COR2ED

THE HEART OF MEDICAL EDUCATION

DEVELOPED BY SLEEP CONNECT

This programme is developed by SLEEP CONNECT, an international group of experts in the field of sleep medicine and is an initiative of COR2ED. The group discusses the latest scientific and clinical insights, identifies educational needs, and develops educational programmes to support healthcare professionals globally to provide the best possible care to their patients.

SLEEP connect® POWERED BY COR2ED

Acknowledgement and disclosures

This SLEEP CONNECT programme is supported through an independent educational grant from Takeda. The programme is therefore independent; the content is not influenced by the supporter and is under the sole responsibility of the experts.

Please note:

- This educational programme is intended for healthcare professionals only.
- The views expressed within this programme are the personal opinions of the expert. They do not necessarily represent the views of the expert's academic institutions, organisations, or the rest of the SLEEP group.

Expert disclosures:

- **Prof. Yves Dauvilliers** has received funds for seminars, board engagements and travel to conferences by Jazz, Idorsia, Takeda, Alkermes, Centessa, Pharmanovia, Avadel and Bioprojet

SLEEP CONNECT ANIMATED VIDEO

NARCOLEPSY TYPE 1: EXPLORING THE EVOLVING TREATMENT LANDSCAPE

Prof. Yves Dauvilliers
University of Montpellier, France

APRIL 2026

EDUCATIONAL OBJECTIVES

1. **Understand the pathophysiology and impact of narcolepsy type 1**
   - Explain the role of **orexin deficiency** and its effect on **EDS, cataplexy and co-morbidities**

2. **Evaluate current and emerging treatment strategies**
   - Compare the **mechanisms, efficacy, and safety** of approved narcolepsy treatments
   - Assess the clinical impact of **emerging therapies** aiming to address the underlying orexin deficiency

EDS, excessive daytime sleepiness.

CLINICAL TAKEAWAYS

- **Narcolepsy type 1 is characterised by selective loss of hypothalamic orexin/hypocretin neurons,** resulting in reduced excitatory drive to monoaminergic and cortical wake-promoting networks. This destabilises the sleep–wake boundary, leading to excessive daytime sleepiness and dysregulated REM sleep, including cataplexy
- **Patients continue to experience residual disease burden despite guideline-recommended therapy,** highlighting the need for novel therapeutic approaches. **Selective hypocretin receptor agonists are a promising new class** designed to directly restore orexin signalling
- **Oveporexton phase 3 trials** (FirstLight and RadiantLight) demonstrated significant improvement in mean sleep latency on the Maintenance of Wakefulness Test (MWT) by Week 12, with no treatment-related serious treatment-emergent adverse events (TEAEs). The most common adverse events were insomnia and urinary frequency or urgency, generally mild to moderate, early-onset and transient
- **Alixorexton phase 2 data** (Vibrance-1) showed achievement of normative wakefulness across doses (4, 6 and 8 mg), with no serious TEAEs. Adverse events were mostly early-onset, mild to moderate and included pollakiuria, insomnia and salivary hypersecretion

