ALKERMES ORAL PRESENTATIONS PRESENTED AT WORLD SLEEP 2025

SEPTEMBER 8, 2025

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Important Information About This Document

This document includes scientific information about alixorexton (formerly referred to as ALKS 2680) that is intended for investors and should be read in conjunction with the press release issued, and investor presentation displayed, by the Company on September 8, 2025. Alixorexton is investigational and has not been approved by the FDA or any other health authority, and its safety and efficacy have not been established.

Note Regarding Forward-Looking Statements

Certain statements set forth in this document may constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning the potential therapeutic and commercial value of alixorexton (formerly referred to as ALKS 2680) and the company's expectations regarding the alixorexton development program. Such forward-looking statements are inherently uncertain and, although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, these statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: whether initial clinical results for alixorexton will be predictive of results of future stages of ongoing clinical studies, future clinical studies or real-world results; whether ongoing or future clinical studies for alixorexton will be initiated or completed on expected timelines or at all; whether alixorexton could be shown to be ineffective or unsafe; potential changes in the cost, scope and duration of the alixorexton development program; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2024 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at www.sec.gov. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this document. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this document.

Vibrance-1: A Randomized Phase 2 Study Evaluating Safety and Efficacy of the Orexin 2 Receptor Agonist Alixorexton (ALKS 2680) in Patients With Narcolepsy Type 1

Vibrance-1 Study

Giuseppe Plazzi,[1] Yves Dauvilliers,[2] Ronald R. Grunstein,[3] Emmanuel Mignot,[4] Gert Jan Lammers,[5] David T. Plante,[6] Erik Buntinx,[7] Rafael del Río Villegas,[8] Hailu Chen,[9] Alexandra Lovett,[9] Craig Hopkinson,[9] Bhaskar Rege,[9] and Marcus Yountz[9]

[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; [2]University of Montpellier, INSERM Institute for Neurosciences of Montpellier, Montpellier, France; [3]Woolcock Institute of Medical Research, Macquarie University, Sydney, Australia; [4]Stanford Center for Sleep Sciences and Medicine, Stanford University School of Medicine, Stanford, CA, USA; [5]Leiden University Medical Center, Leiden, the Netherlands and Stichting Epilepsie Instellingen Nederland, Sleep-Wake Centre, Heemstede, the Netherlands; [6]University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA; [7]ANIMA Research, Alken, Belgium; [8]Universidad CEU San Pablo, CEU Universities, Vithas Madrid Hospitals Madrid, Spain; [9]Alkermes, Inc., Waltham, MA, USA

World Sleep Congress | September 5 – 10, 2025

Financial Relationship Disclosure

Singapore 2025 WORLD SLEEP September 5-10

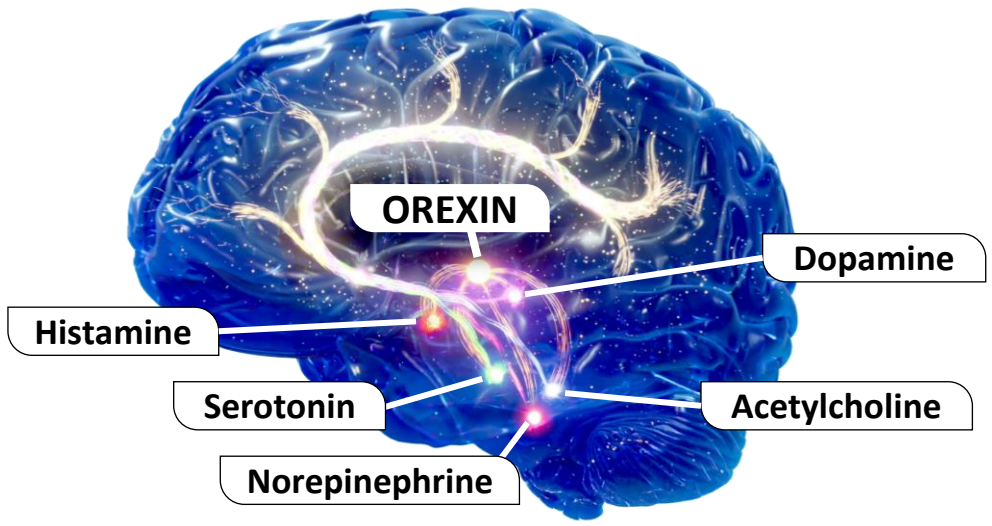
Ineligible companies are those whose primary business is producing, marketing, selling, re-selling, or distributing health care products used by, or on patients.

☐ **No**, I HAVE NOT had a financial relationship with an ineligible company in the past 24 months.
☑ **Yes**, I HAVE had a financial relationship with an ineligible company in the past 24 months.

Relationship type	**Name of company**
Institutional funding	Alkermes (R. Grunstein, Y. Dauvilliers); Lilly (R. Grunstein); Takeda (R. Grunstein); Vanda (R. Grunstein)
Research funding	Avadel (E. Mignot); Alkermes (E. Mignot); Bioprojet (G. Plazzi); Centessa Pharmaceuticals (G. Plazzi); Eisai (E. Mignot); Idorsia (G. Plazzi); Jazz Pharmaceuticals (G. Plazzi, E. Mignot); Orexia Therapeutics (G. Plazzi); Takeda (G. Plazzi, E. Mignot); Vanda (E. Mignot)
Employment	Alkermes (A. Lovett, B. Rege, C. Hopkinson, H. Chen, M. Yountz)
Speaker fees	Eisai (R. Grunstein); SomnoMed (R. Grunstein)
Advisory Board	Aditum Bio LLC (D. Plante); Alkermes (D. Plante): Apnimed (R. Grunstein); Avadel (Y. Dauvilliers); Bioprojet (Y. Dauvilliers); Centessa (D. Plante, Y. Dauvilliers); Harmony Biosciences (D. Plante, Y. Dauvilliers); Idorsia (Bioprojet); Jazz Pharmaceuticals (D. Plante, Y. Dauvilliers); Lilly (R. Grunstein); Takeda (D. Plante, E. Mignot, Y. Dauvilliers); TEVA (D. Plante).

Orexin 2 Receptor Agonism: Opportunity for Addressing Central Disorders of Hypersomnolence

Orexin Regulation of Wakefulness Systems[1]



Alixorexton (ALKS 2680) is a highly potent, oral, selective **orexin 2 receptor (OX2R) agonist** being developed as a **once-daily treatment** for narcolepsy and idiopathic hypersomnia

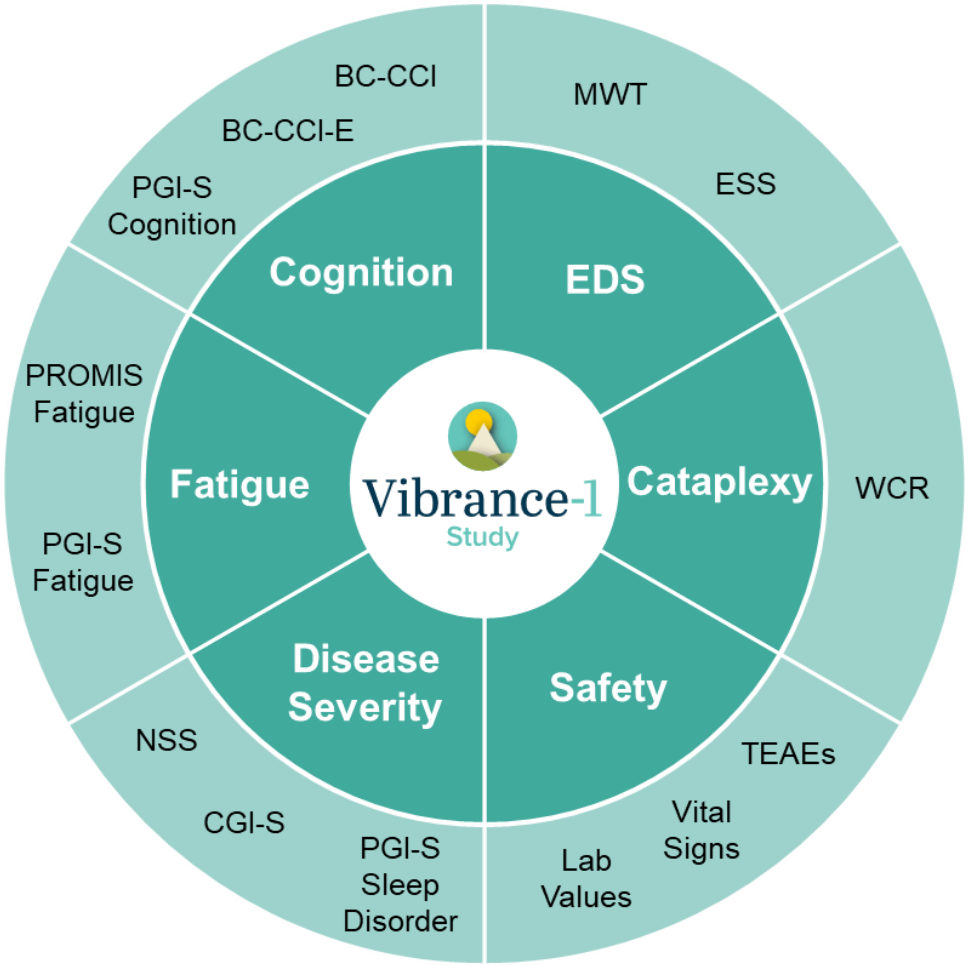
Alixorexton has achieved the following design objectives:

- High potency and selectivity for OX2R in the brain
- Oral, once-daily dosing that mimics the sleep/wake cycle
- A wide therapeutic index and range of doses

In a phase 1b study, alixorexton was generally well tolerated and improved wakefulness across a range of doses in patients with NT1, NT2, and IH, informing dose selection for phase 2 studies[2]

1. Krahn LE, et al. *Adv Ther.* 2022;39(1):221-243. **2.** Grunstein R, et al. Poster at SLEEP 2025 Meeting; June 8-11, 2025; Seattle, WA.
IH = idiopathic hypersomnia; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

Vibrance-1 Examined the Effects of Alixorexton on Measures Relevant to the Clinical Needs of Patients With NT1



BC-CCI = British Columbia Cognitive Complaints Inventory; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Expanded; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS = Narcolepsy Severity Scale; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

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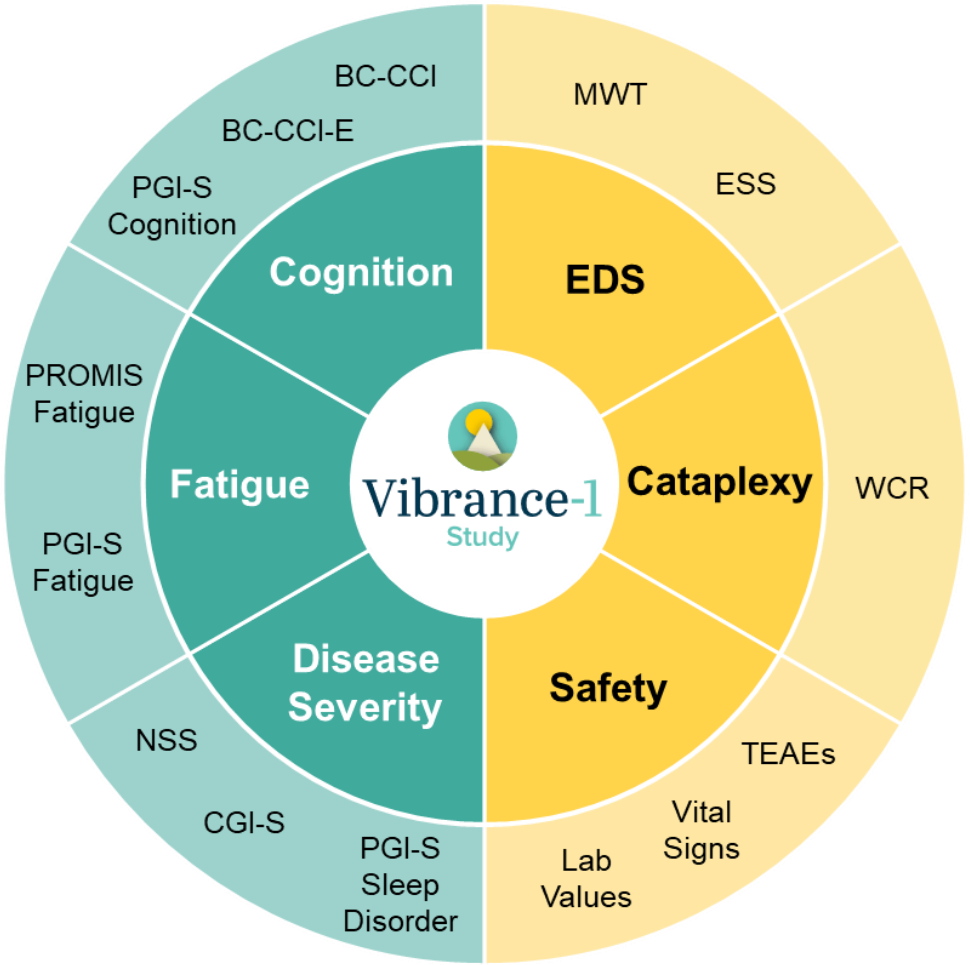

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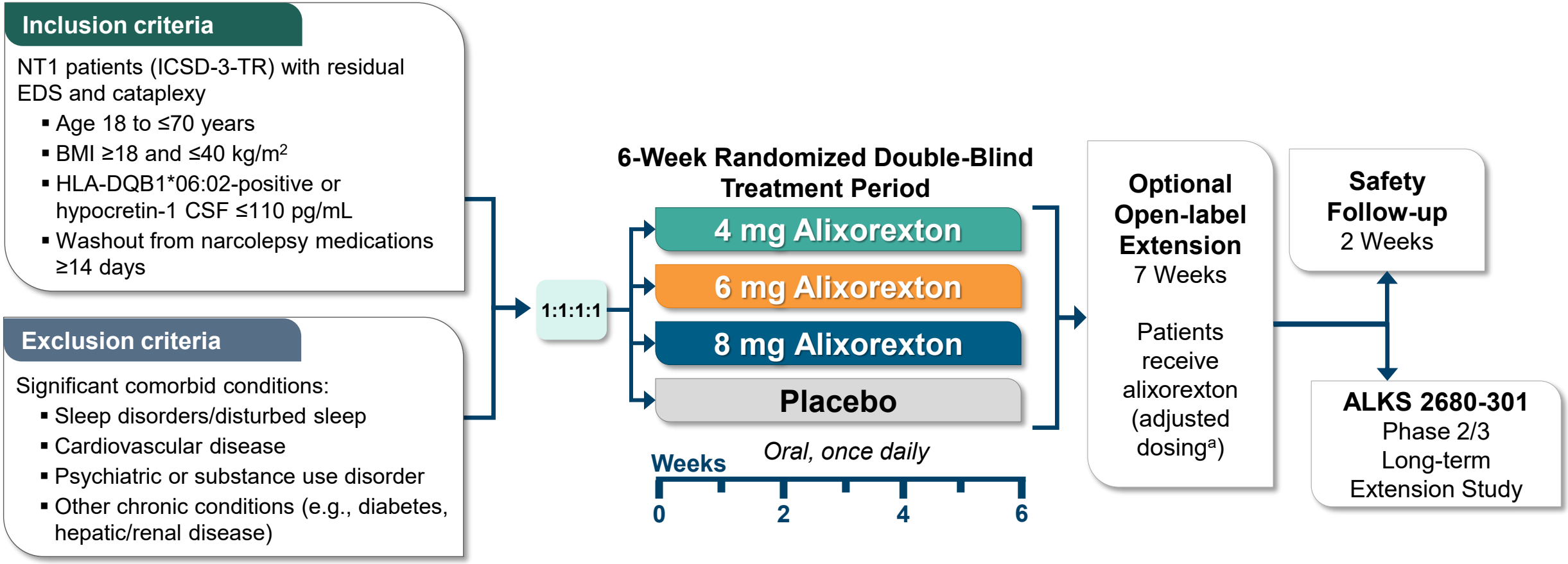
Vibrance-1 Phase 2 Study: 6-Week Double-blind Period Followed by an Open-label Extension Period With Dosing Flexibility



[a]All patients in the open-label extension period start with 6 mg alixorexton. Dose adjustment possible (up or down) during the first 2 weeks of the optional open-label extension period.
BMI = body mass index; CSF = cerebrospinal fluid; EDS = Excessive Daytime Sleepiness; ICSD-3-TR = International Classification of Sleep Disorders, third edition, text revision; NT1 = narcolepsy type 1.

Vibrance-1 Study

Primary Efficacy and Secondary Endpoints Were Evaluated at the End of the 6-week Double-blind Treatment Period

Inclusion criteria

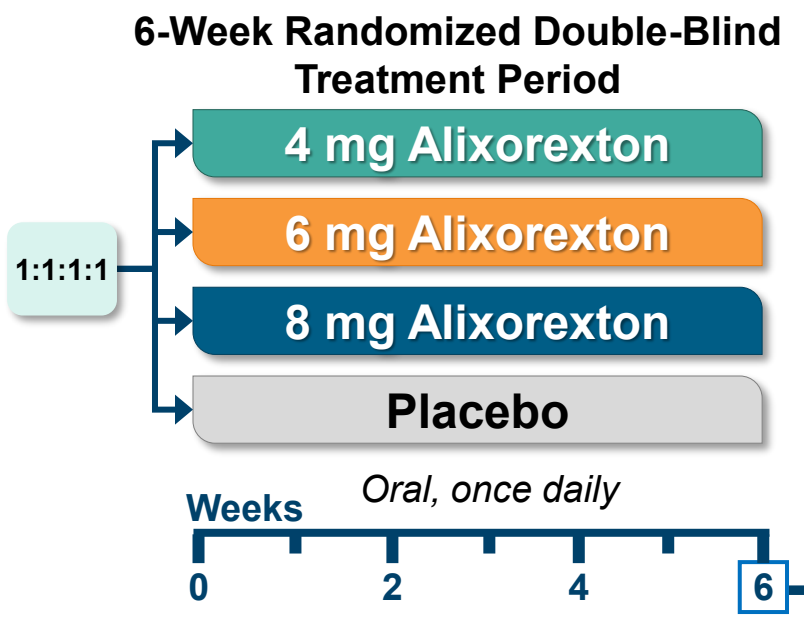
NT1 patients (ICSD-3-TR) with residual EDS and cataplexy

- Age 18 to ≤70 years
- BMI ≥18 and ≤40 kg/m^2
- HLA-DQB1*06:02-positive or hypocretin-1 CSF ≤110 pg/mL
- Washout from narcolepsy medications ≥14 days

Exclusion criteria

Significant comorbid conditions:

- Sleep disorders/disturbed sleep
- Cardiovascular disease
- Psychiatric or substance use disorder
- Other chronic conditions (e.g., diabetes, hepatic/renal disease)



Primary Endpoint

Change in mean sleep latency on the MWT from baseline to Week 6

Key Secondary Endpoints

Change in ESS from baseline to Week 6

Weekly cataplexy rate at Week 6[a]

Safety (Secondary Endpoint)

TEAEs
Vital signs
Laboratory parameters

[a]Weekly cataplexy rate at Week 6 was derived from patients' cataplexy diaries over Weeks 5 and 6.
BMI = body mass index; CSF = cerebrospinal fluid; EDS = Excessive Daytime Sleepiness; ESS = Epworth Sleepiness Scale; ICSD-3-TR = International Classification of Sleep Disorders, third edition, text revision; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; TEAE = treatment-emergent adverse event.

