Vibrance-2 Phase 2 Study of Alixorexton in Patients with Narcolepsy Type 2: Positive Topline Results

November 12, 2025

Forward Looking Statements

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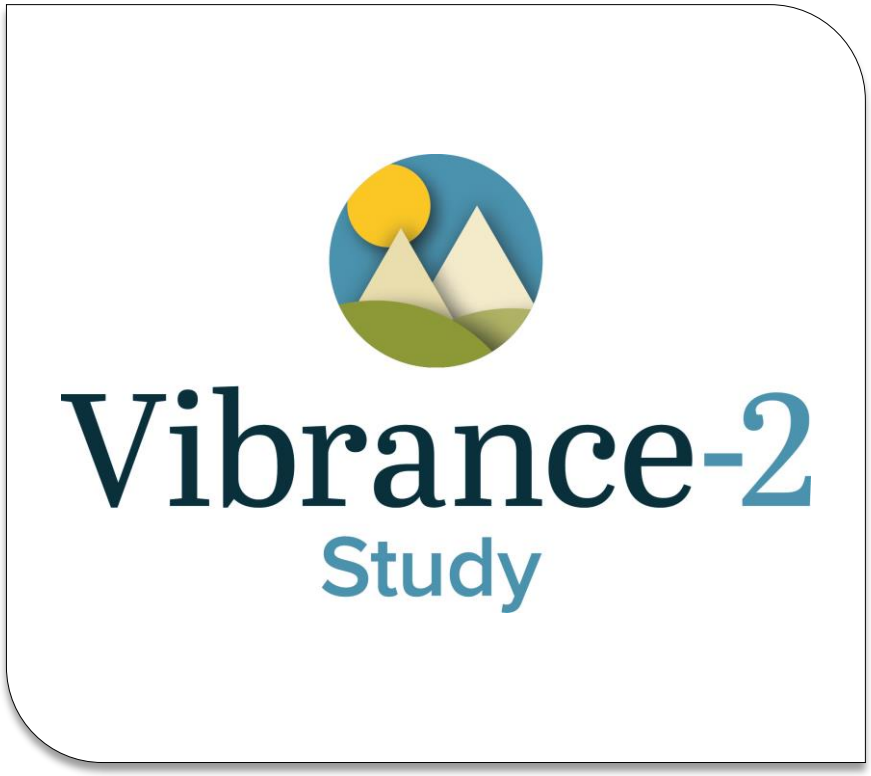
Vibrance-2: Successful Phase 2 Study of Alixorexton in Patients With Narcolepsy Type 2



- Topline results address the study's key objectives:
  - ✓ Efficacy
  - ✓ Safety and Tolerability
  - ✓ Phase 3 Readiness

Vibrance-2: Positive Outcome Supports Advancing to Phase 3

- Alixorexton is the first orexin 2 receptor agonist to demonstrate an efficacy signal with statistically significant and clinically meaningful improvements in MWT and ESS in a large, multi-dose phase 2 study in narcolepsy type 2 (NT2)
- Alixorexton was generally well tolerated, with most TEAEs mild to moderate in severity and no serious TEAEs reported
- Safety and tolerability profile confirmed anticipated dose/response shift in NT2 patients
- Important new findings from Vibrance-2 inform phase 3 program

MWT = Maintenance of Wakefulness Test; ESS = Epworth Sleepiness Scale; NT2 = narcolepsy type 2; TEAE: treatment-emergent adverse events

Vibrance-2 Study

Narcolepsy Type 2: Heterogeneous Patient Population with Significant Unmet Need

- Chronic neurological sleep disorder characterized by excessive daytime sleepiness (EDS), without the presence of cataplexy
- Underlying disease pathology is less clear than NT1; NT2 patients have detectable and variable levels of orexin in CSF
- Variable disease severity and response to treatment
- Significant unmet need and limited number of available treatment options

1 Ruoff C, Rye D. The ICSD-3 and DSM-5 guidelines for diagnosing narcolepsy: clinical relevance and practicality. Curr Med Res Opin. 2016;32(10):1611-1622. doi:10.1080/03007995.2016.1208643
2 Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy – clinical spectrum, aetiopathophysiology, diagnosis and treatment. Nat Rev Neurol. 2019;15(9):519-539.
NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; EDS = excessive daytime sleepiness; CSF = cerebral spinal fluid.

