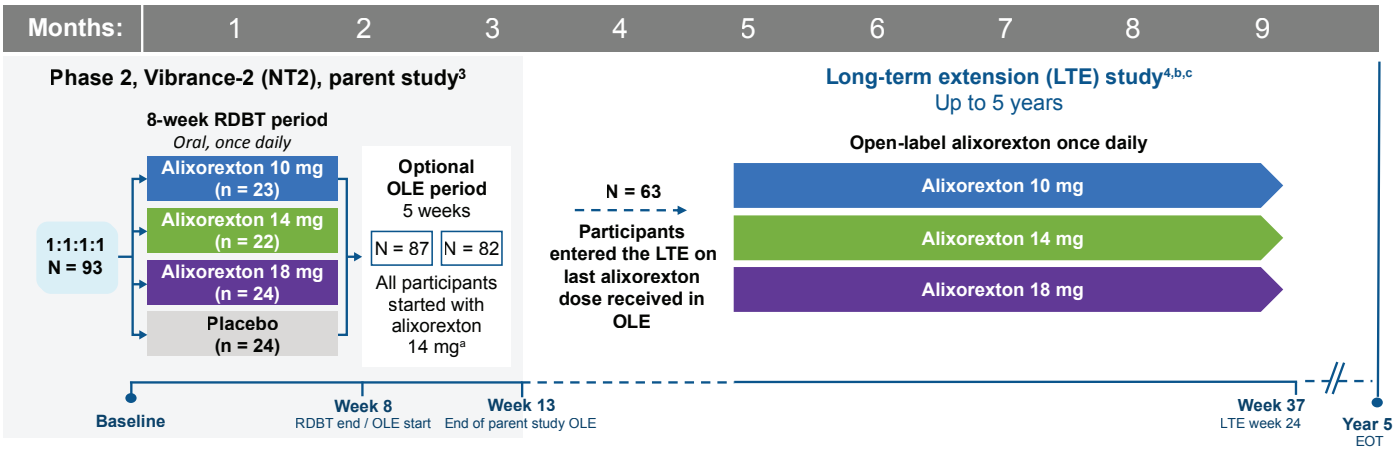
- **Vibrance-1 endpoints and assessments:** The primary endpoint was change from baseline to week 6 in mean sleep latency on the MWT; key secondary endpoints were change in ESS score from baseline to week 6, WCR at week 6[d], and incidence of TEAEs; exploratory assessments included the participant-reported BC-CCI, BC-CCI-E, and PROMIS-Fatigue

[a]All participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. [b]Current analysis includes participants from Vibrance-1 and Vibrance-2. Participants from the Vibrance-3 phase 2 study in idiopathic hypersomnia and phase 3 Brilliance studies in NT1 and NT2 are also eligible to join the LTE upon completion of their respective studies. [c]Dose adjustment was permitted during the first 4 weeks of the LTE; participants may have received more than one dose level. [d]WCR was derived from participants' cataplexy diaries biweekly from baseline up to week 12. At all other timepoints, cataplexy rate was derived weekly. Data cutoff: May 12, 2026.

BC-CCI, British Columbia Cognitive Complaints Inventory; BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LTE, long-term extension; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OLE, open-label extension; PROMIS-Fatigue, Patient-Reported Outcomes Measurement Information System® Item Bank v1.0-Fatigue-Short Form 6a; RDBT, randomized double-blind treatment; WCR, weekly cataplexy rate.

