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

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Financial Relationship Disclosure

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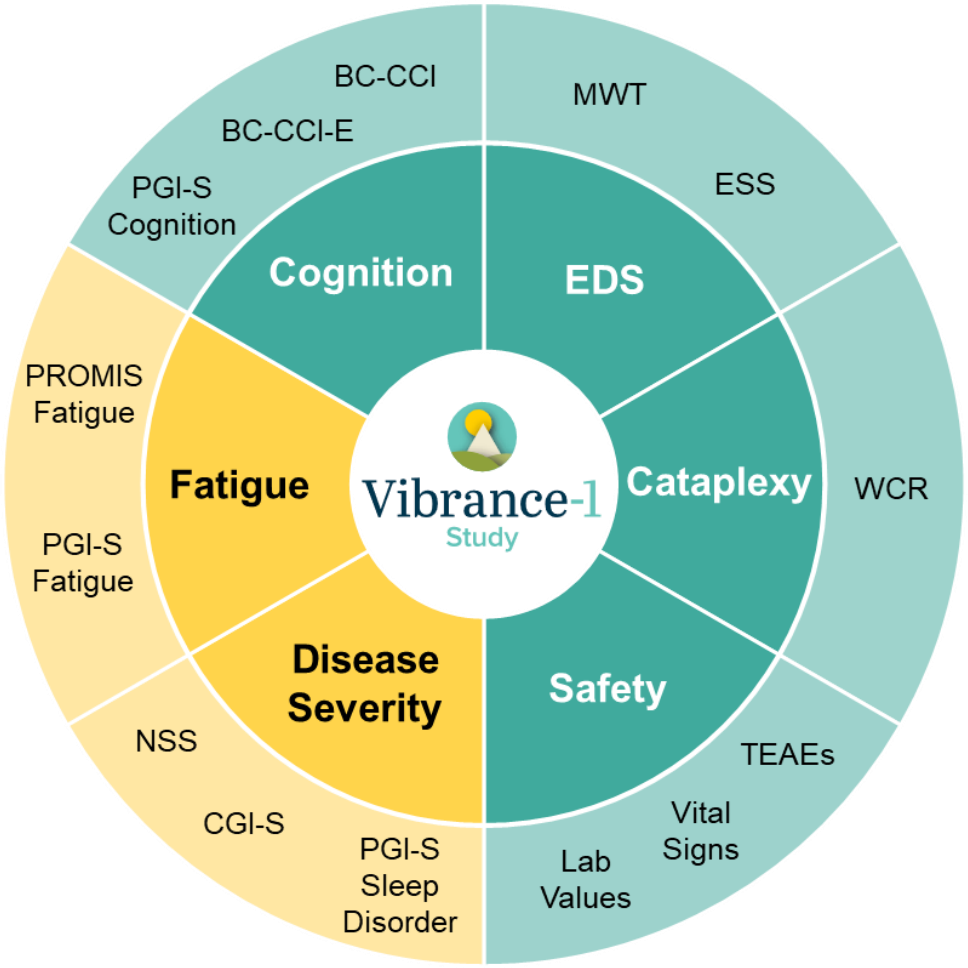
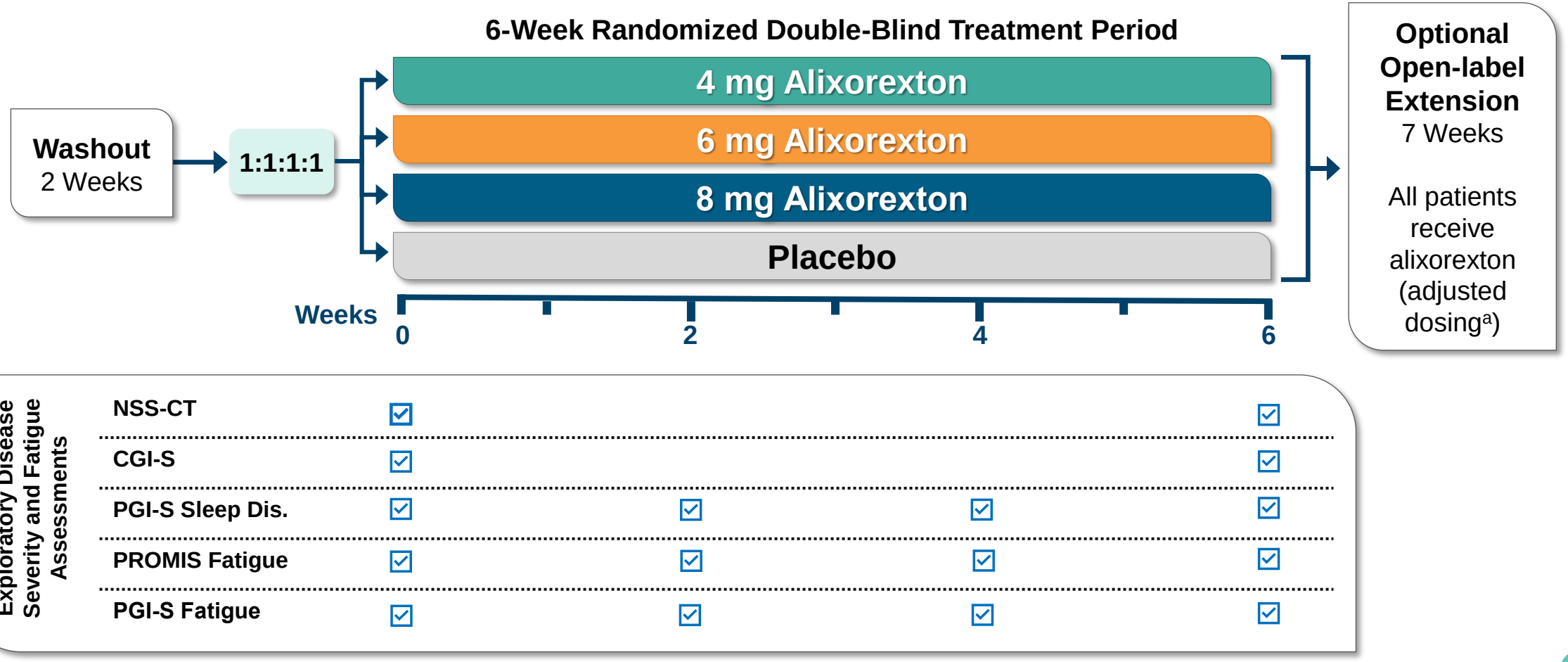
Vibrance-1 Examined the Effects of Alixorexton on Overall Disease Severity and Fatigue in Patients With NT1