NARCOLEPSY TYPE 1 (NT1) PATHOPHYSIOLOGY AND CLINICAL PATHWAY

PATHOPHYSIOLOGY OF NT1

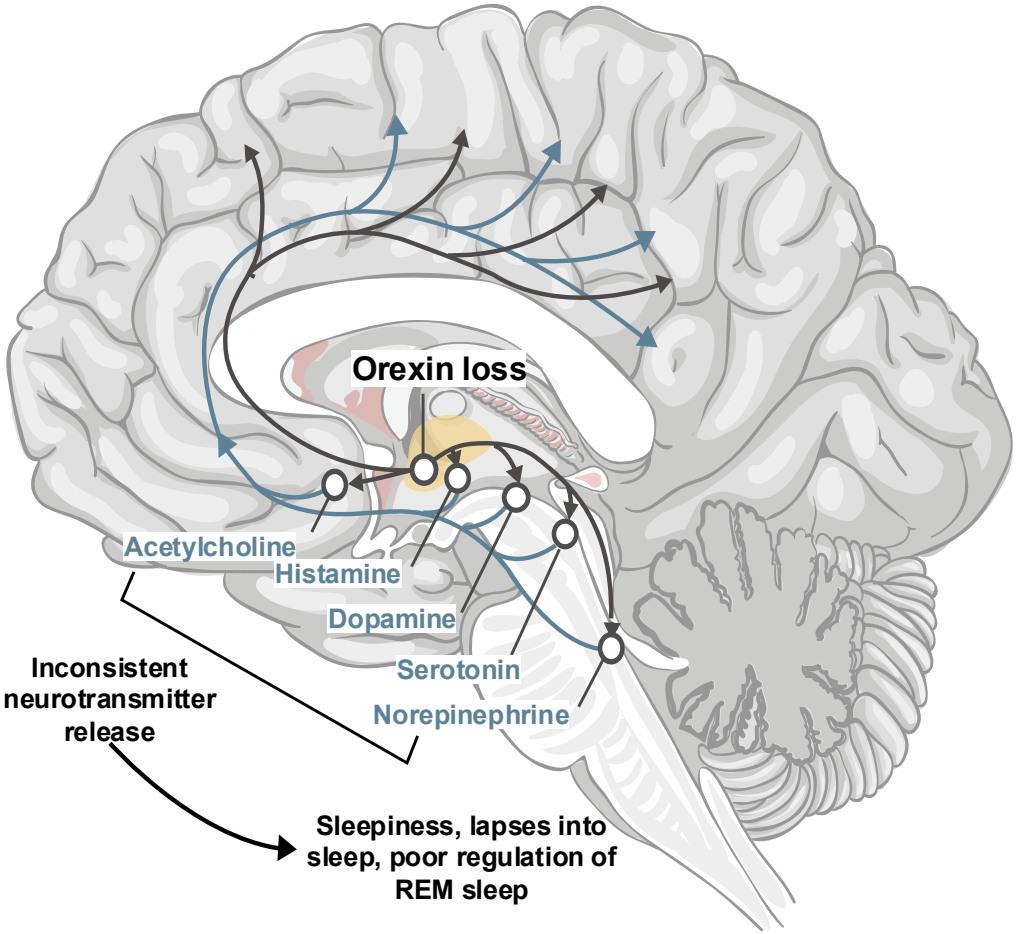
- The central pathological feature of NT1 is **dysfunction of the hypothalamic orexin system**, resulting from the destruction of orexin-producing neurons[1]
- Consequently, individuals exhibit reduced cerebrospinal fluid orexin levels, leading to disruption of the neural circuits that regulate the sleep–wake cycle[1]
- Orexin (hypocretin) is essential for:[2]

- **EDS is the hallmark clinical feature of NT1, occurring in all patients** and frequently accompanied by abrupt transitions into REM sleep and impaired regulation of muscle tone, leading to cataplexy[2]

EDS, excessive daytime sleepiness; NT1 narcolepsy type 1; REM, rapid eye movement