Supplemental Methods (continued)

Supplemental Figure 2. Phase 2 and long-term clinical evaluation of alixorexton in NT2



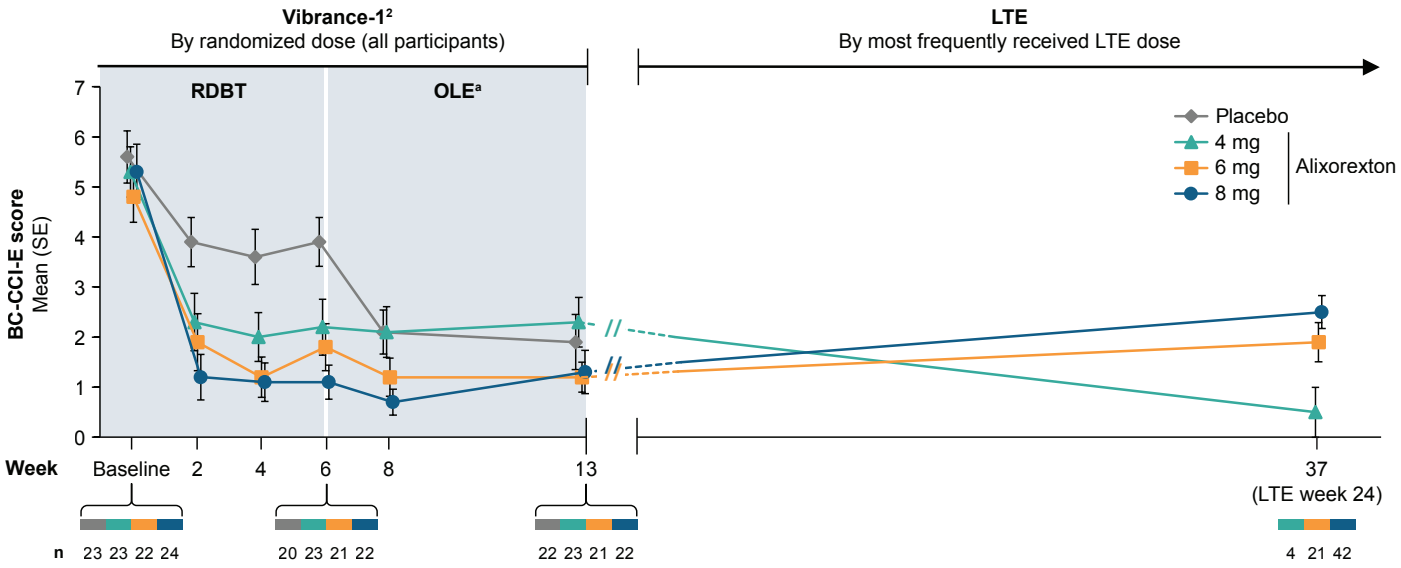
- **Vibrance-2 endpoints and assessments:** Dual primary endpoints were changes from baseline to week 8 in mean sleep latency on the MWT and ESS score; the secondary endpoint was TEAEs by study period; exploratory assessments included the participant-reported BC-CCI, BC-CCI-E, and PROMIS-Fatigue

[a]All participants who entered the OLE were started on alixorexton 14 mg, with dose adjustment permitted for the first 2 weeks of the OLE. [b]Current analysis includes participants from Vibrance-1 and Vibrance-2. Participants from the Vibrance-3 phase 2 study in idiopathic hypersomnia and phase 3 Brilliance studies in NT1 and NT2 are also eligible to join the LTE upon completion of their respective studies. [c]Dose adjustment was permitted during the first 4 weeks of the LTE; participants may have received more than one dose level. Data cutoff: May 12, 2026.

BC-CCI, British Columbia Cognitive Complaints Inventory; BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; EOT, end of treatment; ESS, Epworth Sleepiness Scale; LTE, long-term extension; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OLE, open-label extension; PROMIS-Fatigue, Patient-Reported Outcomes Measurement Information System® Item Bank v1.0-Fatigue-Short Form 6a; RDBT, randomized double-blind treatment; TEAE, treatment-emergent adverse event.