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.

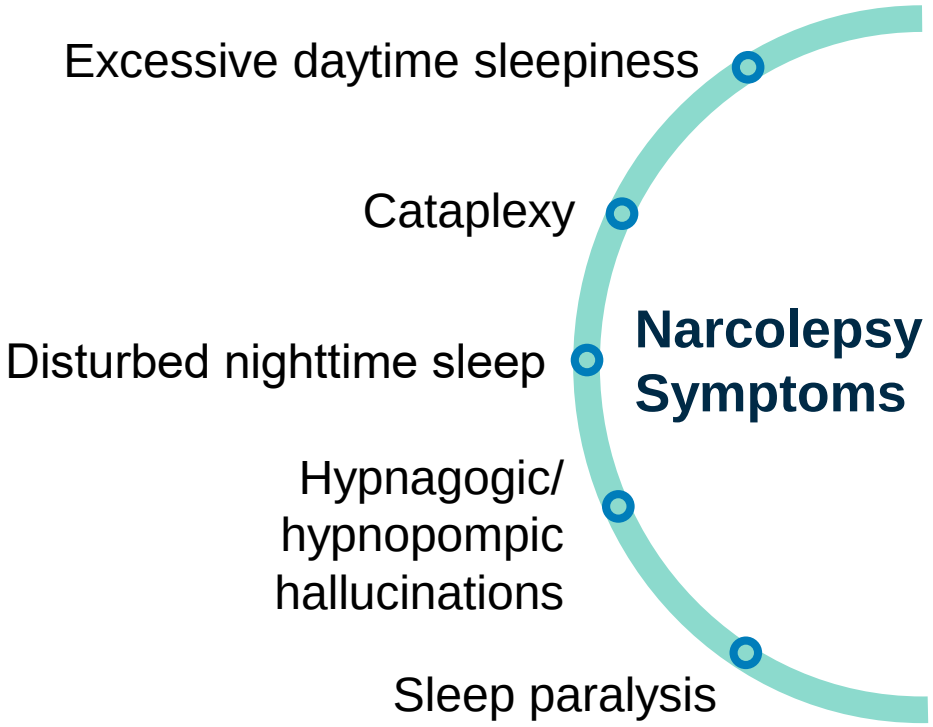
Exploratory Endpoints Were Evaluated During the Double-blind Treatment Period of the Vibrance-1 Phase 2 Study



[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]:

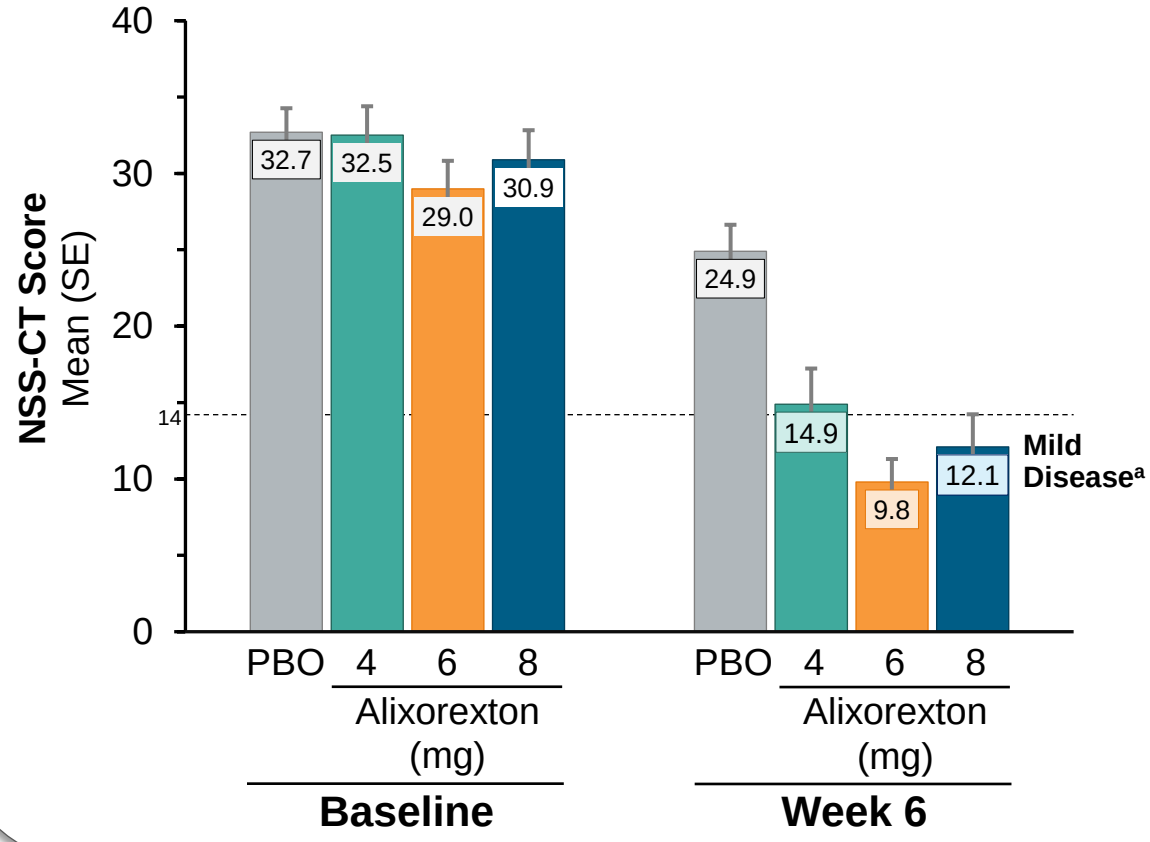
Mild	Moderate	Severe	Very Severe
0-14	15-28	29-42	43-57