1. Xu Q, et al. J Clin Med. 2025 Nov 28;14(23):8444; 2. Rauf R, et al. Brain Behav. 2025 Oct 11;15(10):e70984

OREXIN NEURON LOSS RESULTS IN SLEEPINESS IN NT1

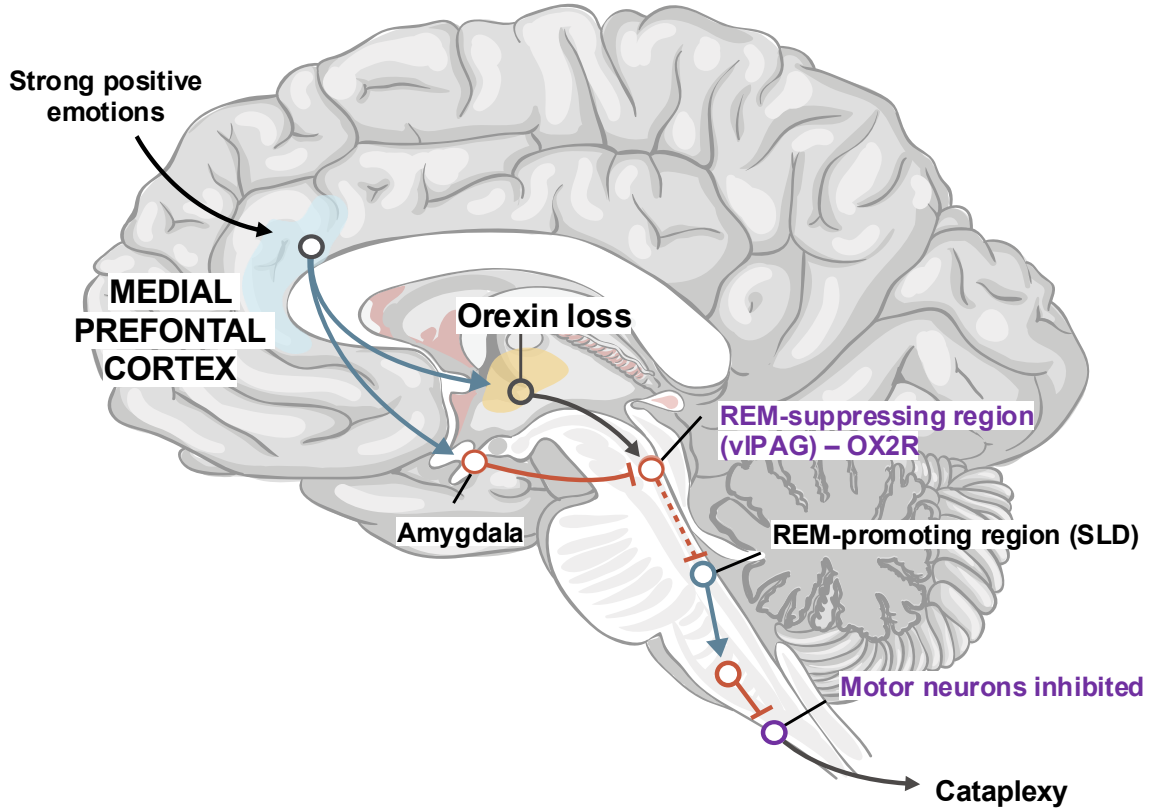


Reduced orexin excitatory input to cortex, hypothalamus, wake-promoting neurotransmitter systems results in sleepiness and abnormal REM sleep regulation

NT1, narcolepsy type 1; REM, rapid eye movement

1. Scammell TE. N Engl J Med. 2015;373:2654-2662 e70984

CATAPLEXY RESULT FROM REDUCED ACTIVITY IN REM SLEEP-INHIBITING BRAIN REGIONS IN NT1

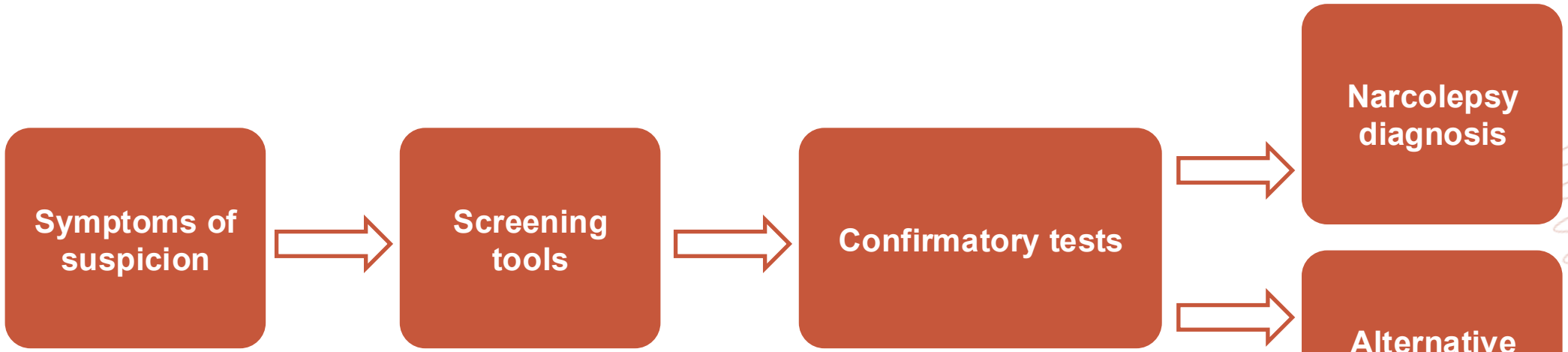


Emotions activate neurons in the mPFC that excite orexin neurons and the amygdala. Loss of orexin excitatory input to the vlPAG, which normally suppresses REM sleep by inhibiting SLD neurons, allows REM-promoting SLD neurons to activate and inhibit motoneurons during wakefulness = **cataplexy**[1,2]