Vibrance-1 Study

Vibrance-1 Phase 2 Study: Baseline Characteristics and Study Disposition

		Alixorexton once daily			
	Placebo (N=23)	4 mg (N=23)	6 mg (N=22)	8 mg (N=24)	Total (N=92)
Disease Severity					
Mean Sleep Latency on MWT (minutes), Mean (SD)	2.8 (3.1)	3.3 (3.3)	3.4 (3.2)	2.8 (2.9)	3.1 (3.1)
ESS, Mean (SD)	18.7 (2.7)	18.2 (2.5)	18.5 (3.1)	18.7 (4.0)	18.5 (3.1)
WCR[a] Mean (SD) Median [min, max]	26.6 (29.9) 14.0 [1.6, 121.0]	37.8 (53.5) 20.5 [4.7, 255.0]	16.8 (9.8) 15.1 [5.0, 49.0]	23.0 (17.3) 15.9 [1.4, 67.5]	26.11 (32.6) 16.8 [1.4, 255.0]
NSS,[b] Mean (SD)	32.7 (7.4)	32.5 (9.1)	29.0 (8.4)	30.9 (9.5)	31.3 (8.6)
Patient Disposition					
Completed Week 6 visit, n (%)	23 (100)	23 (100)	22 (100)	23 (96)	91 (99)

Demographics

Age	33.5 years (mean)
Sex	Females 62%
Race	White 38% Black 9% NR[c] 46%
BMI	28.4 kg/m^2 (mean)

[a]Baseline WCR calculated as the average weekly cataplexy rate over 2 weeks prior to first dose of study drug. [b]No baseline NSS available for 1 patient in the placebo group and 1 patient in the 6 mg alixorexton group. [c]Race not reported in European Union member countries per regulations.
BMI = body mass index; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NR = not reported; NSS = Narcolepsy Severity Scale; SD = standard deviation; WCR = weekly cataplexy rate.

Vibrance-1 Study

Most Patients had Severe Disease at Baseline

		Placebo (N=23)	Alixorexton once daily 4 mg (N=23)	Alixorexton once daily 6 mg (N=22)	Alixorexton once daily 8 mg (N=24)	Total (N=92)
Disease Severity						
Mean Sleep Latency on MWT (minutes), Mean (SD)		2.8 (3.1)	3.3 (3.3)	3.4 (3.2)	2.8 (2.9)	3.1 (3.1)
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Patient Disposition						
Completed Week 6 visit, n (%)		23 (100)	23 (100)	22 (100)	23 (96)	91 (99)

Narcolepsy Severity Scale (NSS)

Daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and disturbed nighttime sleep

Overall Baseline NSS: 31.3 (8.6)

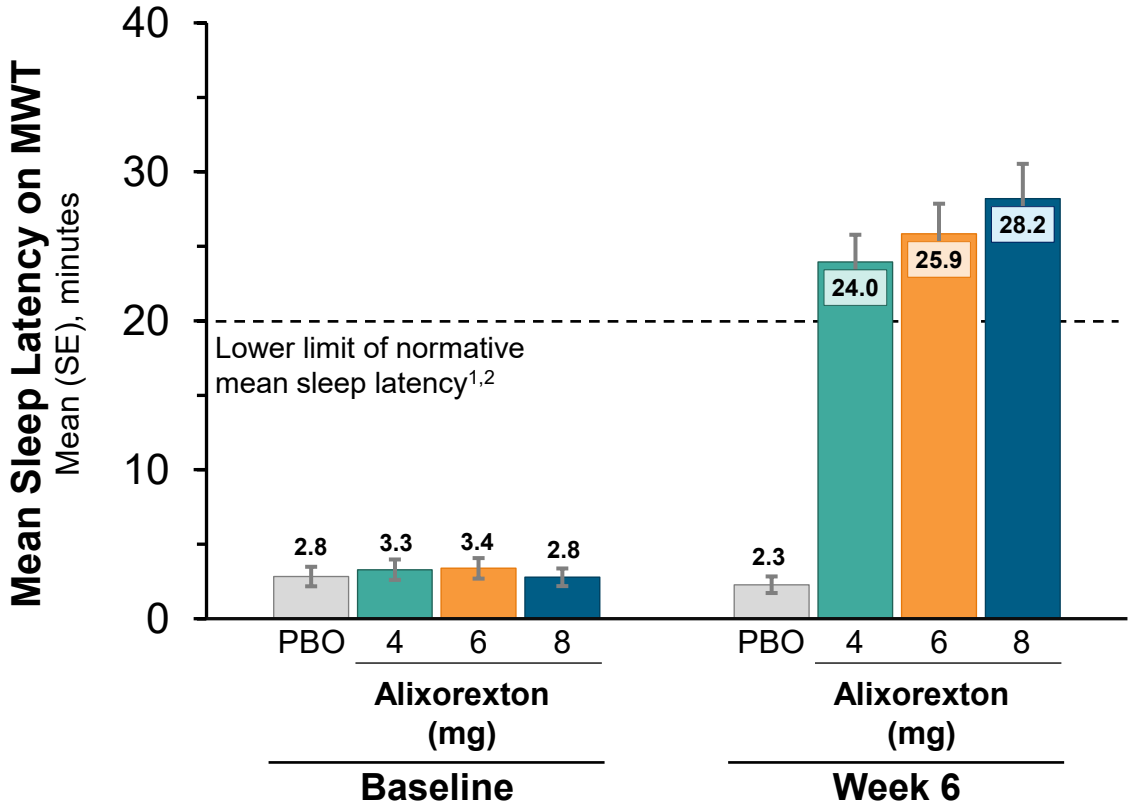
Mild	0-14
Moderate	15-28
Severe	29-42
Very Severe	43-57

[a]Baseline WCR calculated as the average weekly cataplexy rate over 2 weeks prior to first dose of study drug. [b]No baseline NSS available for 1 patient in the placebo group and 1 patient in the 6 mg alixorexton group.

BMI = body mass index; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NR = not reported; NSS = Narcolepsy Severity Scale; SD = standard deviation; WCR = weekly cataplexy rate.

Vibrance-1 Study

Primary Endpoint: Mean Sleep Latency on the MWT Showed Alixorexton Achieved Normative Wakefulness at All Doses



Primary Endpoint Analysis at Week 6

Change from baseline at Week 6 (minutes)[a]	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
LSM	**-0.6**	**21.6**	**23.5**	**25.5**
(95% CI of LSM)	(-4.5, 3.3)	(17.7, 25.6)	(19.4, 27.6)	(21.4, 29.5)
LSM difference vs PBO		**22.2**	**24.1**	**26.0**
(95% CI of LSM difference)		(17.2, 27.2)	(19.0, 29.1)	(21.0, 31.0)
***P* value** (Adjusted for multiplicity)		**0.01**	**<0.0001**	**<0.0001**

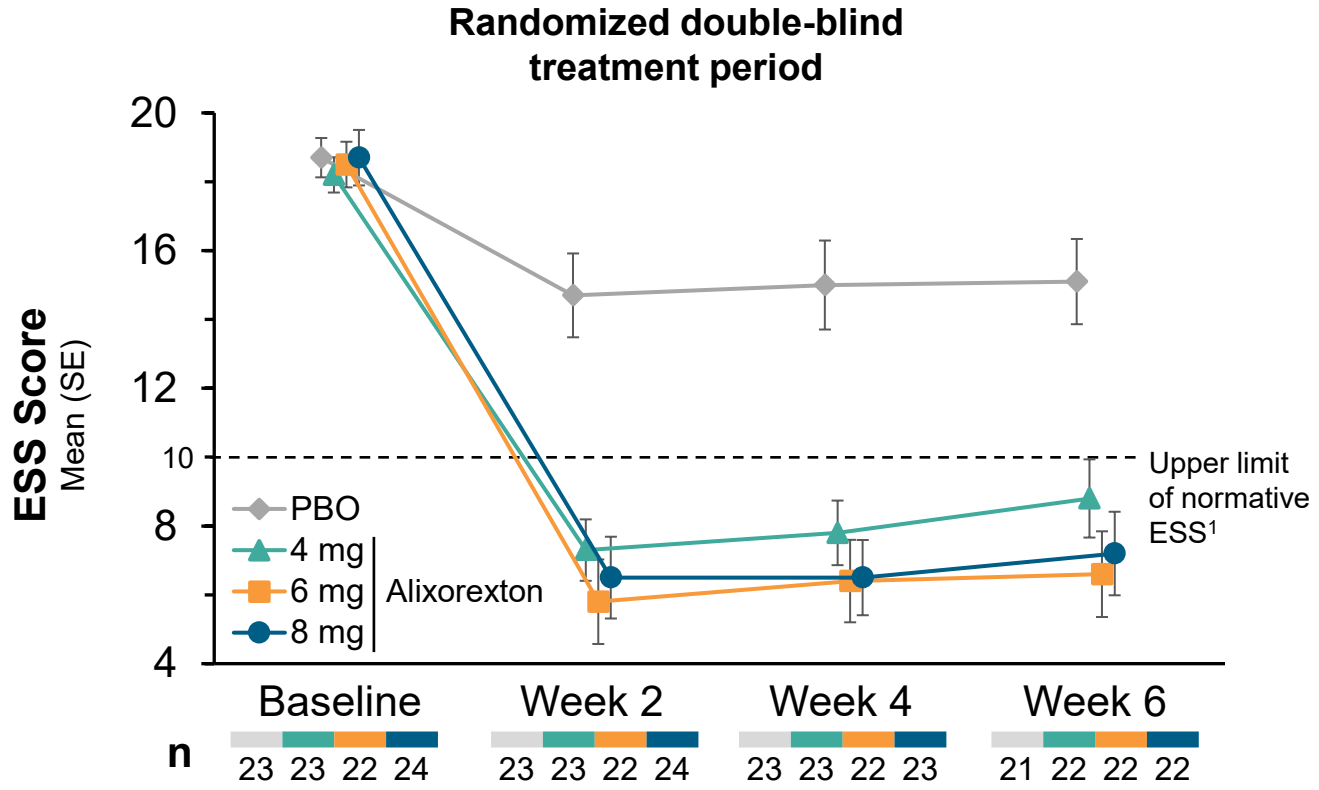
[a]ANCOVA model. Missing data were imputed using multiple imputation.

1. Krahn LE, et al. *J Clin Sleep Med*. 2021;17(12):2489-2498. **2.** Doghramji K, et al. *Electroencephalogr Clin Neurophysiol.* 1997;103(5):554-562.

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MWT = Maintenance of Wakefulness Test; PBO = placebo; SE = standard error; WCR = weekly cataplexy rate.

Vibrance-1 Study

Key Secondary Endpoint: Epworth Sleepiness Scale Showed Alixorexton Achieved Normative Wakefulness at All Doses



Key Secondary Endpoint Analysis at Week 6

Change from baseline at Week 6[a]	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
LSM	**-3.1**	**-9.6**	**-11.8**	**-11.4**
(95% CI of LSM)	(-5.6, -0.7)	(-12.0, -7.1)	(-14.3, -9.3)	(-13.9, -9.0)
LSM difference vs PBO		**-6.4**	**-8.7**	**-8.3**
(95% CI of LSM difference)		(-9.6, -3.3)	(-11.9, -5.5)	(-11.4, -5.2)
***P* value** (Adjusted for multiplicity)		**0.01**	**<0.0001**	**<0.0001**

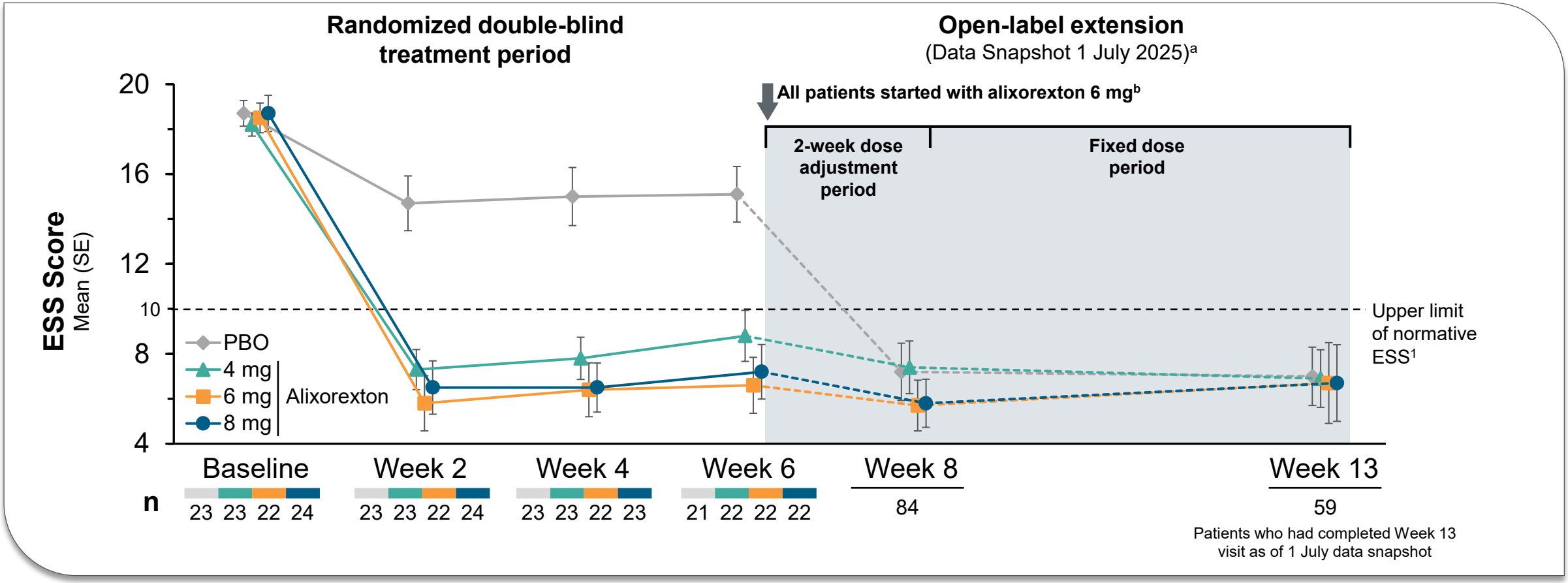
[a]ANCOVA model. Missing data were imputed using multiple imputation.

1. Johns MW, Sleep 1991; 14: 540-5.

ANCOVA = analysis of covariance; CI = confidence interval; ESS = Epworth Sleepiness Scale; LSM = least square means; PBO = placebo; SE = standard error.

Vibrance-1 Study

Alixorexton Improved ESS Scores as Early as Week 2 and Sustained the Effect Through Week 13



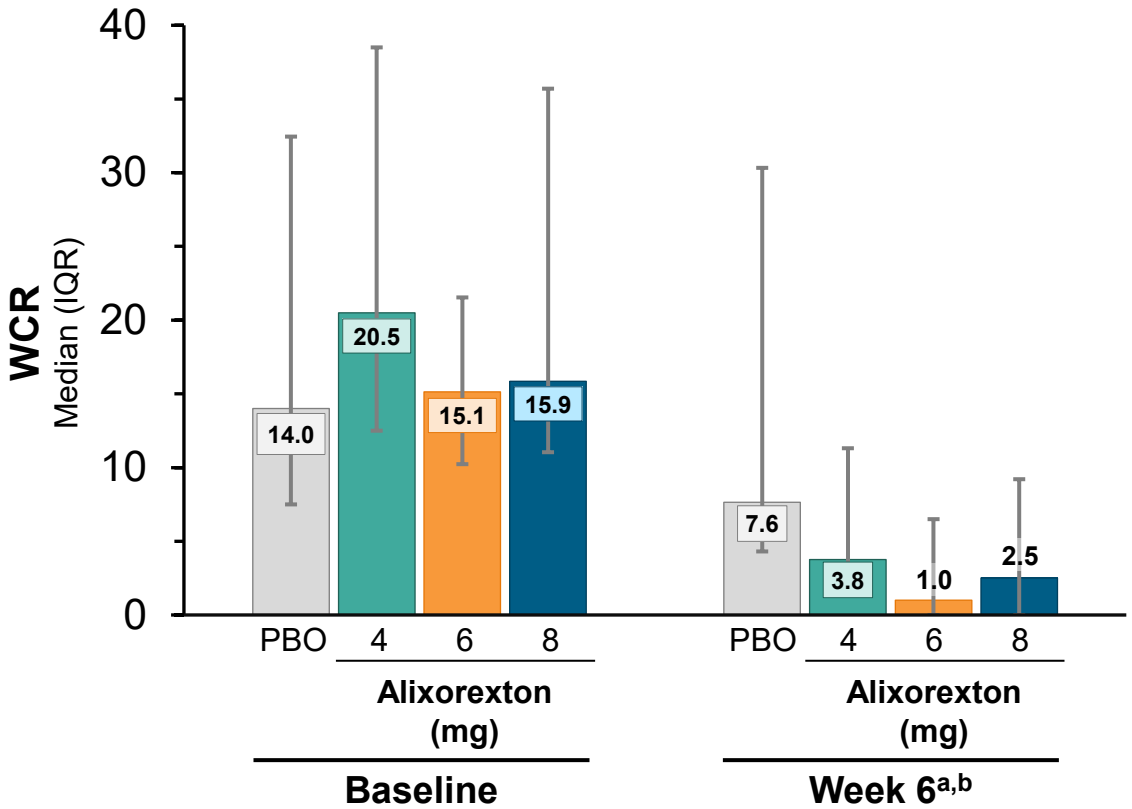
[a]This snapshot of the open-label extension reflects data as of 1 July 2025 from the 59 patients who had completed the Week 13 visit as of that date. Not all patients had completed the open-label extension at the time of this snapshot. [b]During the open-label extension (shaded area), all patients were switched to alixorexton 6 mg with dose adjustments during the first 2 weeks at the investigator's discretion.