Supplemental Results

Supplemental Figure 3. Impact of participant-reported cognitive impairment on quality of life, assessed using the 3-item BC-CCI-E, in participants with NT1



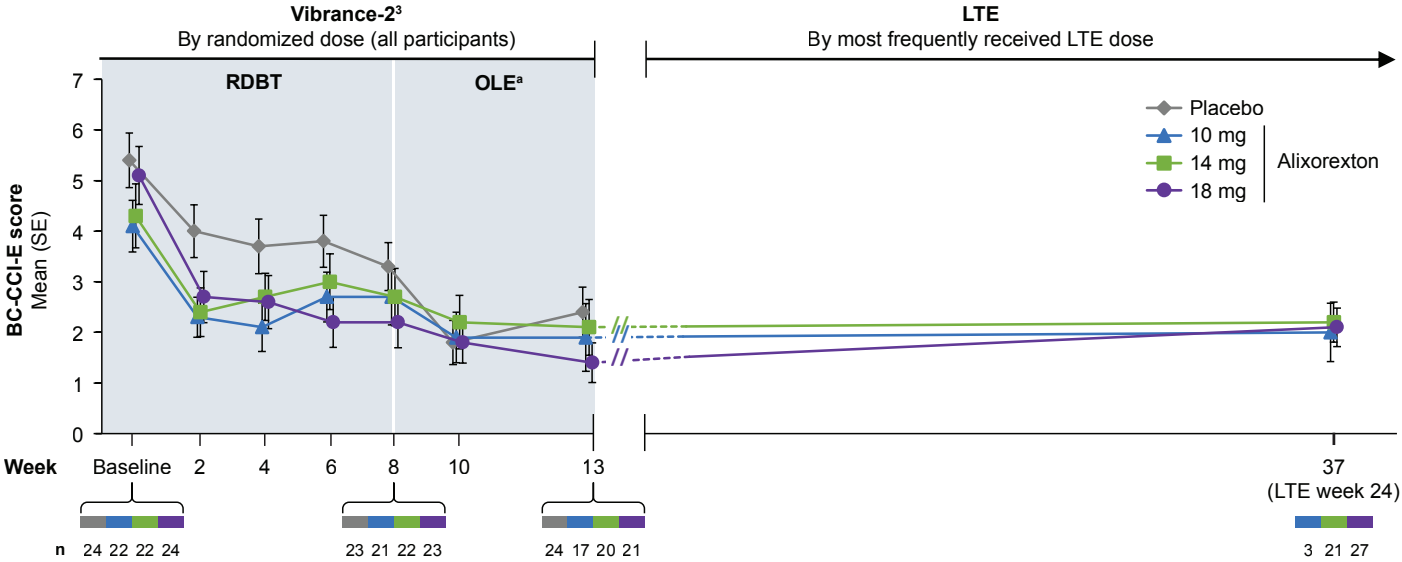
[a]All participants who entered the OLE were started on alixorexton 6 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment.

Dashed lines mark the transition to the LTE; connectors do not represent observed data. LTE groups were based on the most frequently received LTE dose and do not correspond to the respective parent-study randomized groups. Data cutoff: May 12, 2026.

BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; LTE, long-term extension; NT1, narcolepsy type 1; OLE, open-label extension; RDBT, randomized double-blind treatment; SE, standard error.

Supplemental Results (continued)

Supplemental Figure 4. Impact of participant-reported cognitive impairment on quality of life, assessed using the 3-item BC-CCI-E, in participants with NT2



[a]All participants who entered the OLE were started on alixorexton 14 mg, with dose adjustment permitted for the first 2 weeks of the OLE. Participants are shown throughout the OLE by their original RDBT period randomization assignment.

Dashed lines mark the transition to the LTE; connectors do not represent observed data. LTE groups were based on the most frequently received LTE dose and do not correspond to the respective parent-study randomized groups. Data cutoff: May 12, 2026.

BC-CCI-E, British Columbia Cognitive Complaints Inventory-Expanded; LTE, long-term extension; NT2, narcolepsy type 2; OLE, open-label extension; RDBT, randomized double-blind treatment; SE, standard error.

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