Vibrance-2 Study

Vibrance-2 Phase 2 Study: 8-Week Double-blind Period Followed by an Open-label Extension Period With Dosing Flexibility

Inclusion criteria

NT2 patients (ICSD-3-TR) with residual EDS

- Age 18 to ≤70 years
- BMI ≥18 and ≤40 kg/m^2
- Washout from narcolepsy medications ≥14 days
- MSL of ≤15 minutes across MWT during screening period

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)

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8-Week Randomized Double-Blind Treatment Period

- 10 mg Alixorexton
- 14 mg Alixorexton
- 18 mg Alixorexton
- Placebo

Oral, once daily

Weeks: 0, 2, 4, 6, 8

Optional Open-label Extension
5 Weeks

Patients receive alixorexton (adjusted dosing[a])

Safety Follow-up
2 Weeks

ALKS 2680-301
Phase 2/3 Long-term Extension Study

[a]All patients in the open-label extension period start with 14 mg alixorexton. Dose adjustment possible (up or down) during the first 2 weeks of the optional open-label extension period.
BMI = body mass index; MSL = mean sleep latency; MWT = Maintenance of Wakefulness Test; EDS = excessive daytime sleepiness; ICSD-3-TR = International Classification of Sleep Disorders, third edition, text revision; NT2 = narcolepsy type 2.

Vibrance-2 Study

Dual Primary Efficacy and Secondary Endpoints Were Evaluated at the End of the 8-Week Double-blind Treatment Period

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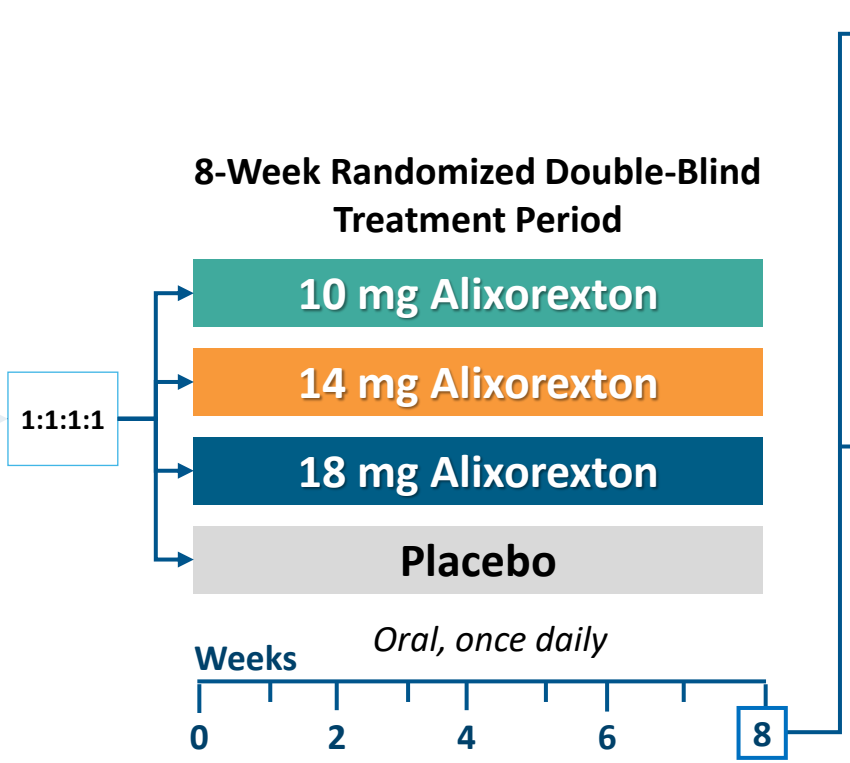