1. Johns MW, Sleep 1991; 14: 540-5.

ESS = Epworth Sleepiness Scale; PBO = placebo; SE = standard error.

Vibrance-1 Study

Key Secondary Endpoint: WCR at Week 6 Showed Alixorexton Reduced Cataplexy Events Versus Placebo



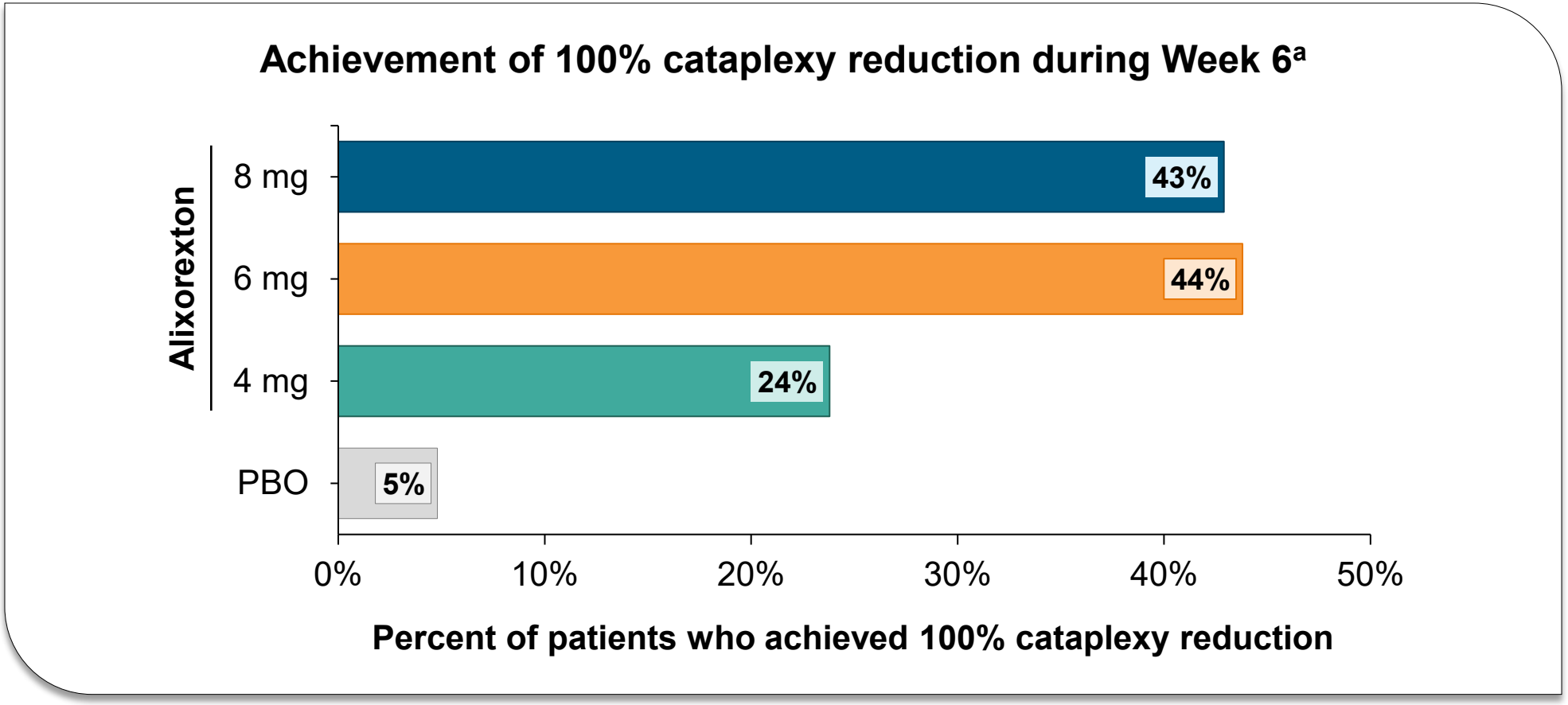
Key Secondary Endpoint Analysis

WCR at Week 6[a,c]	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
Mean incidence rate (95% CI of incidence rate)	**13.1** (7.5, 22.9)	**6.4** (3.6, 11.3)	**4.0** (2.2, 7.4)	**8.4** (4.7, 15.3)
Rate ratio vs PBO (95% CI of rate ratio)		**0.49** (0.23, 1.05)	**0.31** (0.14, 0.70)	**0.64** (0.30, 1.41)
***P* value** (Adjusted for multiplicity)		0.169	**0.01**	0.452

[a]Weekly cataplexy rate at Week 6 was derived from patients' cataplexy diaries over Weeks 5 and 6. [b]The minimum number of required cataplexy diaries was 10 days over week 5 and 6. [c]Cataplexy events on missing diary days were imputed using multiple imputation. Negative binomial model was used after 100 imputed datasets. Treatment group, baseline weekly cataplexy rate and region were included in the model.
CI = confidence interval; IQR = interquartile range; PBO = placebo; WCR = weekly cataplexy rate.

Vibrance-1 Study

Many Patients on Alixorexton Experienced No Cataplexy During Week 6



[a]The minimum number of required cataplexy diaries was 5 days weekly.
PBO = placebo.

Vibrance-1 Study

Alixorexton was Generally Well Tolerated Over 6 Weeks of Treatment

n (%)	Placebo (N=23)	Alixorexton once daily 4 mg (N=23)	Alixorexton once daily 6 mg (N=22)	Alixorexton once daily 8 mg (N=24)
Any TEAE[a]	11 (48)	20 (87)	20 (91)	21 (88)
Mild	8 (35)	13 (57)	15 (68)	11 (46)
Moderate	3 (13)	6 (26)	5 (23)	8 (33)
Severe	0	1 (4)	0	2 (8)
TEAEs in ≥10% among all alixorexton-treated patients				
Pollakiuria	1 (4)	15 (65)	11 (50)	12 (50)
Insomnia	0	4 (17)	7 (32)	8 (33)
Salivary Hypersecretion	0	5 (22)	5 (23)	7 (29)
Micturition Urgency	1 (4)	2 (9)	4 (18)	4 (17)
Vision Blurred	1 (4)	2 (9)	1 (5)	7 (29)
Drug-related TEAEs[a,b]	6 (26)	18 (78)	17 (77)	19 (79)
Serious TEAEs	0	0	0	0
TEAEs leading to study drug discontinuation	0	0	0	1 (4)

[a]If a patient had multiple adverse events, the highest severity is presented in summary by severity, and the highest relationship to study drug is presented in summary by relationship.
[b]Relationship of TEAE to the drug as determined by the investigator. TEAE = treatment-emergent adverse event.

Vibrance-1 Study

Alixorexton was Generally Well Tolerated Over 6 Weeks of Treatment

- Most TEAEs were mild to moderate in severity
- There were no serious TEAEs reported
- Most commonly reported TEAEs occurred within the 1st week of dosing
  - Most insomnia events resolved within 1 week
  - Most urinary events (pollakiuria and micturition urgency) were generally persistent
  - Most vision blurred events were mild, transient or intermittent, and resolved within 3 days
- No clinically meaningful changes in patients treated with alixorexton were noted in heart rate, blood pressure, liver function, or visual exams

TEAE = treatment-emergent adverse event.

Vibrance-1 Study

Conclusions

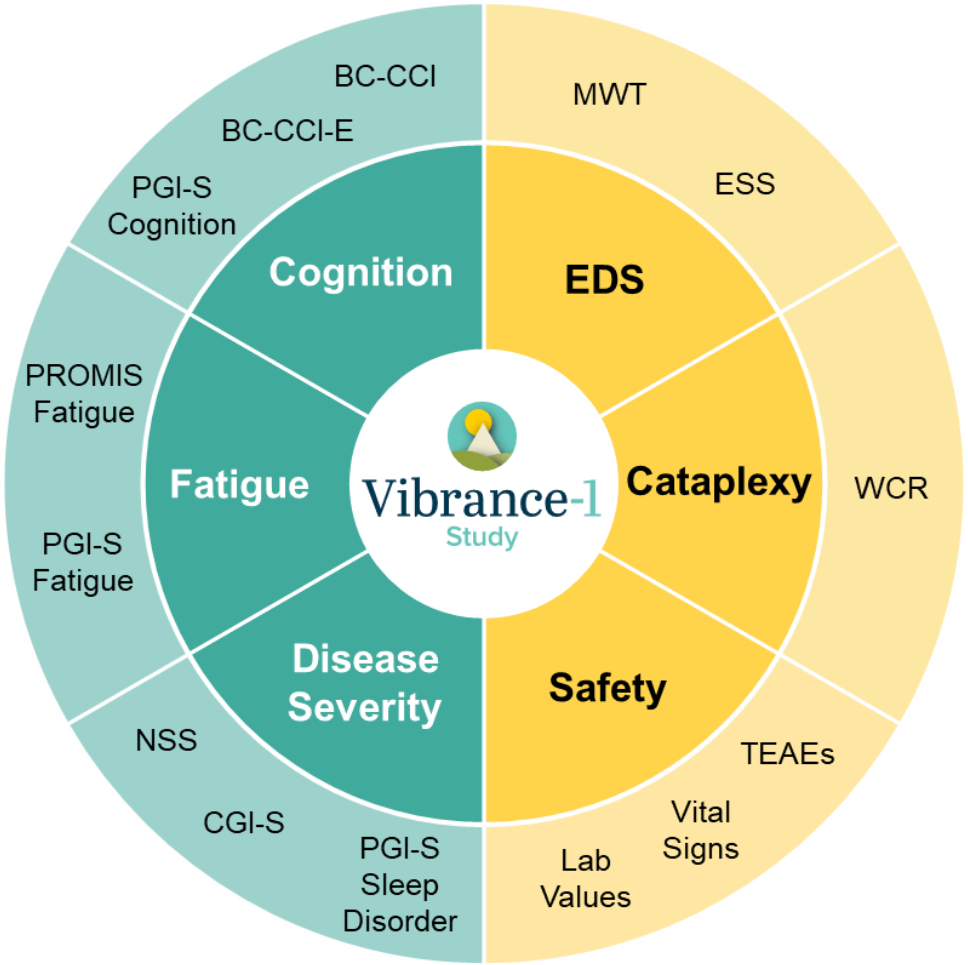
Once-daily alixorexton:

- Demonstrated statistically significant, clinically meaningful improvements on the MWT and ESS at Week 6 compared with placebo, achieving a normative wakefulness profile at all doses tested
  - Improvements on the ESS were observed as early as Week 2 and sustained through Week 13[a]
- Reduced WCR at all doses; achieved statistical significance at the 6 mg dose. Many patients had no cataplexy during Week 6 at all doses tested
- Was generally well tolerated, with most TEAEs mild to moderate in severity and no serious TEAEs reported
  - No clinically meaningful changes in heart rate, blood pressure, liver function, or visual exams

Results from Vibrance-1 will inform dose selection for a planned global phase 3 study in patients with NT1

[a]Based on data snapshot on 1 July 2025, which included 59 patients who completed the Week 13 visit.
ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

Vibrance-1 Demonstrated Clinically Meaningful Improvements on Outcomes Important to Patients With NT1



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Acknowledgments

The authors would like to thank:

- The patients
- Their families and caregivers
- Vibrance-1 investigators and their staff

Funding provided by Alkermes

Improvement in the Severity of Narcolepsy Symptoms and Fatigue in Patients With Narcolepsy Type 1 Treated With the Orexin 2 Receptor Agonist Alixorexton (ALKS 2680)

Vibrance-1 Study

Yves Dauvilliers,[1] Ronald R. Grunstein,[2] Emmanuel Mignot,[3] Gert Jan Lammers,[4] David T. Plante[5] Erik Buntinx,[6] Rafael del Río Villegas,[7] Hailu Chen,[8] Craig Hopkinson,[8] Bhaskar Rege,[8] Marcus Yountz,[8] Michael J. Doane,[8] and Giuseppe Plazzi[9]

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World Sleep Congress | September 5 – 10, 2025

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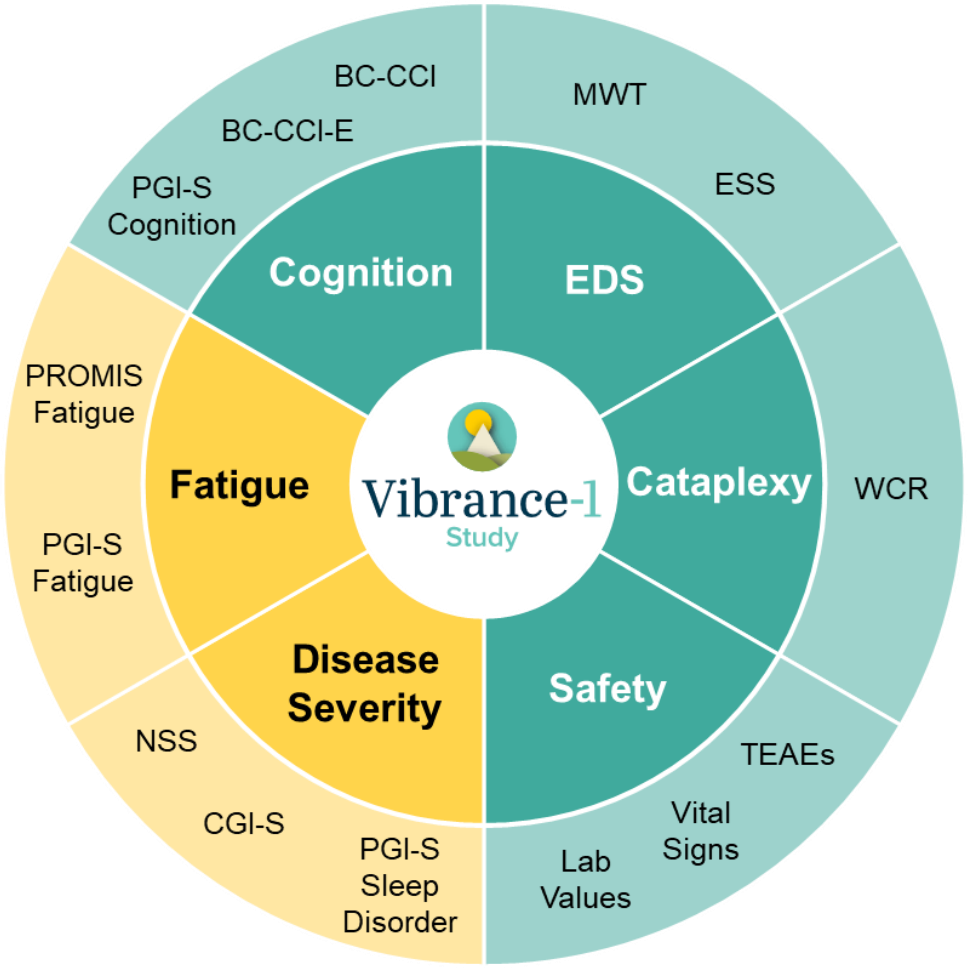
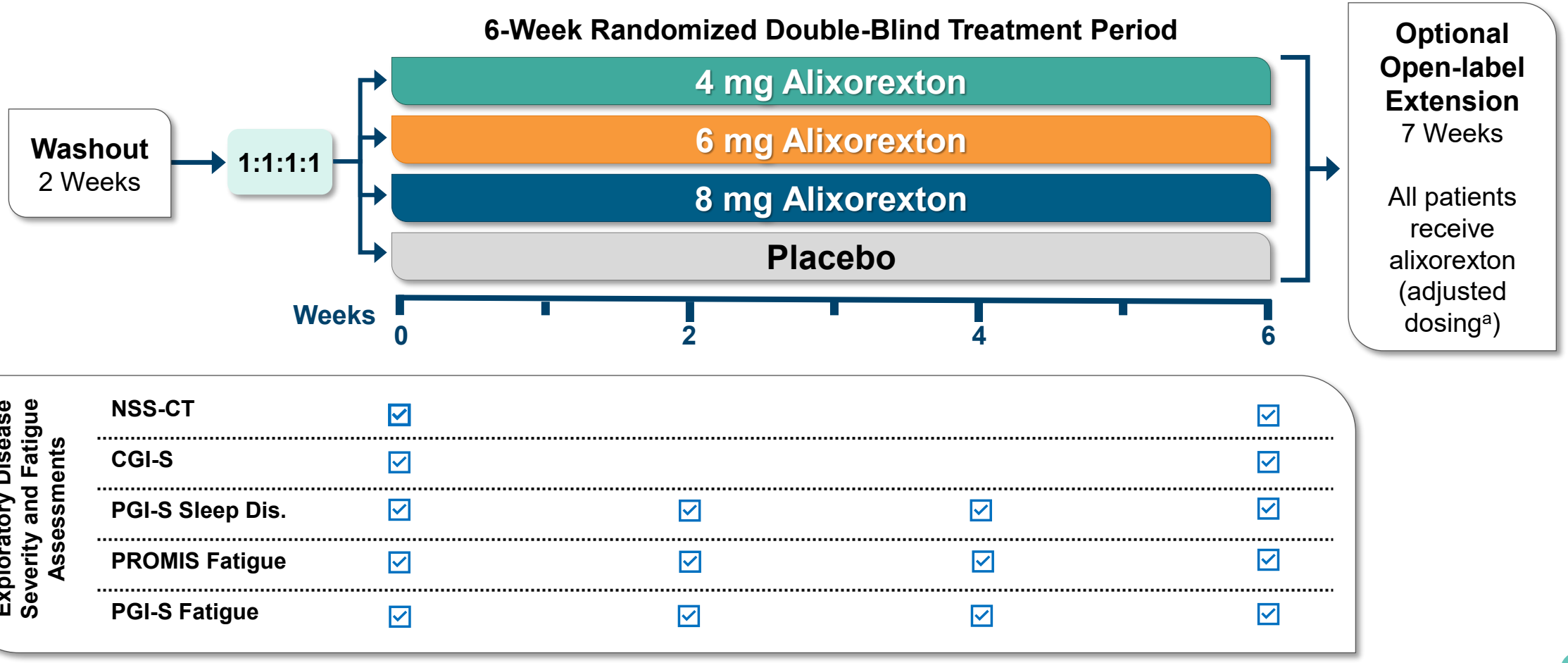
Research funding	Avadel (E. Mignot); Alkermes (E. Mignot); Bioprojet (G. Plazzi); Centessa Pharmaceuticals (G. Plazzi); Eisai (E. Mignot); Idorsia (G. Plazzi); Jazz Pharmaceuticals (G. Plazzi, E. Mignot); Orexia Therapeutics (G. Plazzi); Takeda (G. Plazzi, E. Mignot); Vanda (E. Mignot)
Employment	Alkermes (B. Rege, C. Hopkinson, H. Chen, M. Doane, M. Yountz)
Speaker fees	Eisai (R. Grunstein); SomnoMed (R. Grunstein)
Advisory Board	Aditum Bio LLC (D. Plante); Alkermes (D. Plante): Apnimed (R. Grunstein); Avadel (Y. Dauvilliers); Bioprojet (Y. Dauvilliers); Centessa (D. Plante, Y. Dauvilliers); Harmony Biosciences (D. Plante, Y. Dauvilliers); Idorsia (Bioprojet); Jazz Pharmaceuticals (D. Plante, Y. Dauvilliers); Lilly (R. Grunstein); Takeda (D. Plante, E. Mignot, Y. Dauvilliers); TEVA (D. Plante).