mPFC, medial prefrontal cortex; OX2R, orexin receptor type 2; REM, rapid eye movement; SLD, sublaterodorsal nucleus; vlPAG, ventrolateral periaqueductal grey

1. Adapted from Scammell TE. N Engl J Med. 2015;373:2654-2662 e70984; 2. Mahoney CE, et al. Nat Rev Neurosci. 20:83-93

CLINICAL PATHWAY OF DIAGNOSIS OF NARCOLEPSY



Primary symptoms
- EDS
- Cataplexy
- Sleep paralysis
- Fragmented sleep
- Hallucinations

Comorbidities/ secondary symptoms
- Anxiety
- Depression
- ADHD
- Metabolic dysfunctions

- Detailed sleep history
- ESS
- Sleep diaries
- Actigraphy

Primary tests
- Polysomnography
- Multiple sleep latency test

Secondary tests
- Hypocretin levels in CSF
- Genetic testing

- Chronic sleep deprivation
- Sleep apnea
- Idiopathic hypersomnia
- Shift work disorder
- Etc.

ADHD, attention-deficit/hyperactivity disorder; CSF, cerebrospinal fluid; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale.

1. Hastings NE, et al. Brain Behav. 2025 Dec;15(12):e71116. doi: 10.1002/brb3.71116

PATIENT CASE STUDY PART 1: DIAGNOSIS AND CURRENT TREATMENT

PATIENT CASE STUDY[a]

JOHN D., 28-YEAR-OLD MALE WITH NT1, DIAGNOSED 5 YEARS AGO; PERSISTENT SYMPTOMS DESPITE MULTIPLE GUIDELINE-DIRECTED THERAPIES

Baseline (Age 23) NT1 diagnosis

- Severe EDS (ESS 19/24)
- Daily cataplexy (3-5 episodes/day)
- Fragmented nocturnal sleep, occasional sleep paralysis
- PSG + MSLT: mean sleep latency 3.2 min; 3 SOREMPs

→ **NT1 diagnosis**

Year 0-1: 1L Therapy

- Modafinil 200-400 mg/day
- Partial improvement in wakefulness (ESS ↓ to 14)
- Persistent cataplexy

Year 1-2: Add-on Anticataplectic therapy

- Venlafaxine XR 75 mg/day
- Cataplexy reduced to ~1 episode/day
- Dose limited by tolerability (insomnia, palpitations)

Year 2-4: Treatment optimisation

- Switched to sodium oxybate (titrated to 9 g/night) together with modafinil
- Marked cataplexy reduction (≤1 episode/week)
- Improved nocturnal sleep; residual EDS persists (ESS 12-13)