- 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

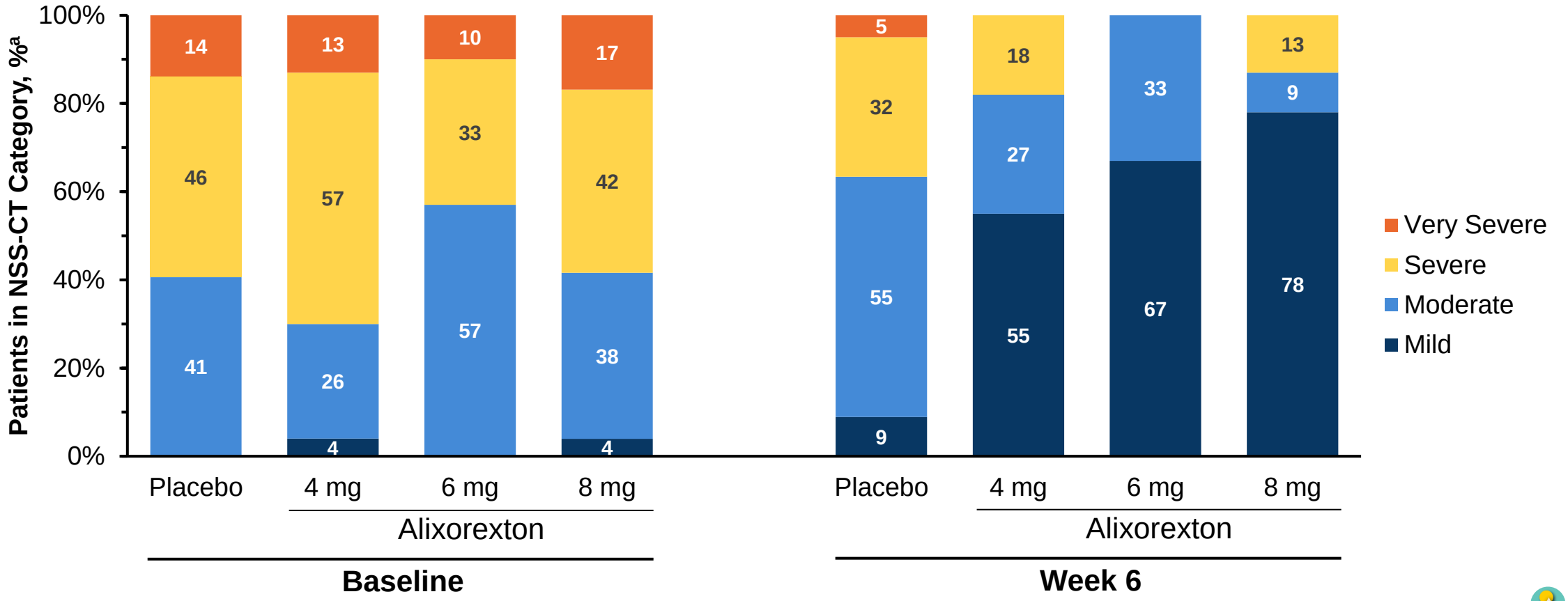


Change from baseline at Week 6 (Exploratory Endpoint)	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
LSM	**-7.1**	**-16.2**	**-19.5**	**-18.1**
(95% CI of LSM)	(-11.1, -3.0)	(-20.2, -12.1)	(-24.1, -14.8)	(-22.1, -14.0)
LSM difference vs PBO		**-9.1**	**-12.4**	**-11.0**
(95% CI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