Vibrance-1 Examined the Effects of Alixorexton on Overall Disease Severity and Fatigue in Patients With NT1



BC-CCI = British Columbia Cognitive Complaints Inventory; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Expanded; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS = Narcolepsy Severity Scale; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

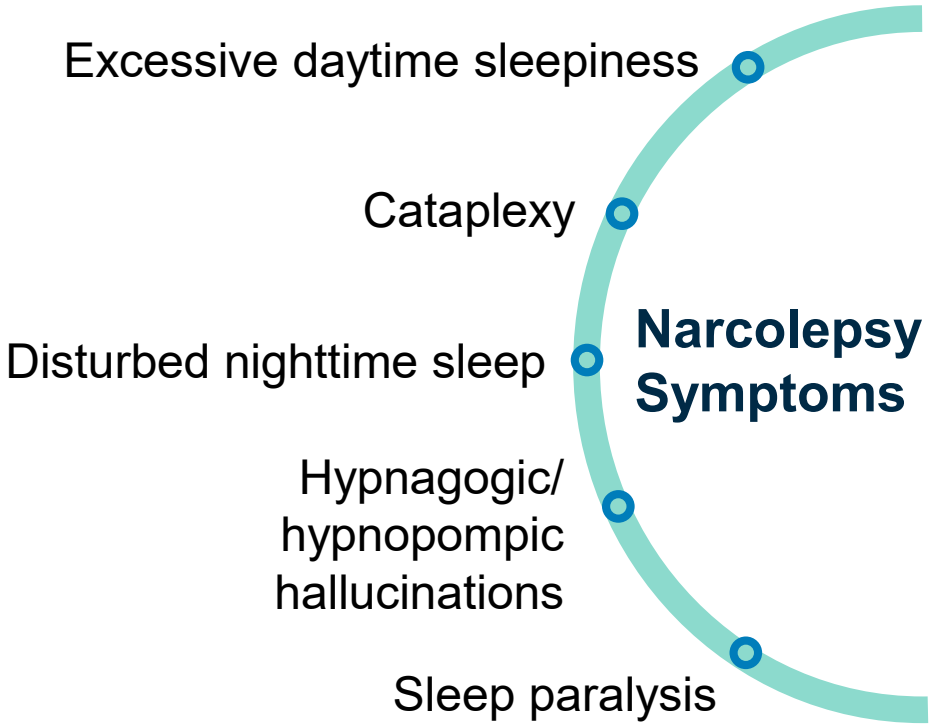
Exploratory Endpoints Were Evaluated During the Double-blind Treatment Period of the Vibrance-1 Phase 2 Study



[a]All patients in the open-label extension period start with 6 mg alixorexton. Dose adjustment possible (up or down) during the first 2 weeks of the optional open-label extension period.
CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS-CT = Narcolepsy Severity Scale – Clinical Trials; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; WCR = Weekly Cataplexy Rate.

Vibrance-1 Study

Narcolepsy Severity Scale for Clinical Trials (NSS-CT) Measures the Severity and Impact of the Core Symptoms of Narcolepsy



- 15 items that assess frequency and impact of symptoms on daily life for the past 7 days[1,2]
- The maximum total score is 57 points; the total score can be categorized into the following levels of severity[1,2]:

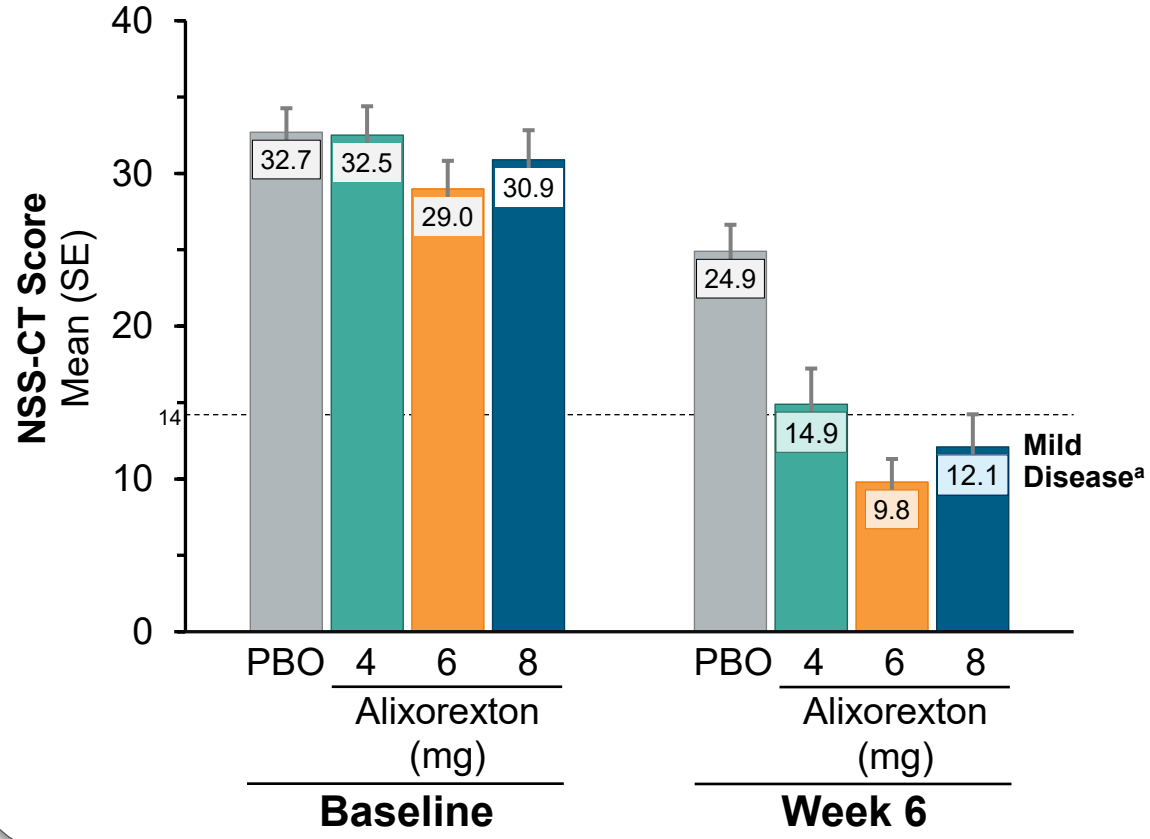
Mild	Moderate	Severe	Very Severe
0-14	15-28	29-42	43-57

- 8 points is the minimum clinically important difference for evaluating treatment response[1]

1. Dauvilliers Y, et al. *Sleep* 2020;43(6):1-11. **2.** Dauvilliers Y, et al. *Neurology* 2017;88(14):1358-1365.

Vibrance-1 Study

Alixorexton Significantly Improved Narcolepsy Symptom Severity in Patients With NT1 from Baseline to Week 6

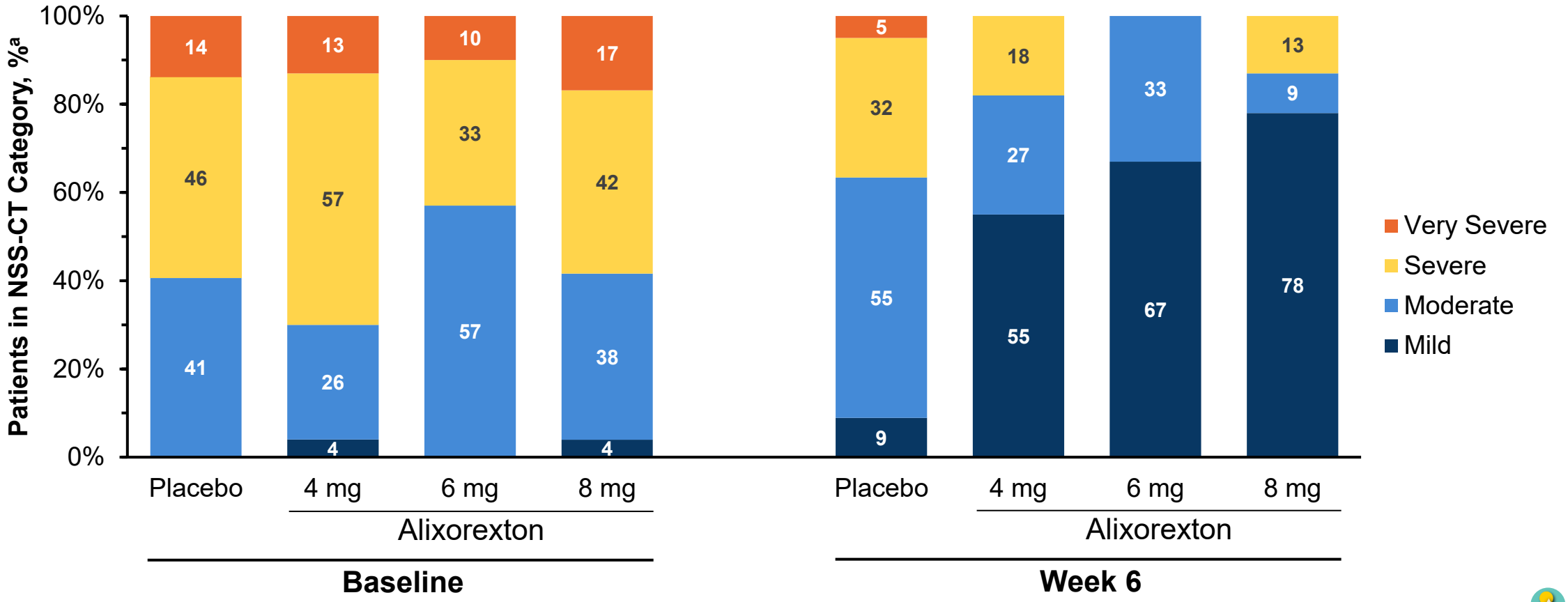


Change from baseline at Week 6 (Exploratory Endpoint)	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	Alixorexton once daily 6 mg (N=22)	Alixorexton once daily 8 mg (N=24)
LSM	**-7.1**	**-16.2**	**-19.5**	**-18.1**
(95% CI of LSM)	(-11.1, -3.0)	(-20.2, -12.1)	(-24.1, -14.8)	(-22.1, -14.0)
LSM difference vs PBO		**-9.1**	**-12.4**	**-11.0**
(95% CI of LSM difference)		(-14.3, -3.9)	(-18.0, -6.7)	(-16.2, -5.8)
***P* value** (nominal)		**0.0008**	**<0.0001**	**<0.0001**

[a]NSS-CT severity ratings: mild, 0-14; moderate, 15-28; severe, 29-42; very severe, 43-57.
CI = confidence interval; LSM = least square means; NSS-CT = Narcolepsy Severity Scale-Clinical Trials; PBO = placebo; SE = standard error.

Vibrance-1 Study

Most Patients on Alixorexton Reported Mild Narcolepsy Severity at Week 6



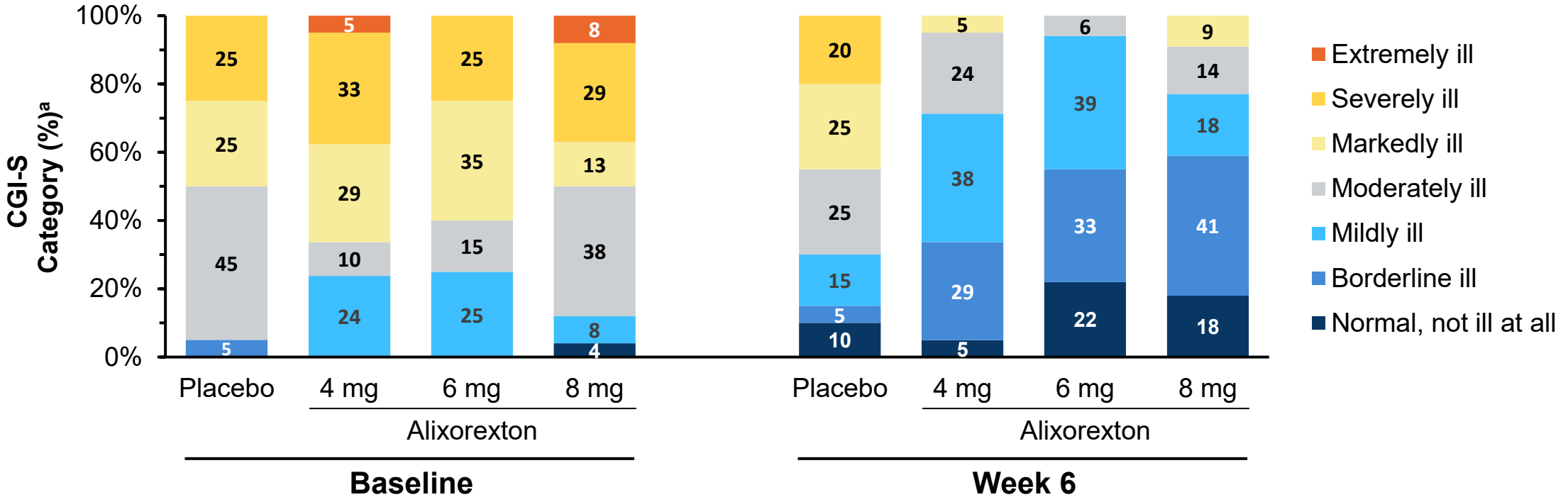
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
NSS-CT = Narcolepsy Severity Scale-Clinical Trials.

Vibrance-1 Study

Clinicians Rated Patients on Alixorexton as Having Less Severe Symptoms on CGI-S at Week 6 Compared to Placebo and Baseline

CGI-S

A single-item, **clinician-reported** assessment to evaluate the patient's current severity of illness on a 7-point Likert scale



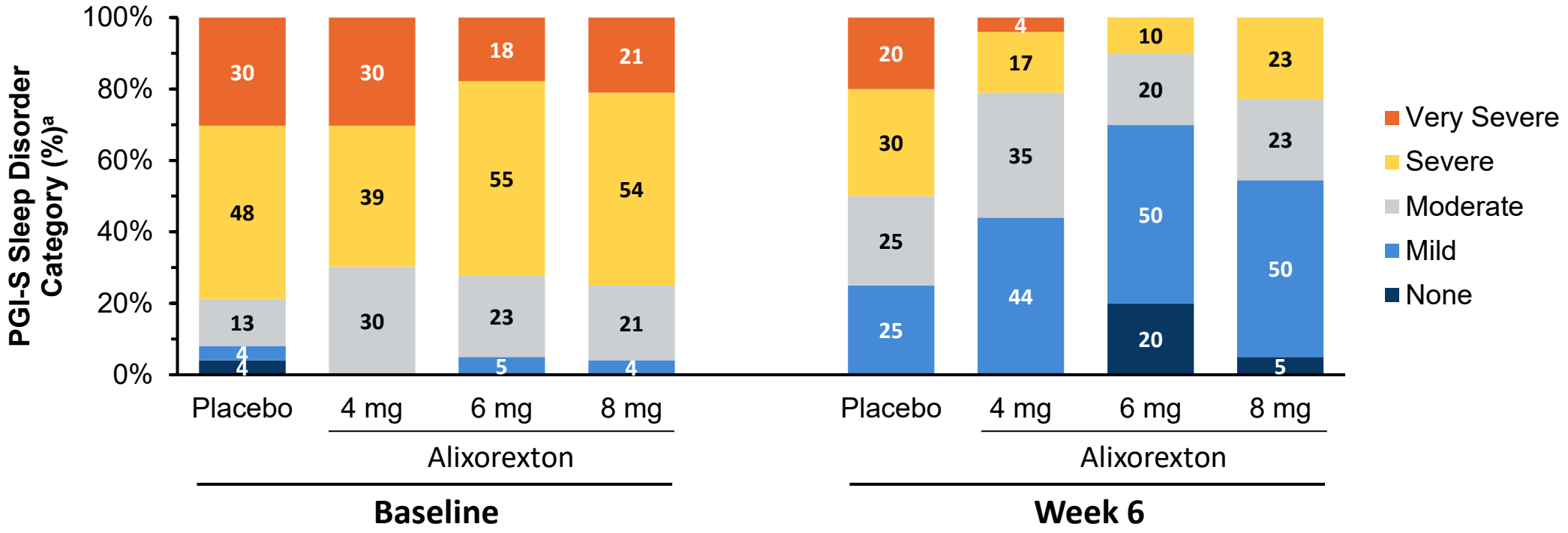
At week 6, all doses were significantly different from placebo (P = 0.0145 at 4 mg, P = 0.0001 at 6 mg, and P = 0.0011 at 8 mg, all nominal).
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
CGI-S = Clinical Global Impression of Severity.