Year 5 (Age 28): Disease burden

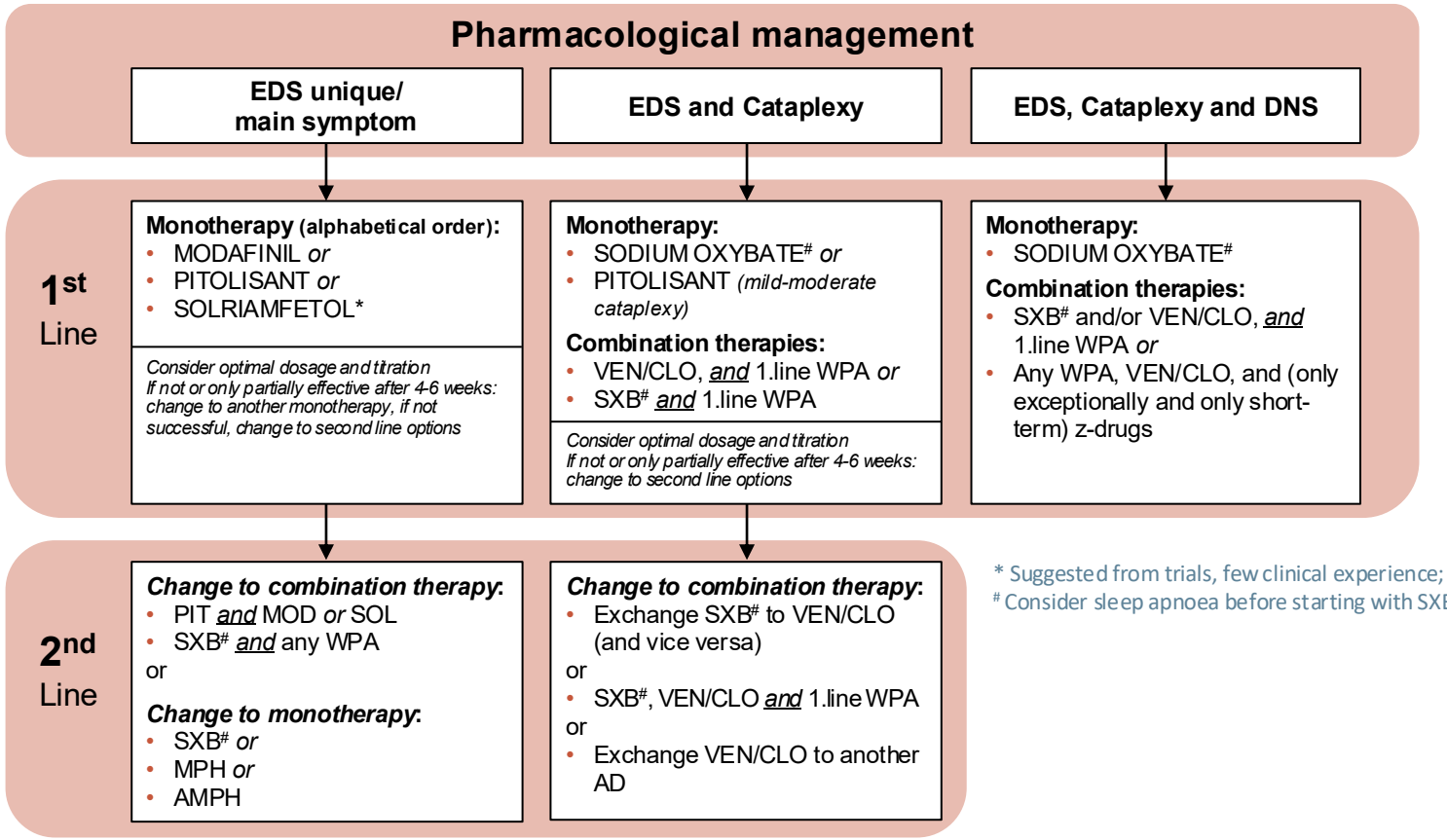
- Residual EDS (ESS ≥11)
- Occasional breakthrough cataplexy
- Ongoing impact on work performance and quality of life

[a]This material is based on a hypothetical case scenario created for educational purposes and does not represent any real patient.

1L, first-line; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MSLT, multiple sleep latency test; NT1, narcolepsy type 1; PSG, polysomnogram; SOREMP; sleep-onset rapid eye movement period; XR, extended release formulation.

NARCOLEPSY TREATMENT GUIDELINES

EUROPEAN GUIDELINES AND EXPERT STATEMENTS ON THE MANAGEMENT OF NARCOLEPSY IN ADULTS



* Suggested from trials, few clinical experience;
# Consider sleep apnoea before starting with SXB

Drug	EDS	Cataplexy	DNS
Modafinil	↑↑	↓↓	
Pitolisant	↑↑	↑-	
Sodium oxybate	↑↑	↑↑	↑↑
Solriamfetol	↑↑*	↓↓	
Venlafaxine / clomipramine		↓↓#	
Methylphenidate / amphetamines	↑-	↓↓	