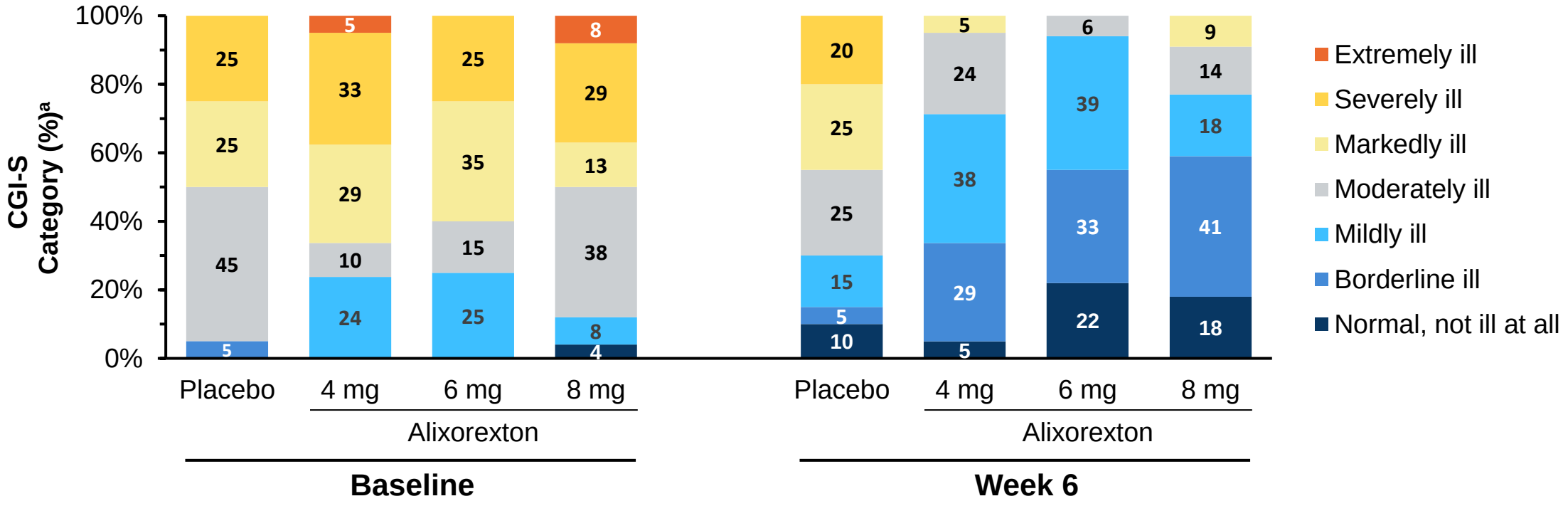
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
NSS-CT = Narcolepsy Severity Scale-Clinical Trials.