Vibrance-1 Study

Patients on Alixorexton Reported Less Severe Disease on PGI-S at Week 6 Compared to Placebo and Baseline

PGI-S Sleep Disorder

A single-item, **patient-reported** assessment on the severity of their sleep disorder over the past 7 days on a scale of 0 to 4



At week 6, the 6 mg and the 8 mg dose were significantly different from placebo (P = 0.0006 and P =.0287, respectively, both nominal). For the 4 mg dose, nominal P value = 0.0633.
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
PGI-S = Patient Global Impression of Severity.

Vibrance-1 Study

Fatigue Is a Persistent, Severe, and Debilitating Unmet Need That Impacts the Lives of Patients With Narcolepsy

- Most narcolepsy patients experience fatigue, which often persists even with treatment[1-3]
- Fatigue negatively affects patients' mental health, functional outcomes and overall quality of life[4]

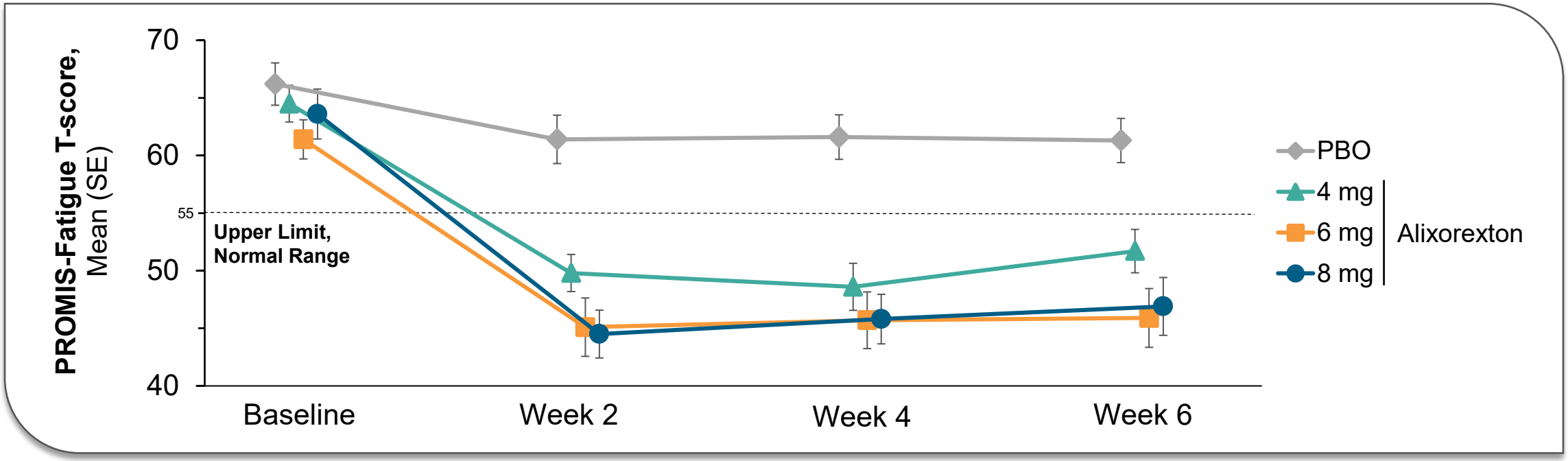
Commonly Used and Established Patient-reported Measures Specific to Fatigue

PROMIS-Fatigue 6a Short Form	• A 6-item questionnaire scored on a 5-point Likert scale assessing the severity of fatigue in the past 7 days • Items are scored and transformed to T-scores, ranging from 33.4 to 76.8 • Scores less than 55 are considered normal, while scores ≥70 are considered severe
PGI-S Fatigue	• A single item assessing patient-reported severity of fatigue over the past 7 days with scale responses of none, mild, moderate, severe, or very severe

PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System.

1. AASM 2023. International Classification of Sleep Disorders – Third Edition: Text Revision, Darien, IL. **2.** Maski K, et al. *J Clin Sleep Med* 2017;13(3):419-425. **3.** Doane M, et al. Poster presented at Psych Congress 2023. **4.** Droogleever F, et al. *Sleep*, 21(2), 163-169.

Alixorexton Significantly Reduced PROMIS-Fatigue Scores from Baseline to Week 6 in Patients With NT1

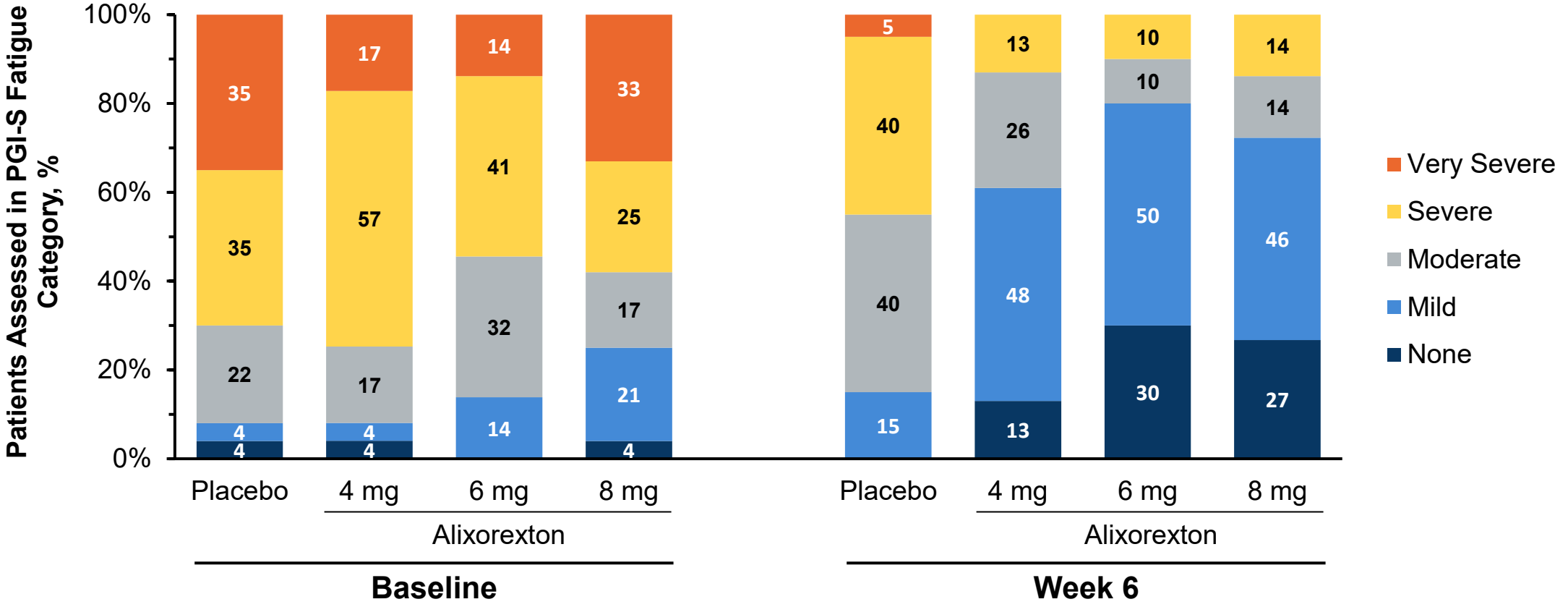


Change from baseline at Week 6 (Exploratory endpoint)	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
LSM (95% CI of LSM)	**-3.3** (-7.5, 0.8)	**-12.1** (-16.2, -7.9)	**-15.7** (-20.0, -11.4)	**-16.2** (-20.4, -12.1)
LSM difference vs PBO (95% CI of LSM difference)		**-8.7** (-14.1, -3.3)	**-12.4** (-17.9, -6.8)	**-12.9** (-18.3, -7.5)
***P* value** (Nominal)		**0.0018**	**<0.0001**	**<0.0001**

CI = confidence interval; LSM = least square means; PBO = placebo; PROMIS = Patient Reported Outcomes Measurement Information System; SE = standard error.

Vibrance-1 Study

Patients on Alixorexton Reported Less Fatigue on PGI-S at Week 6 Compared to Placebo and Baseline



At week 6, all doses were significantly different from placebo (P = 0.0019 for the 4 mg dose, P = 0.0003 for the 6 mg dose, and P = 0.0005 for the 8 mg dose, all nominal).
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
PGI-S = Patient Global Impression of Severity.

Vibrance-1 Study

Conclusions

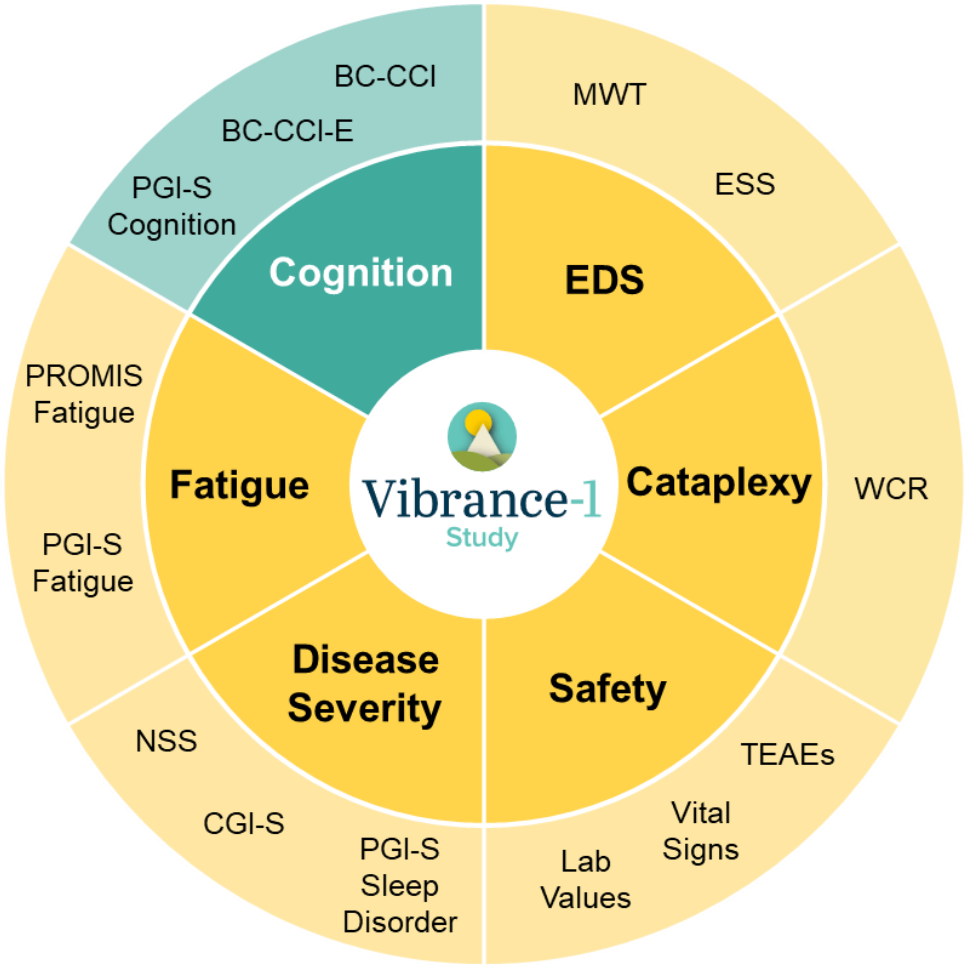
Alixorexton demonstrated statistically significant, clinically meaningful improvements on established scales:

- Clinician- and patient-reported severity of narcolepsy symptoms
  - NSS-CT, PGI-S Sleep Disorder, and CGI-S
- Patient-reported fatigue
  - PROMIS-Fatigue and PGI-S Fatigue

Alixorexton is the first orexin 2 receptor agonist demonstrating normalized fatigue scores in addition to clinically meaningful improvements in severity of symptoms in patients with NT1

Vibrance-1 Study

Alixorexton May Address Many of the Clinical Needs of Patients with NT1, Including Overall Disease Severity and Fatigue



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Acknowledgments

The authors would like to thank:

- The patients
- Their families and caregivers
- Vibrance-1 investigators and their staff

Funding provided by Alkermes

Improvement in Patient-reported Cognitive Functioning in Patients with Narcolepsy Type 1 Treated With the Orexin 2 Receptor Agonist Alixorexton (ALKS 2680)

Vibrance-1 Study

Giuseppe Plazzi,[1] Yves Dauvilliers,[2] Ronald R. Grunstein,[3] Emmanuel Mignot,[4] Gert Jan Lammers,[5] David T. Plante,[6] Erik Buntinx,[7] Rafael del Río Villegas,[8] Hailu Chen,[9] Craig Hopkinson,[9] Bhaskar Rege,[9] Marcus Yountz,[9] and Michael J. Doane[9]

[1]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; [2]University of Montpellier, INSERM Institute for Neurosciences of Montpellier, Montpellier, France; [3]Woolcock Institute of Medical Research, Macquarie University, Sydney, Australia; [4]Stanford Center for Sleep Sciences and Medicine, Stanford University School of Medicine, Stanford, CA, USA; [5]Leiden University Medical Center, Leiden, the Netherlands and Stichting Epilepsie Instellingen Nederland, Sleep-Wake Centre, Heemstede, the Netherlands; [6]University of Wisconsin-Madison, School of Medicine and Public Health, Madison, WI, USA; [7]ANIMA Research, Alken, Belgium; [8]Universidad CEU San Pablo, CEU Universities, Vithas Madrid Hospitals Madrid, Spain; [9]Alkermes, Inc., Waltham, MA, USA

World Sleep Congress | September 5 – 10, 2025

Financial Relationship Disclosure

Singapore 2025 WORLD SLEEP September 5-10

Ineligible companies are those whose primary business is producing, marketing, selling, re-selling, or distributing health care products used by, or on patients.

☐ **No**, I HAVE NOT had a financial relationship with an ineligible company in the past 24 months.
☑ **Yes**, I HAVE had a financial relationship with an ineligible company in the past 24 months.

Relationship type	**Name of company**
Institutional funding	Alkermes (R. Grunstein, Y. Dauvilliers); Lilly (R. Grunstein); Takeda (R. Grunstein); Vanda (R. Grunstein)
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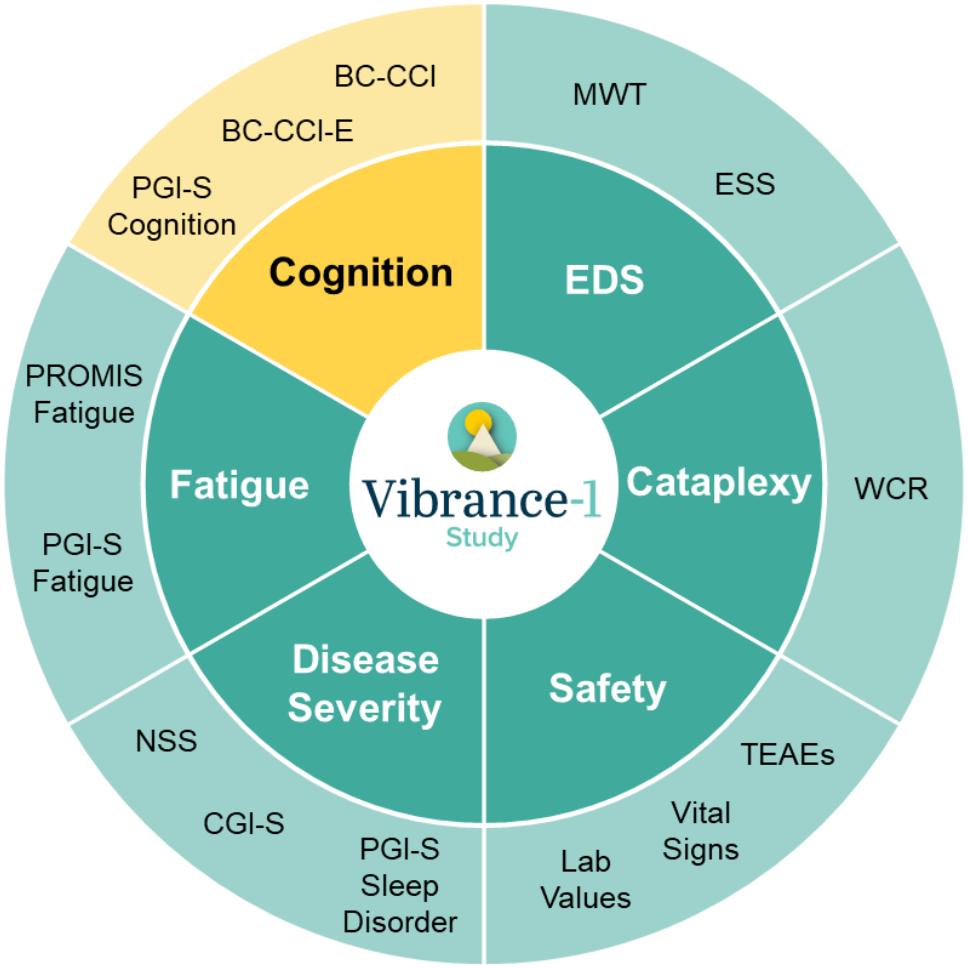
Vibrance-1 Examined the Effects of Alixorexton on Cognitive Impairment in Patients With NT1