Recommendations
For strong ↑↑ For weak ↑- Against weak ↓-
Against strong ↓↓
* needs further evaluation from clinical practice
# based on expert opinion exclusively

- Despite guideline-recommended pharmacological management, a substantial residual disease burden persists, highlighting the need for novel therapeutic approaches
- Selective hypocretin receptor agonists represent a promising new class

AD, antidepressant; AMPH, amphetamine; CLO, clomipramine (low-dose); DNS, disrupted nocturnal; sleep; EDS, excessive daytime sleepiness; MOD, modafinil; MPH, methylphenidate; PIT, pitolisant; SOL, solriamfetol; SXB, sodium oxybate; VEN, venlafaxine; WPA, wake-promoting agents (MOD, SOL, PIT, MPH, AMPH); z-drugs, non-benzodiazepine hypnotics (e.g. zolpidem, zopiclone, zaleplon)

Bassetti CL, et al. Eur J Neurol. 2021;28(9):2815-30

PHARMACOLOGY OF PHARMACOLOGICAL TREATMENTS FOR NARCOLEPSY IN ADULTS

Drug	Dosing Schedule[a]	t½ (h)	Mechanism of Action
Modafinil	Initial: 100-200 mg once daily; may increase weekly by 100 mg up to 400 mg, once or divided	15	Weak DAT inhibitor
Armodafinil	Initial: 50-150 mg once daily; may increase weekly by 50 mg up to 250 mg, once or divided	~15	Weak DAT inhibitor
Pitolisant	Initial: 8.9 mg daily for 1 week, then 17.8 mg; max 35.6 mg; CYP2D6 poor metabolisers[b]: half max dose	~20	H3-receptor antagonist / inverse agonist
Sodium oxybate (IR)	Initiate at 4.5 g/night orally, divided into two doses (at bedtime and 2.5-4 h later); titrate by 1.5 g/night at weekly intervals; recommended dosage: 6-9 g/night	0.5-1	GABA-B modulator
Low-sodium oxybate	Initiate at 4.5 g/night orally, divided into two doses (at bedtime and 2.5-4 h later); titrate by 1.5 g/night at weekly intervals; recommended dosage: 6-9 g/night	0.67	GABA-B modulator
Once-nightly oxybate	Initiate at 4.5 g once per night orally; titrate to effect in increments of 1.5 g per night at weekly intervals; recommended dosage: 6-9 g once-nightly orally	0.5-1	GABA-B modulator
Solriamfetol	Initial: 75 mg once daily; may increase every ≥3 days to 150 mg	~7.1	DAT and NET inhibitor
Methylphenidate	Initial: 10 mg twice daily; may increase weekly by 5-10 mg; max 60 mg in 2-3 divided doses	2-7	DAT inhibitor
Dextroamphetamine	Initial: 10 mg once daily; may increase weekly by 10 mg; max 60 mg once daily or divided	~12	DAT and NET inhibitor

[a]Dosing schedules represent general guidelines; individual titration based on efficacy and tolerability is recommended;
[b]CYP2D6 poor metabolizers require dose adjustment for pitolisant.

CYP2D6, cytochrome P450 2D6; DAT, dopamine transporter; ER, extended release formulation; GABA, γ- aminobutyric acid; H3 receptor, histamine H3 receptor; IR, immediate release formulation; NET, norepinephrine transporter; t½, elimination half-life,

1. Xu Q, et al. J Clin Med. 2025 Nov 28;14(23):8444

PATIENT CASE STUDY (PART 2): CLINICAL TRIAL REFERRAL

PATIENT CASE STUDY[a]

INSTEAD OF FURTHER TREATMENT ESCALATION, JOHN D. IS REFERRED TO THE FIRSTLIGHT TRIAL INVESTIGATING OVEPOREXTON (TAK-861)