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



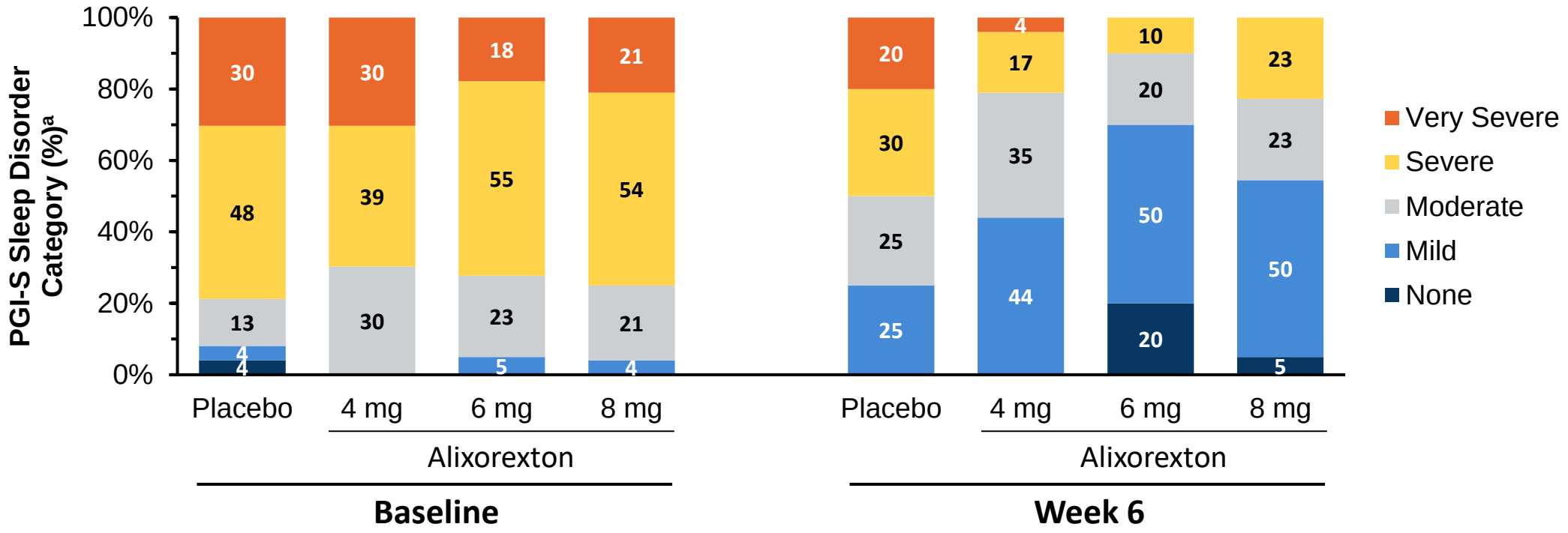
At week 6, all doses were significantly different from placebo (P = 0.0145 at 4 mg, P = 0.0001 at 6 mg, and P = 0.0011 at 8 mg, all nominal).
[a]Values shown within bars are rounded to the nearest whole number and may not sum to 100%.
CGI-S = Clinical Global Impression of Severity.

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]

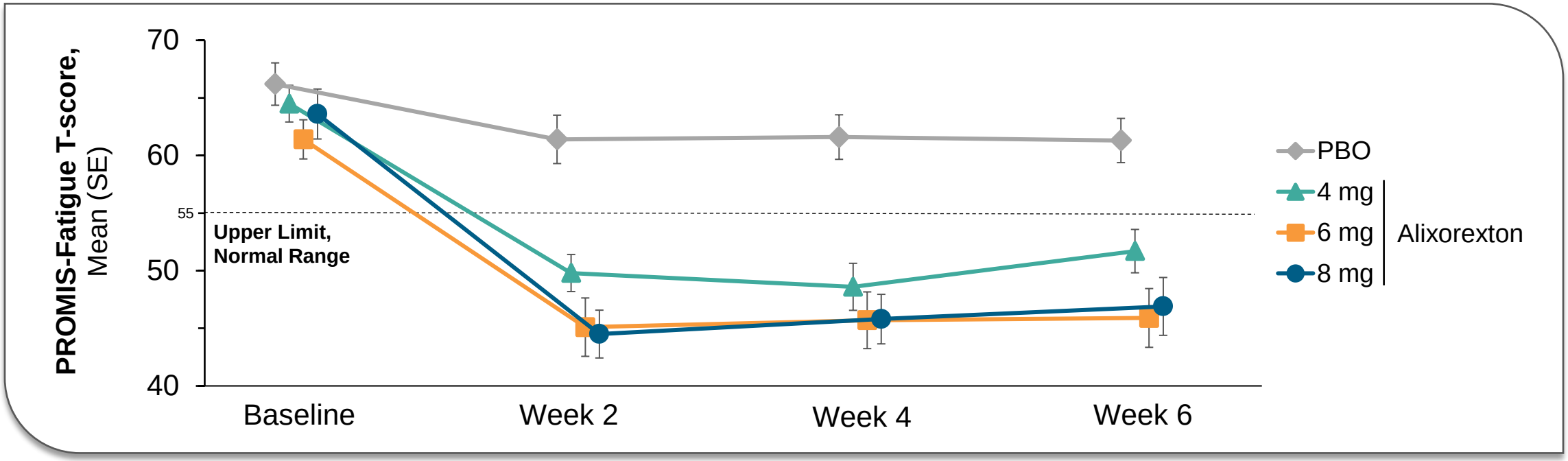
Commonly Used and Established Patient-reported Measures Specific to Fatigue