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Cognitive Impairment is Among the Most Common and Disruptive Symptoms Reported by People With Narcolepsy

- Beyond sleepiness and cataplexy, people with narcolepsy frequently report experiencing cognitive impairment and overall "brain fog"[1-3]
- There are negative impacts of cognitive impairment across individuals' lives, including to school/work, relationships, risk of accidents, and quality of life[2-5]
- Cognitive impairment may persist even when excessive daytime sleepiness is adequately controlled[4,6]

Patients Describe Negative Impacts Across:

Memory

Problem Solving

Attention

Processing Speed

Word Finding

Expressing Thoughts

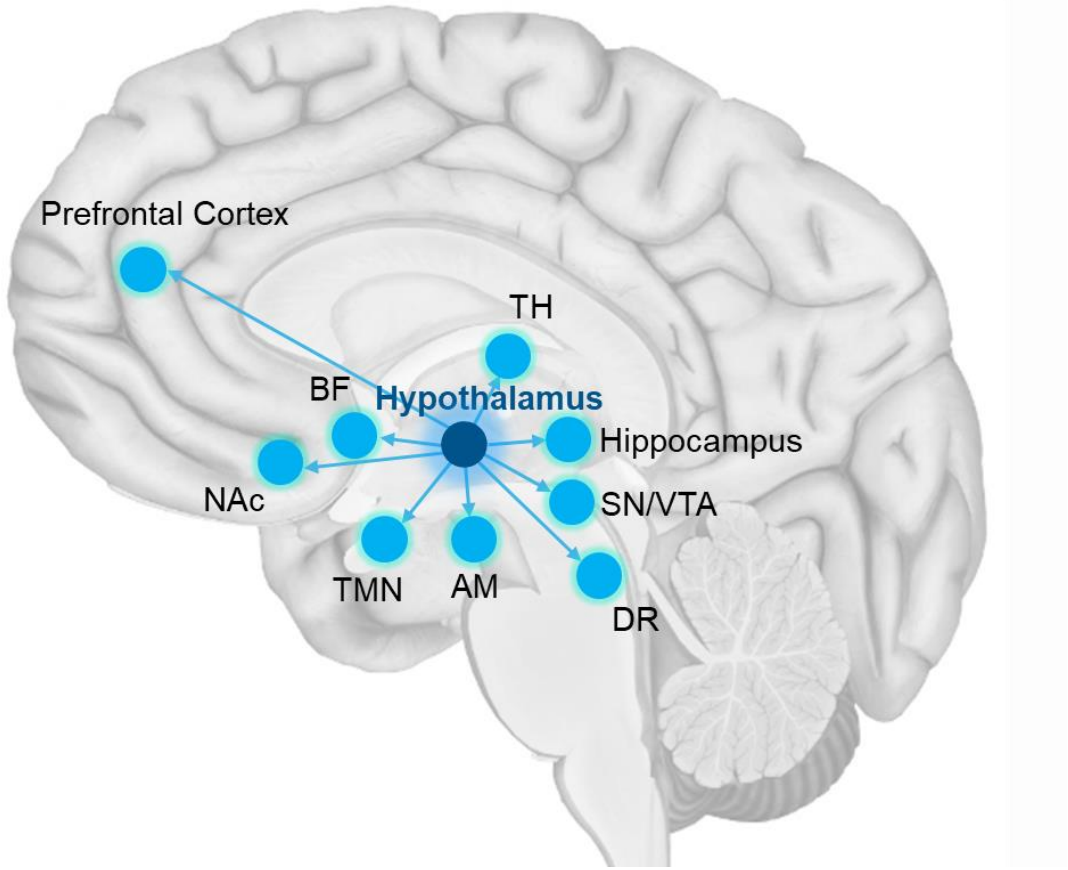
1. Cano C, et al. *Sleep.* 2024;47(9):zsae150. **2.** Doane M, et al. Poster presented at US Psych 2023. **3.** Maski K, et al. *J Clin Sleep Med.* 2017;13(3):419-425. **4.** Harel B et al. *Sleep Advances.* 2024; 26;5(1):zpae043. **5.** Blackwell J, et al. *Sleep Medicine Reviews.* 2017;34:82-93. **6.** Winter Y, et al. Poster presented at APSS 2024.

OX2R Agonism May Enhance Cognition by Activating Receptors Expressed Throughout Cognitive Circuitry

Orexin pathway

Originates in hypothalamus and engages distributed neuronal circuitry

Promotes adaptive behavioral responses



1. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. **2.** Sakurai T. *Nat Rev Neurosci.* 2007;8(3):171-181. **3.** Alexandre C, et al. *Curr Opin Neurobiol.* 2013;23(5):752-759. **4.** Sarter M, et al. *Brain Res Rev.* 2006;51(2):145-160. **5.** Katzman MA, et al. *Brain Sci.* 2022;12(2):150.

AM = amygdala; BF = basal forebrain; DR = dorsal raphe; NAc = nucleus accumbens; OX2R = orexin 2 receptor; SN = substantia nigra; TH = thalamus; TMN = tuberomammillary nucleus; VTA = ventral tegmental area.

OX2R Agonism May Enhance Cognition by Activating Receptors Expressed Throughout Cognitive Circuitry

Orexin pathway

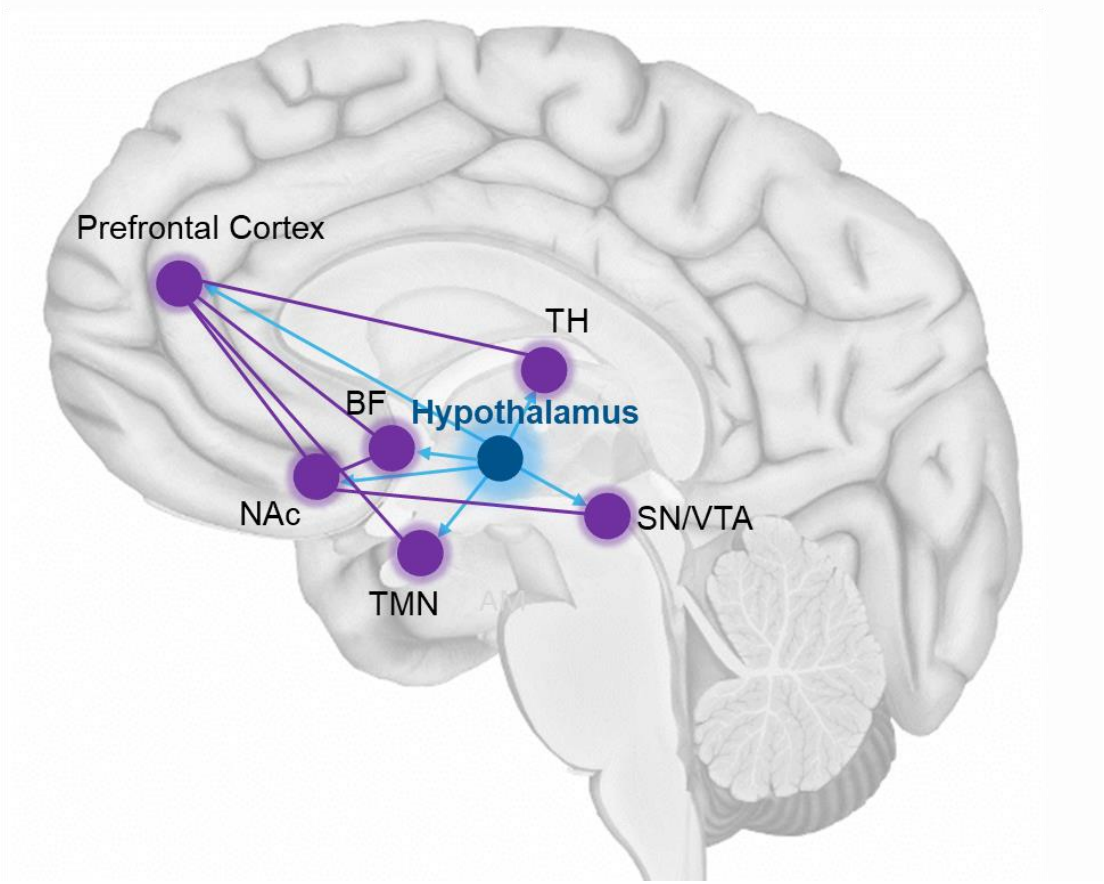
Originates in hypothalamus and engages distributed neuronal circuitry

Promotes adaptive behavioral responses

Attention Pathway

Cortical, sensory, and basal ganglia circuitry receives orexin neuron projections and expresses orexin 2 receptors

Important for vigilance, signal processing and goal-directed behavior



1. Marcus JN, et al. *J Comp Neurol*. 2001;435(1):6-25. **2.** Sakurai T. *Nat Rev Neurosci.* 2007;8(3):171-181. **3.** Alexandre C, et al. *Curr Opin Neurobiol.* 2013;23(5):752-759. **4.** Sarter M, et al. *Brain Res Rev.* 2006;51(2):145-160. **5.** Katzman MA, et al. *Brain Sci.* 2022;12(2):150.

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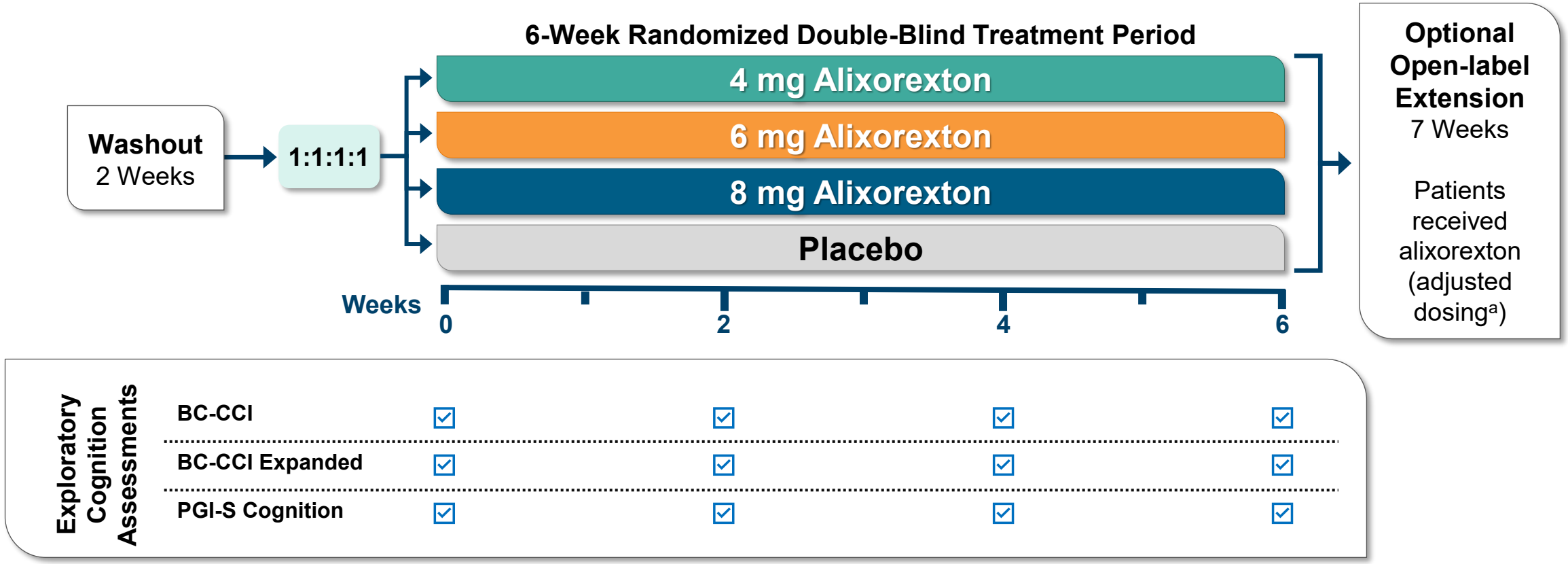
Exploratory Endpoints Were Evaluated During the Double-blind Treatment Period of the Vibrance-1 Phase 2 Study



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BC-CCI = British Columbia Cognitive Complaints Inventory; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; PGI-S = Patient Global Impression of Severity; WCR = Weekly Cataplexy Rate.

Vibrance-1 Study

BC-CCI Assesses the Severity and Impact of Cognitive Impairment From the Patient's Perspective

Cognitive Impairment

Perceived Severity

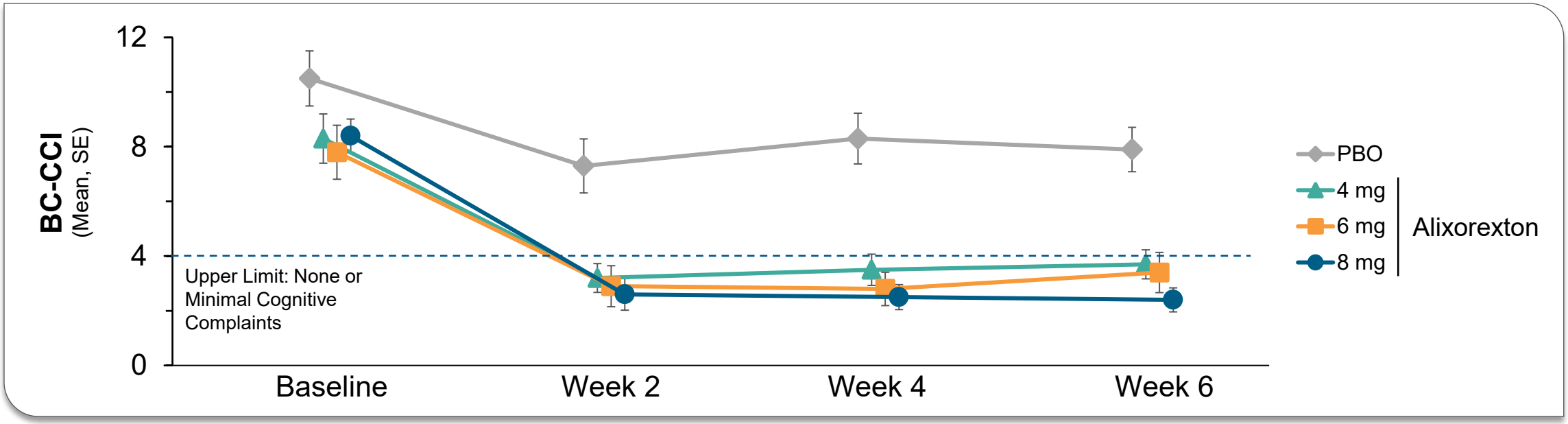
Items include:

- Forgetfulness/memory problems
- Poor concentration
- Trouble expressing thoughts
- Trouble finding the right word
- Slow thinking speed
- Trouble figuring things out or solving problems

Rating Categories	
Severe	15 – 18
Moderate	9 – 14
Mild	5 – 8
None or Minimal	0 – 4

BC-CCI = British Columbia Cognitive Complaints Inventory.

Alixorexton Significantly Reduced Severity of Cognitive Impairment on the BC-CCI From Baseline to Week 6

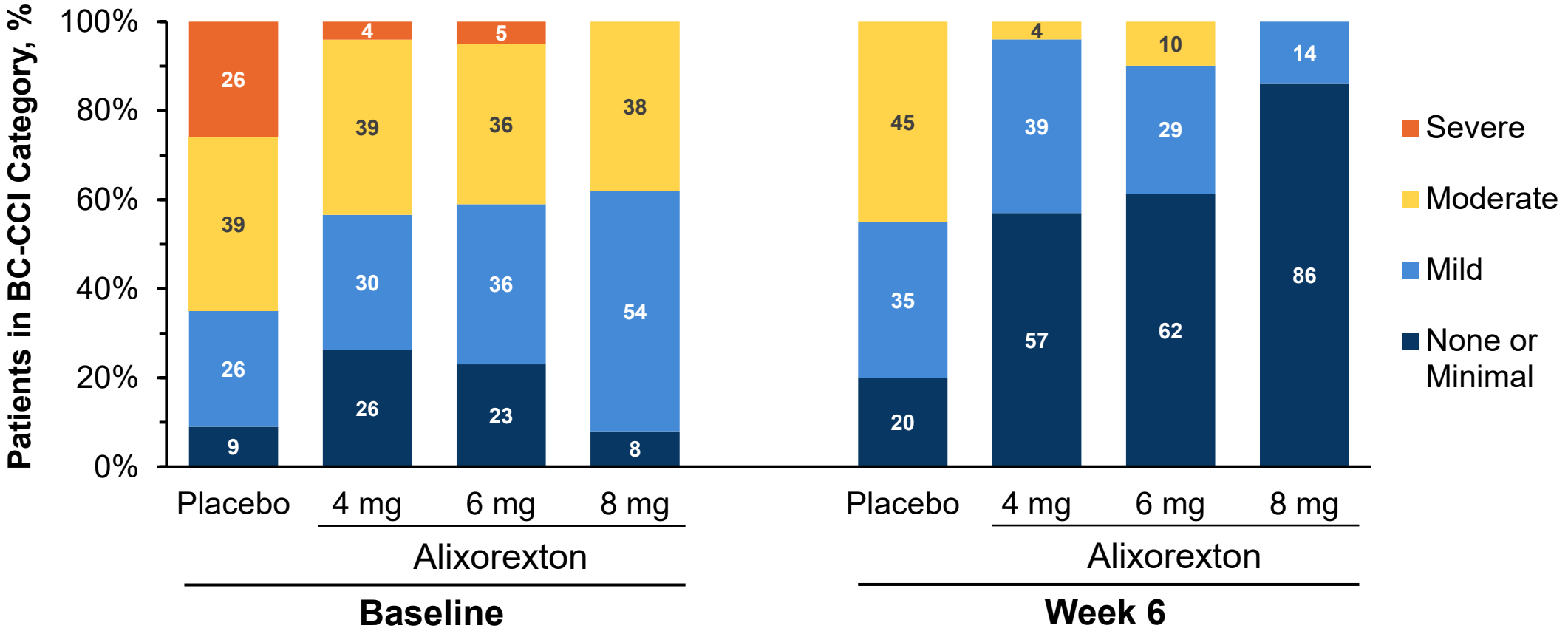


Change from baseline at Week 6 (Exploratory endpoint)	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
Baseline, mean (SD)	**10.5** (4.8)	**8.3** (4.3)	**7.8** (4.6)	**8.4** (3.0)
LSM (95% CI of LSM)	**-1.2** (-2.4, 0.0)	**-4.7** (-5.9, -3.5)	**-4.9** (-6.2, -3.7)	**-6.0** (-7.3, -4.8)
LSM difference vs PBO (95% CI of LSM difference)		**-3.5** (-5.1, -1.9)	**-3.7** (-5.4, -2.1)	**-4.8** (-6.4, -3.2)
***P* value** (Nominal)		**<0.0001**	**<0.0001**	**<0.0001**

BC-CCI = British Columbia Cognitive Complaints Inventory; CI = confidence interval; LSM = least squares means; PBO = placebo; SD = standard deviation; SE = standard error.