Dual Primary Endpoints

- Change in mean sleep latency on the MWT from baseline to Week 8
- Change in ESS from baseline to Week 8

Safety (Secondary Endpoint)

- TEAEs
- Vital signs
- Laboratory parameters

MWT = Maintenance of Wakefulness Test; ESS = Epworth Sleepiness Scale; TEAE = treatment-emergent adverse events

Vibrance-2 Study

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

		Alixorexton once daily			
	Placebo (N=24)	10 mg (N=23)	14 mg (N=22)	18 mg (N=24)	Total (N=93)
Disease Severity					
Mean Sleep Latency on MWT (minutes), Mean (SD)	6.0 (4.1)	5.3 (3.4)	5.5 (3.7)	5.7 (4.6)	5.6 (3.9)
ESS, Mean (SD)	17.6 (3.4)	17.7 (3.0)	17.5 (3.1)	16.8 (3.0)	17.4 (3.1)
Patient Disposition					
Completed Week 8 visit, n (%)	24 (100)	21 (91)	22 (100)	23 (96)	90 (97)

Demographics

Age	33.8 years (mean)
Sex	Females 69%
Race	White 50% Black 9% Asian 4% Other 7% NR[ab] 31%
BMI	27.38 kg/m^2 (mean)

[a]Race not reported in European Union member countries per regulations. [b]Sum may exceed 100 due to rounding.
BMI = body mass index; ESS = Epworth Sleepiness Scale; MWT = Maintenance of Wakefulness Test; NR = not reported.