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

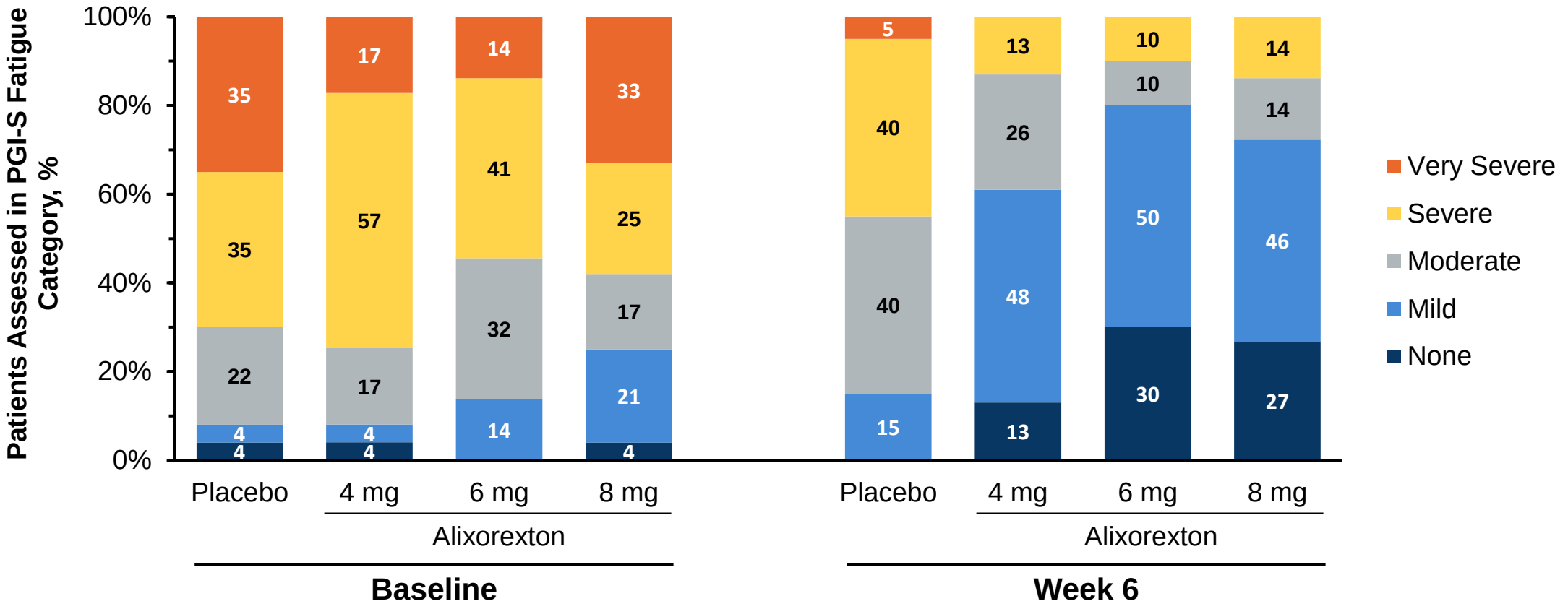


Change from baseline at Week 6 (Exploratory endpoint)	PBO (N=23)	Alixorexton once daily 4 mg (N=23)	6 mg (N=22)	8 mg (N=24)
LSM (95% CI of LSM)	**-3.3** (-7.5, 0.8)	**-12.1** (-16.2, -7.9)	**-15.7** (-20.0, -11.4)	**-16.2** (-20.4, -12.1)
LSM difference vs PBO (95% CI of LSM difference)		**-8.7** (-14.1,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