Vibrance-1 Study

Most Patients on Alixorexton Reported No or Minimal Cognitive Impairment on the BC-CCI at Week 6



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Vibrance-1 Study

BC-CCI Assesses the Severity and Impact of Cognitive Impairment From the Patient's Perspective

Cognitive Impairment

Perceived Severity

Items include:

- Forgetfulness/memory problems
- Poor concentration
- Trouble expressing thoughts
- Trouble finding the right word
- Slow thinking speed
- Trouble figuring things out or solving problems

Rating Categories	
Severe	15 – 18
Moderate	9 – 14
Mild	5 – 8
None or Minimal	0 – 4

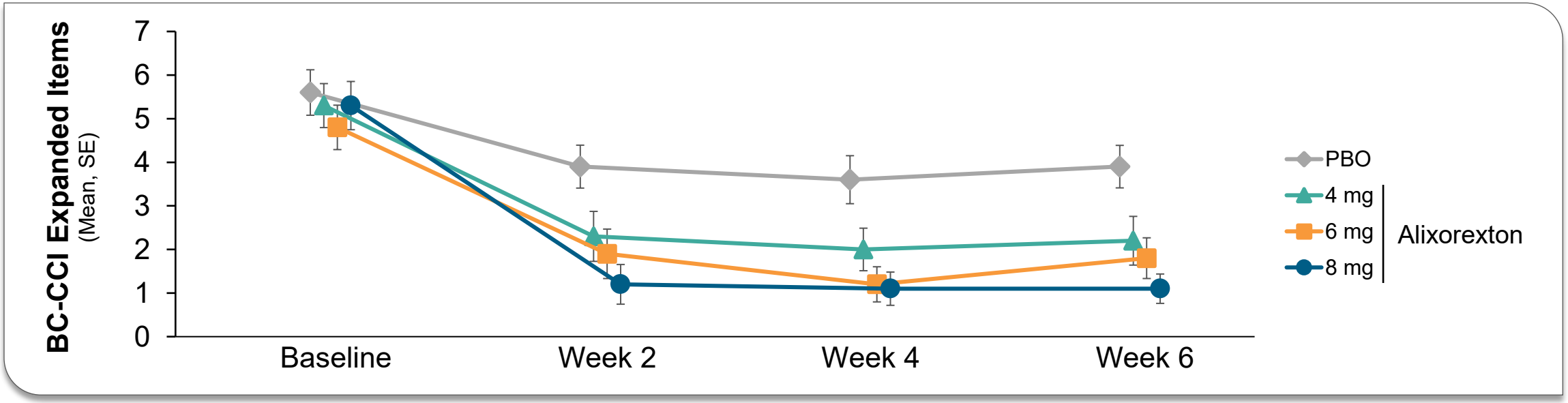
Perceived Impact

Expanded version assesses difficulty with:

- Job
- Relationships with friends and family
- Social activities, recreational activities, or hobbies

BC-CCI = British Columbia Cognitive Complaints Inventory.

Alixorexton Significantly Reduced the Impact of Cognitive Impairment on NT1 Patients From Baseline to Week 6



Change from baseline at Week 6 (Exploratory endpoint)	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
Baseline, mean (SD)	**5.6** (2.5)	**5.3** (2.4)	**4.8** (2.4)	**5.3** (2.7)
LSM (95% CI of LSM)	**-1.1** (-1.9, -0.2)	**-2.8** (-3.6, -1.9)	**-3.0** (-3.9, -2.1)	**-3.8** (-4.6, -2.9)
LSM difference vs PBO (95% CI of LSM difference)		**-1.7** (-2.8, -0.6)	**-1.9** (-3.0, -0.8)	**-2.7** (-3.8, -1.6)
***P* value** (Nominal)		**0.0034**	**0.001**	**<0.0001**

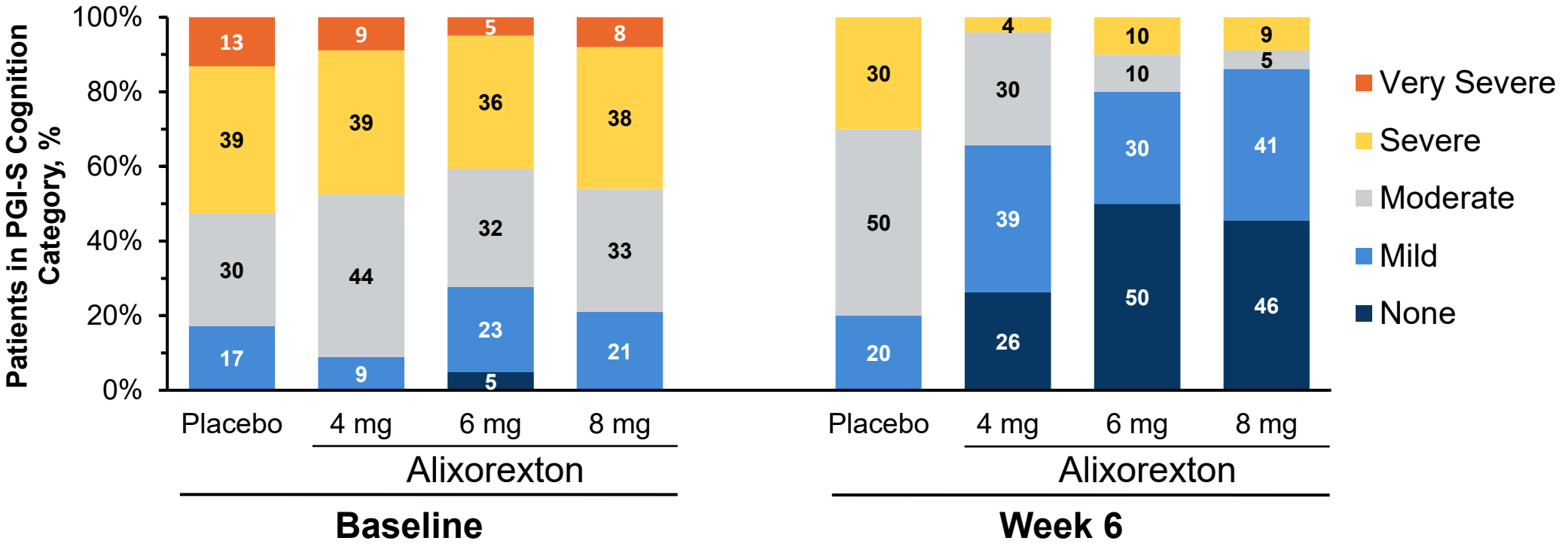
Vibrance-1 Study

BC-CCI = British Columbia Cognitive Complaints Inventory; CI = confidence interval; LSM = least squares means; PBO = placebo; SD = standard deviation; SE = standard error.

Most Patients Treated with Alixorexton Reported Mild or No Cognitive Impairment on PGI-S Cognition at Week 6

PGI-S Cognition

Single-item, patient-reported assessment of problems with concentration, memory, and thinking skills during past 7 days



At week 6, all doses of alixorexton were significantly different from placebo ($P = 0.0015$ for the 4 mg dose, $P = 0.0004$ for the 6 mg dose, and $P < 0.0001$ for the 8 mg dose, all nominal).
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
PGI-S = Patient Global Impression of Severity.

Vibrance-1 Study

Conclusions

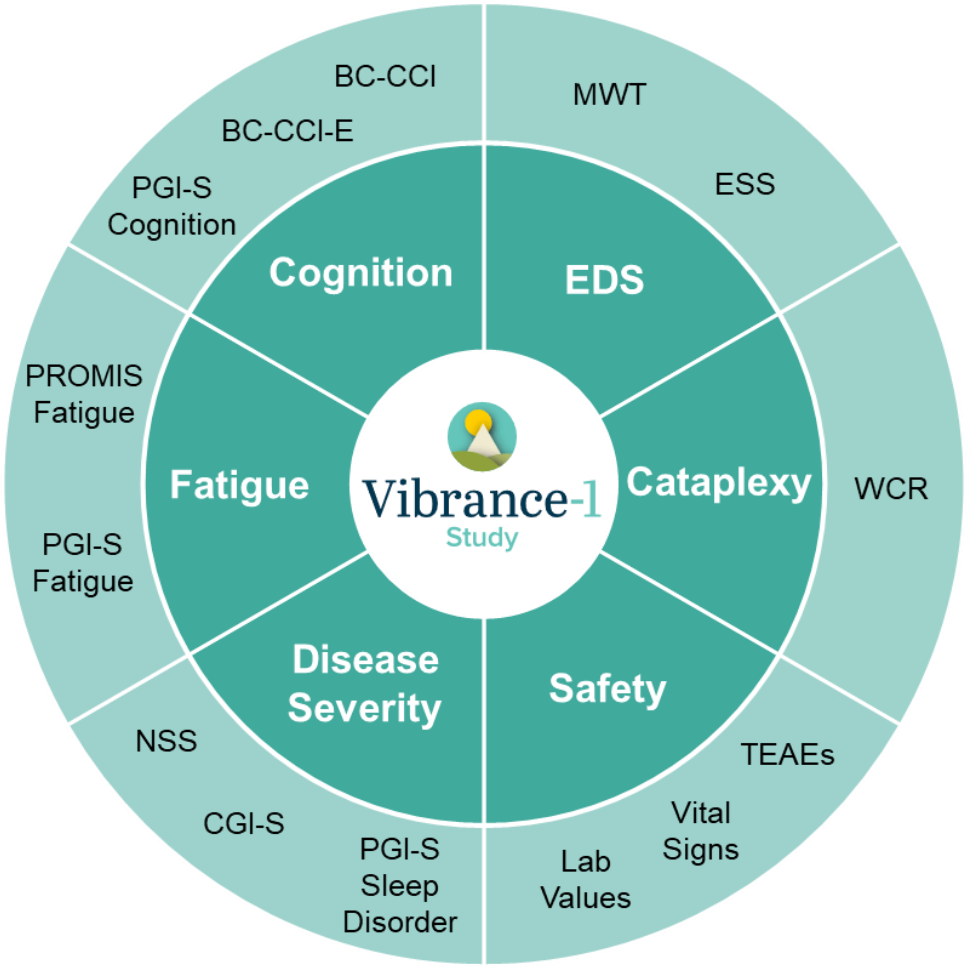
Alixorexton demonstrated statistically significant and clinically meaningful improvements from baseline on established measures evaluating the severity and impact of cognitive impairment in patients with NT1

- BC-CCI: improvements observed on overall patient-reported outcome measure encompassing a range of cognitive domains
  - Severity: memory, attention, word finding, problem solving, processing speed, and expressing thoughts
  - Impact: work, relationships and daily activities (expanded items)
- PGI-S: findings of patient-reported severity consistent with BC-CCI

Alixorexton is the first OX2R agonist to demonstrate normalization of cognitive functioning on patient-reported scales in the NT1 population

Vibrance-1 Study

Vibrance-1 Examined the Effects of Alixorexton on Measures Relevant to the Clinical Needs of Patients With NT1



BC-CCI = British Columbia Cognitive Complaints Inventory; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Expanded; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS = Narcolepsy Severity Scale; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

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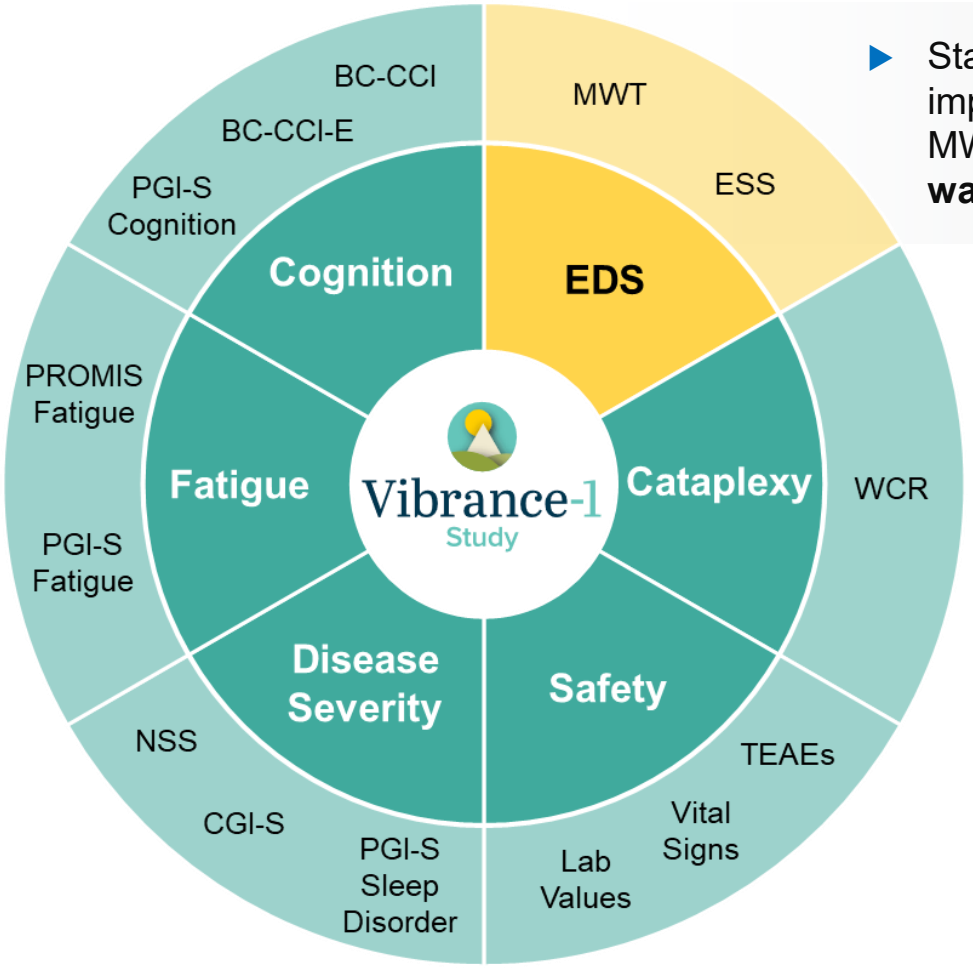

- Statistically significant, clinically meaningful improvements compared to placebo on the MWT and ESS, achieving a **normative wakefulness profile**

BC-CCI = British Columbia Cognitive Complaints Inventory; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Expanded; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS = Narcolepsy Severity Scale; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

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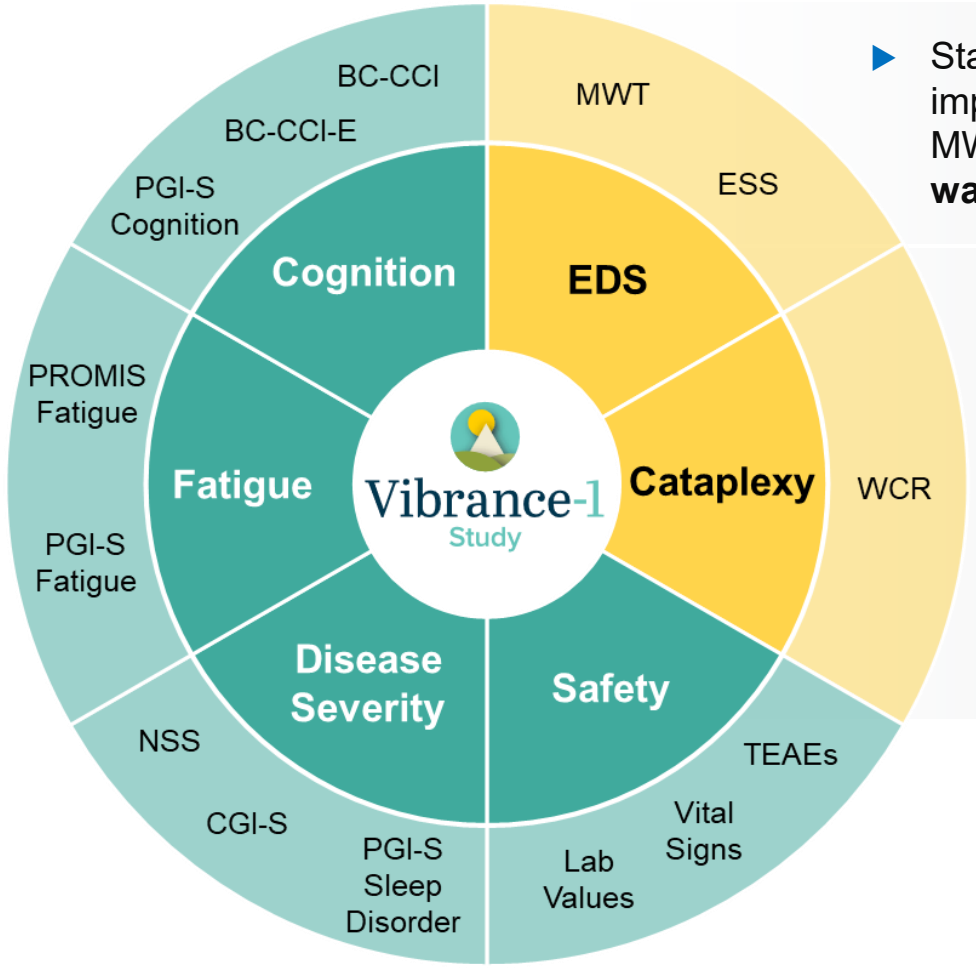