Vibrance-2 Study

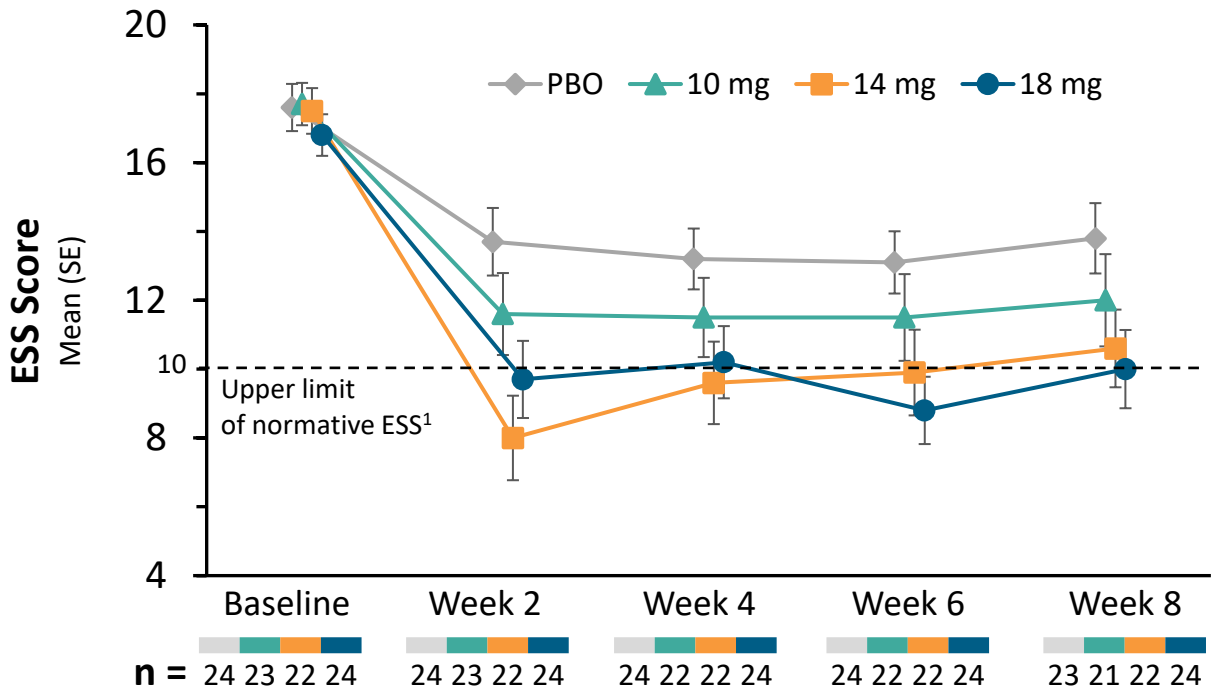
Vibrance-2: Safety and Tolerability

- Alixorexton was generally well tolerated over 8 weeks of treatment[a]
- Most TEAEs were mild to moderate in severity
- There were no serious TEAEs reported
- Most common TEAEs[b]: pollakiuria, insomnia, micturition urgency, dizziness and headache
  - No dose response relationship observed in frequency or severity of most common TEAEs
- No safety signals were observed in hepatic or renal parameters, vital signs or ECGs and no treatment-related clinically meaningful changes observed on ophthalmic exams

[a]Data cutoff as of the end of the double-blind randomized treatment period. Safety data collection is ongoing, and data are subject to change.
[b]TEAEs in ≥10% among all alixorexton-treated patients;
TEAE = treatment-emergent adverse event; ECG = electrocardiogram