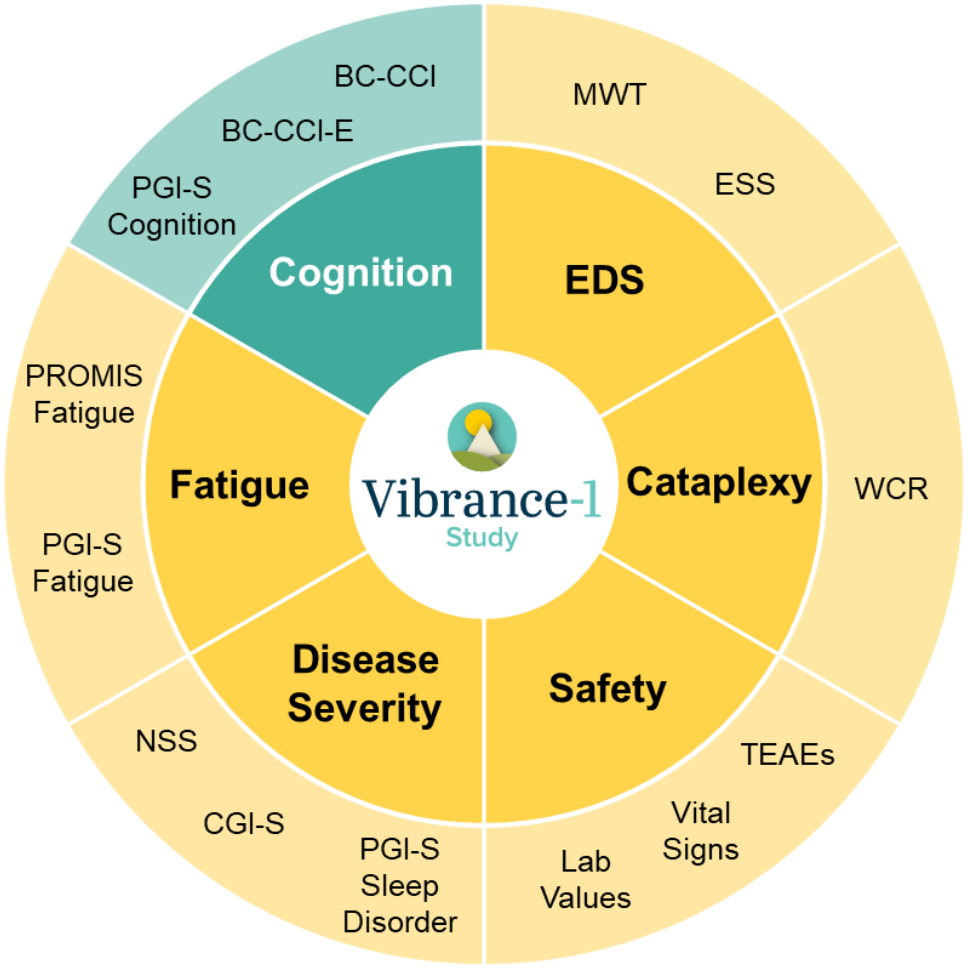
Alixorexton demonstrated statistically significant, clinically meaningful improvements on established scales:

- 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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- Vibrance-1 investigators and their staff

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