- Statistically significant, clinically meaningful improvements compared to placebo on the MWT and ESS, achieving a **normative wakefulness profile**
- Clinically meaningful improvement in **WCR** at all doses compared to placebo, with statistical significance achieved at the 6 mg dose

BC-CCI = British Columbia Cognitive Complaints Inventory; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Expanded; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS = Narcolepsy Severity Scale; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

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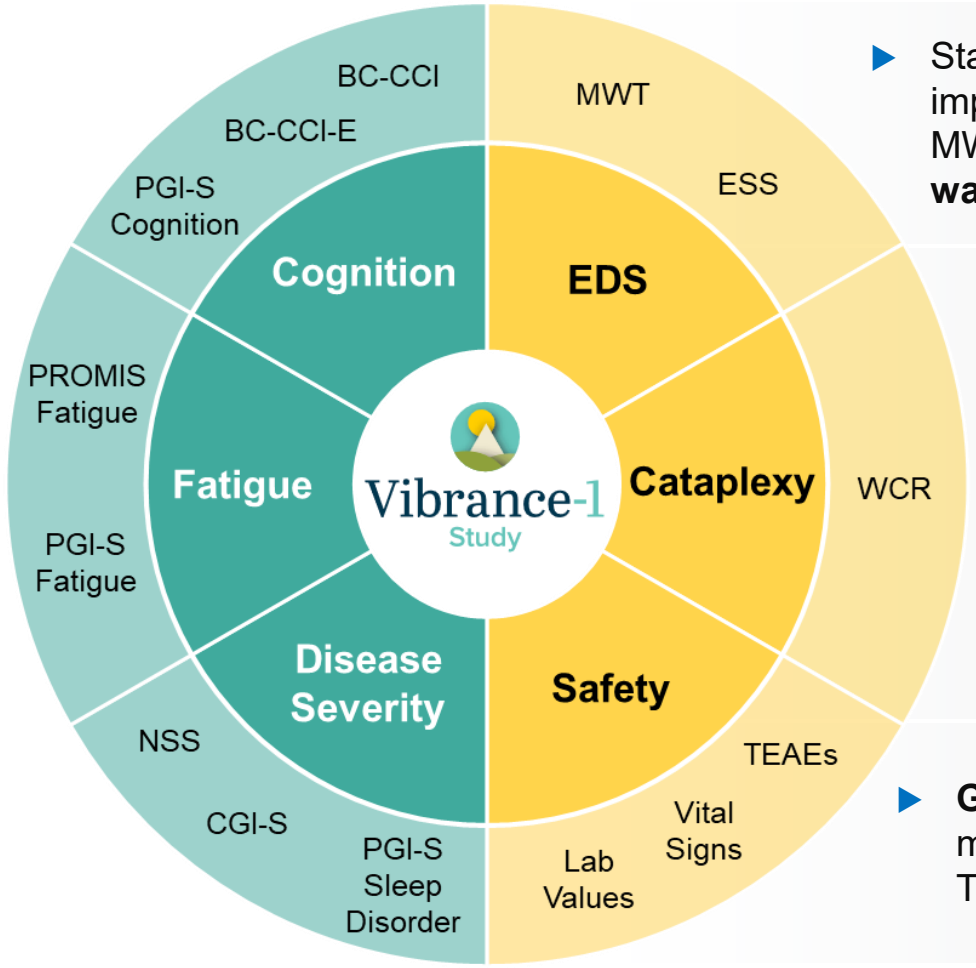

- Statistically significant, clinically meaningful improvements compared to placebo on the MWT and ESS, achieving a **normative wakefulness profile**
- Clinically meaningful improvement in **WCR** at all doses compared to placebo, with statistical significance achieved at the 6 mg dose
- **Generally well tolerated**, with most TEAEs mild to moderate in severity and no serious TEAEs reported

BC-CCI = British Columbia Cognitive Complaints Inventory; BC-CCI-E = British Columbia Cognitive Complaints Inventory – Expanded; CGI-S = Clinical Global Impression of Severity; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NSS = Narcolepsy Severity Scale; PGI-S = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; TEAE = treatment-emergent adverse event; WCR = weekly cataplexy rate.

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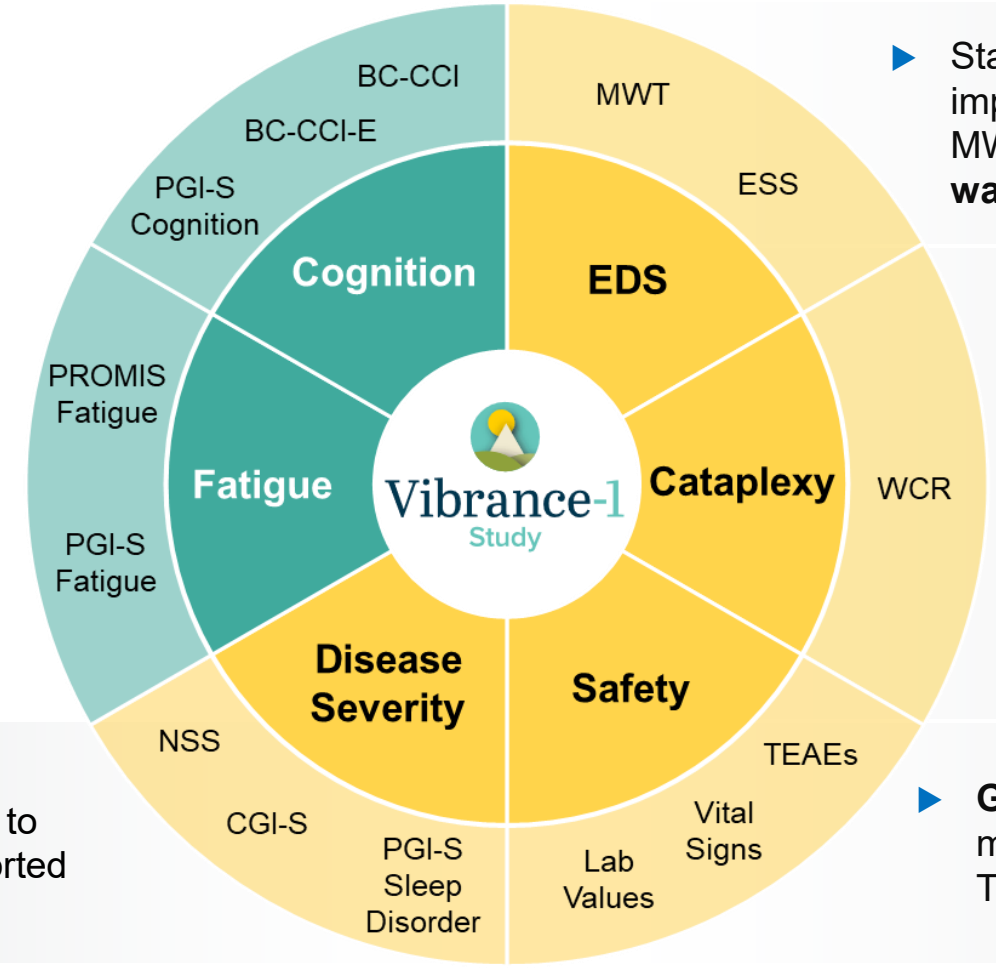

- Statistically significant, clinically meaningful improvements compared to placebo on the MWT and ESS, achieving a **normative wakefulness profile**
- Clinically meaningful improvement in **WCR** at all doses compared to placebo, with statistical significance achieved at the 6 mg dose
- Statistically significant, clinically meaningful improvements compared to placebo on patient-and clinician-reported **narcolepsy symptom severity**
- **Generally well tolerated**, with most TEAEs mild to moderate in severity and no serious TEAEs reported

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Vibrance-1 Examined the Effects of Alixorexton on Measures Relevant to the Clinical Needs of Patients With NT1

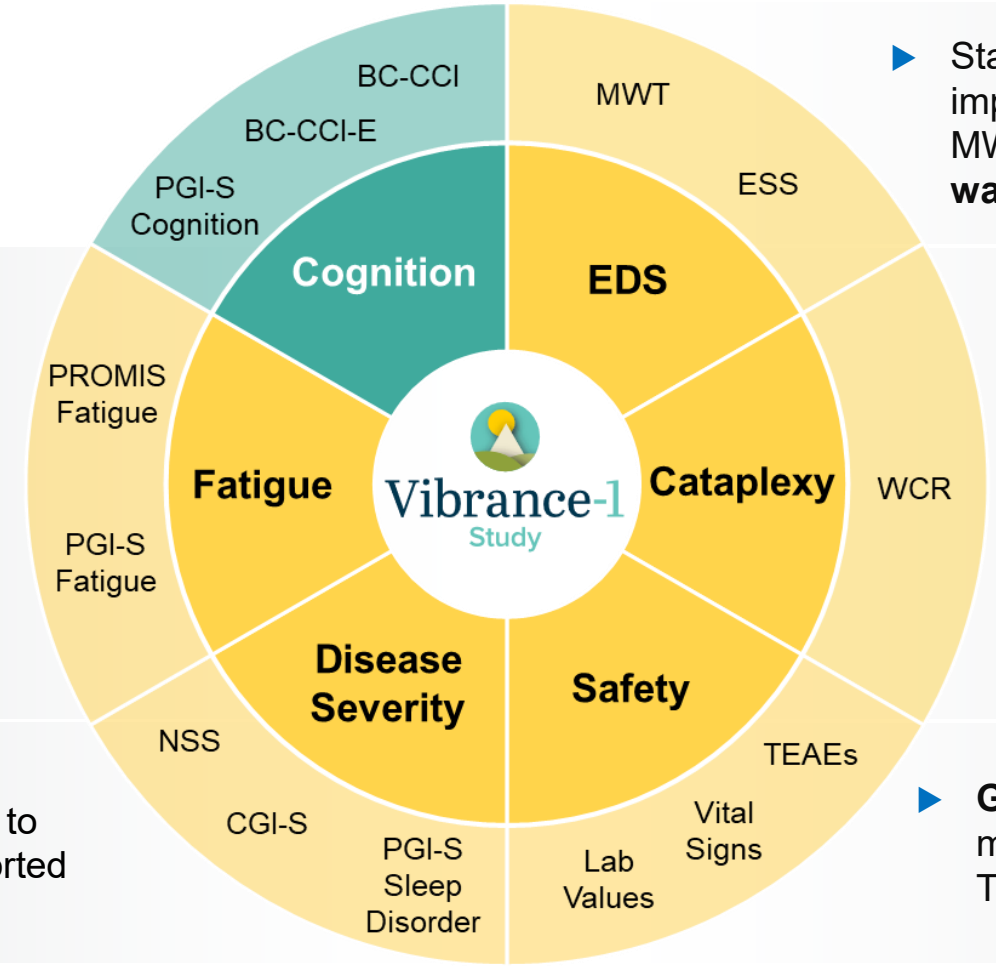
- Statistically significant, clinically meaningful improvements compared to placebo on the MWT and ESS, achieving a **normative wakefulness profile**

- Statistically significant, clinically meaningful improvements on two established **patient-reported fatigue** scales compared to placebo

- Clinically meaningful improvement in **WCR** at all doses compared to placebo, with statistical significance achieved at the 6 mg dose

- Statistically significant, clinically meaningful improvements compared to placebo on patient-and clinician-reported **narcolepsy symptom severity**

- **Generally well tolerated**, with most TEAEs mild to moderate in severity and no serious TEAEs reported



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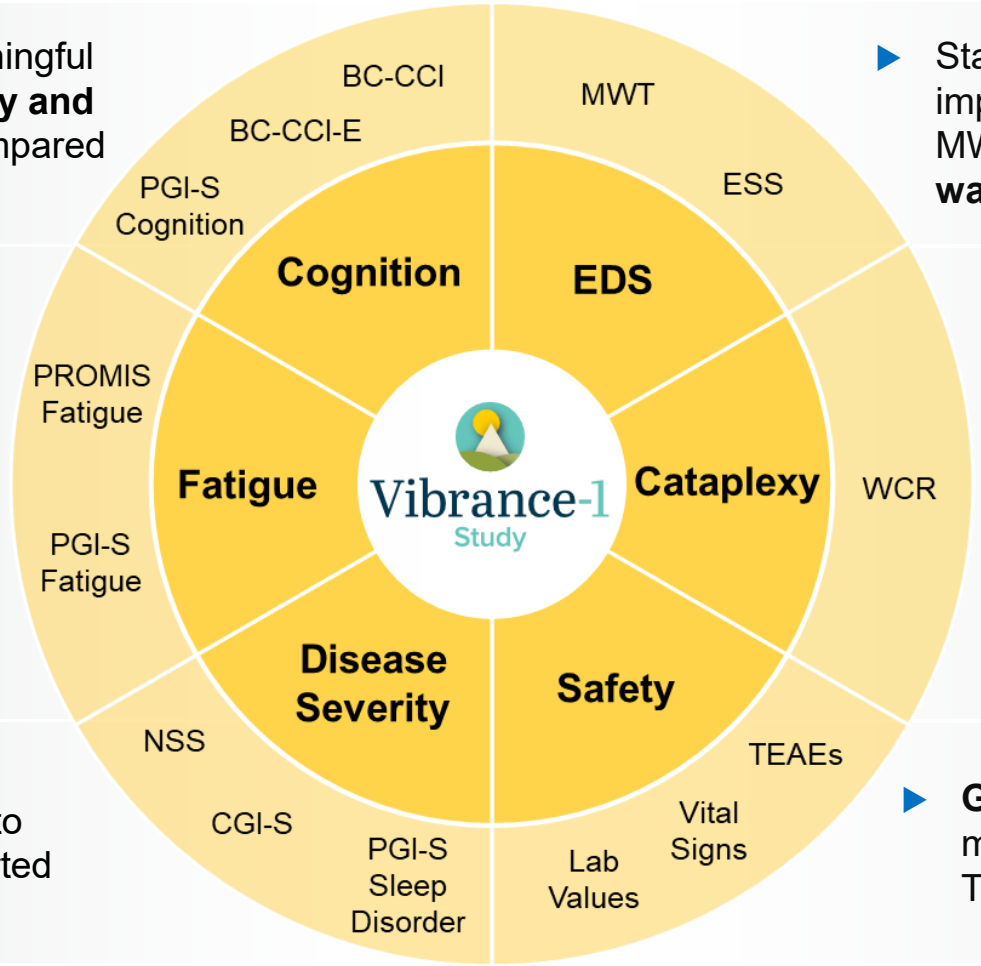
Vibrance-1 Examined the Effects of Alixorexton on Measures Relevant to the Clinical Needs of Patients With NT1

- Statistically significant, clinically meaningful reduction in **patient-reported severity and impact of cognitive impairment** compared to placebo

- Statistically significant, clinically meaningful improvements on two established **patient-reported fatigue** scales compared to placebo

- Statistically significant, clinically meaningful improvements compared to placebo on patient-and clinician-reported **narcolepsy symptom severity**



- Statistically significant, clinically meaningful improvements compared to placebo on the MWT and ESS, achieving a **normative wakefulness profile**

- Clinically meaningful improvement in **WCR** at all doses compared to placebo, with statistical significance achieved at the 6 mg dose

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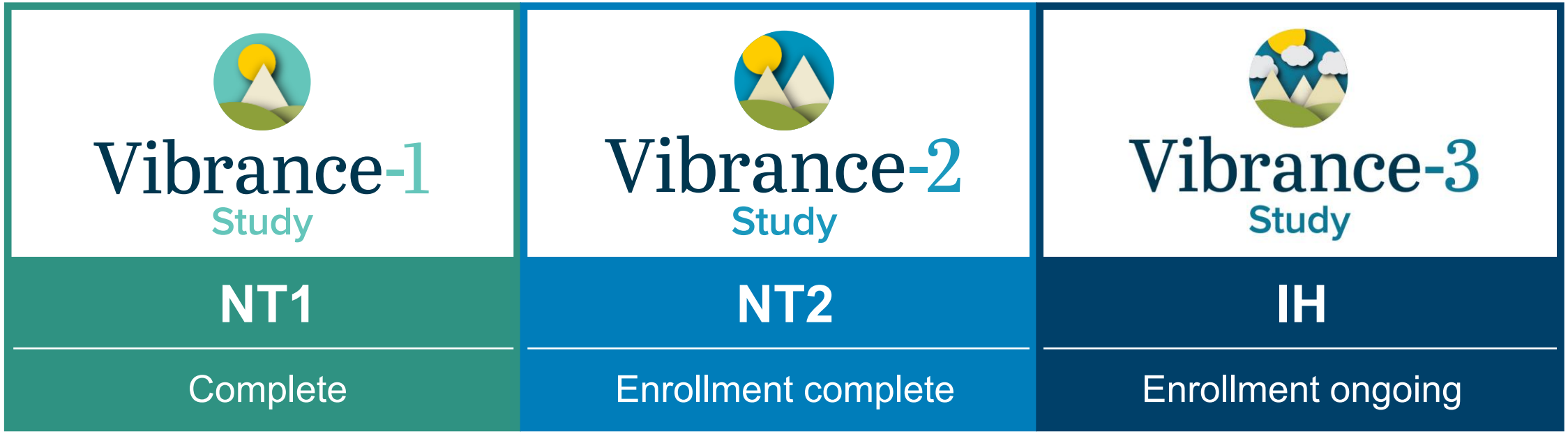
Once-daily Alixorexton Is Being Evaluated in NT1, NT2, and IH



Results from Vibrance-1 will inform dose selection for the global phase 3 development program in patients with NT1

1. Alkermes, Inc. NCT06358950 (Vibrance-1). https://clinicaltrials.gov/study/NCT06358950. **2.** Alkermes, Inc. NCT06555783 (Vibrance-2). https://www.clinicaltrials.gov/study/NCT06555783. **3.** Alkermes, Inc. NCT06843590 (Vibrance-3). https://clinicaltrials.gov/study/NCT06843590.
NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; IH = idiopathic hypersomnia.

Acknowledgments

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- The patients
- Their families and caregivers
- Vibrance-1 investigators and their staff

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