Vibrance-2 Study

ESS: Alixorexton Improved Excessive Daytime Sleepiness Symptoms Across All Doses



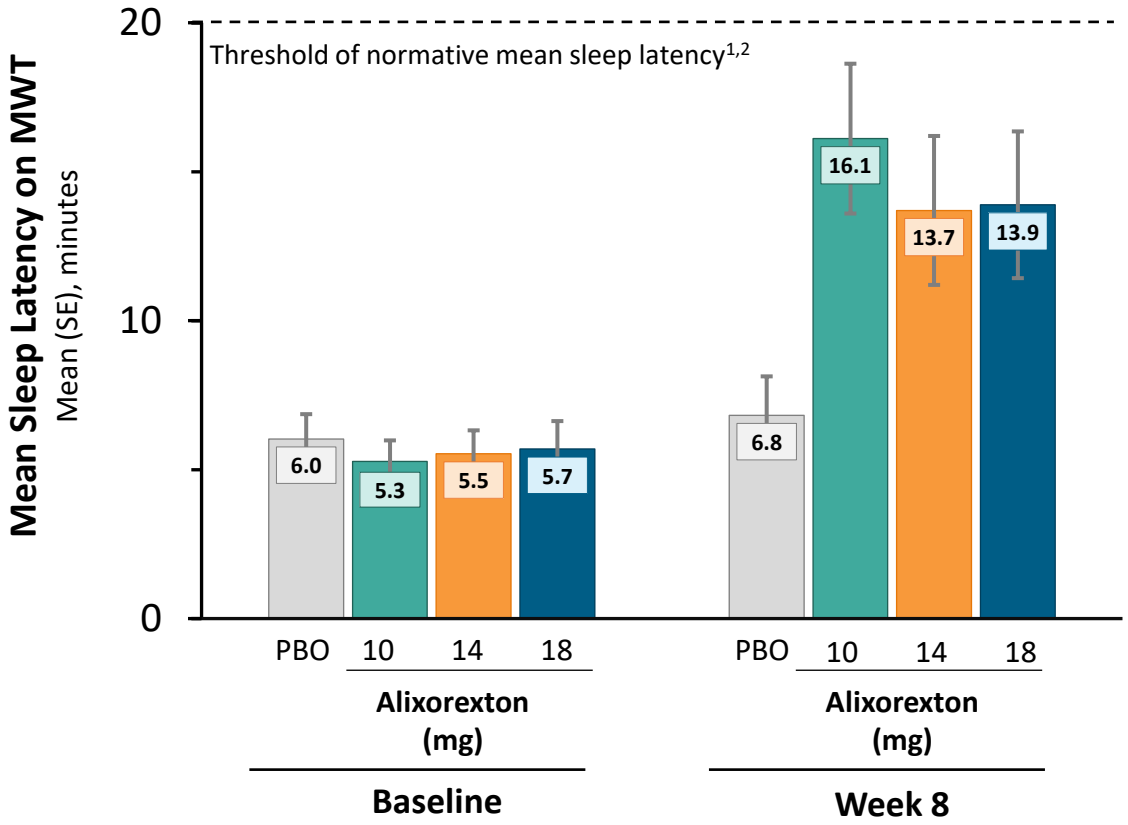
Primary Endpoint Analysis at Week 8

Change from baseline at Week 8[a]	PBO (N=24)	Alixorexton once daily 10 mg (N=23)	14 mg (N=22)	18 mg (N=24)
LSM	**-3.7**	**-5.8**	**-6.9**	**-7.2**
(95% CI of LSM)	(-5.9, -1.5)	(-8.1, -3.5)	(-9.1, -4.6)	(-9.4, -5.1)
LSM difference vs PBO		**-2.1**	**-3.2**	**-3.6**
(95% CI of LSM difference)		(-5.3, 1.1)	(-6.3, -0.1)	(-6.7, -0.5)
***P* value** (Adjusted for multiplicity)		0.1945	0.0774	**0.0464***
***P* value** (Unadjusted for multiplicity)		0.1945	0.0464	**0.0232***

[a]ANCOVA model. Missing data were imputed using multiple imputation.
*Statistically significant following multiplicity adjustment.
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-2 Study

MWT: Alixorexton Demonstrated Clinically Meaningful Improvements in Mean Sleep Latency at All Doses



Primary Endpoint Analysis at Week 8

Change from baseline at Week 8 (minutes)[a]	PBO (N=24)	Alixorexton once daily 10 mg (N=23)	14 mg (N=22)	18 mg (N=24)
LSM	**1.6**	**10.8**	**8.3**	**8.2**
(95% CI of LSM)	(-2.6, 5.7)	(6.5, 15.1)	(4.1, 12.5)	(4.1, 12.4)
LSM difference vs PBO		**9.3**	**6.7**	**6.7**
(95% CI of LSM difference)		(3.3, 15.2)	(0.9, 12.6)	(0.9, 12.4)
***P* value** (Adjusted for multiplicity)		NA[b]	**0.0485***	**0.0466***
***P* value** (Unadjusted for multiplicity)		0.0023	**0.0243***	**0.0233***

[a]ANCOVA model. Missing data were imputed using multiple imputation.
[b]Study employed hierarchical analysis procedure to control for multiplicity which precluded the assessment of statistical significance of the MWT endpoint at the 10 mg dose.
*Statistically significant following multiplicity adjustment.
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.

Vibrance-2 Study

MWT Efficacy Insights in Vibrance-2

Intra-day time course of MWT response

Strong, consistent response observed primarily at the 2-hour and 4-hour post-dose assessments

- Mean wakefulness more variable at the 6-hour and 8-hour post-dose assessments
- Pattern not previously observed with shorter duration exposures
- Pharmacodynamic response was inconsistent with plasma PK

Phase 3 program expected to advance a range of doses and incorporate split dosing regimens

MWT = Maintenance of Wakefulness Test; PK = pharmacokinetic

Vibrance-2 Study

Vibrance-2: Positive Outcome Supports Advancing to Phase 3

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Vibrance-2 Study

Alixorexton Vibrance Phase 2 Program

	Vibrance-1 Study	Vibrance-2 Study	Vibrance-3 Study
Patients	**NT1 (n=92)**	**NT2 (n=93)**	**IH**
Duration*	**6 weeks**	**8 weeks**	**8 weeks**
Doses	**4, 6, and 8 mg**	**10, 14, and 18 mg**	**10, 14, and 18 mg**
Key Endpoints	MWT | ESS | Cataplexy Rates	MWT | ESS	ESS | IHSS
Status	Completed. Positive outcome.	Completed. Positive outcome.	Enrollment ongoing

ESS = Epworth Sleepiness Scale; IH = idiopathic hypersomnia; IHSS = Idiopathic Hypersomnia Severity Scale; MWT = Maintenance of Wakefulness Test; NT1 = narcolepsy type 1; NT2 = narcolepsy type 2
* Randomized, double-blind, placebo-controlled period.

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