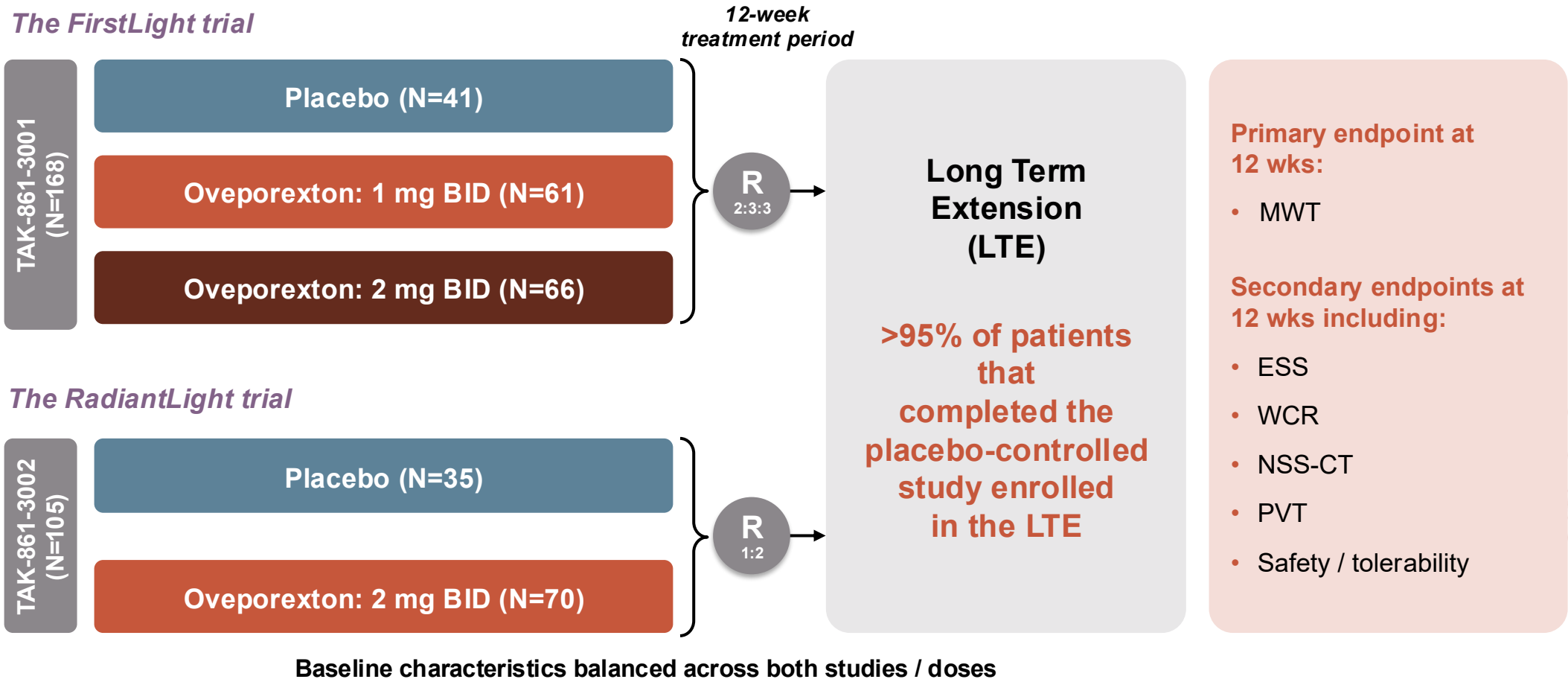
Year 5 (Age 28) Disease burden	0-12 weeks: The FirstLight Trial	Current: LTE enrolment
• On stable, guideline-directed therapy for 5 years : Oxybate + modafinil • Residual EDS (ESS ≥11) • Cataplexy: 4-6 per week • Ongoing impact on work performance and quality of life	• Referred for enrolment in a phase 3 trial of oveporexton: **The FirstLight trial**	• Completed the treatment cycles and moved on to the ongoing **long-term extension (LTE)**

[a]This material is based on a hypothetical case scenario created for educational purposes and does not represent any real patient

EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale

OVEPOREXTON (TAK-861)
PHASE 3 TRIALS

THE FIRSTLIGHT & THE RADIANTLIGHT STUDY DESIGNS: OVEPOREXTON



Baseline characteristics balanced across both studies / doses

BID, twice daily; ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; PVT, Psychomotor Vigilance Test; R, randomisation; WCR, Weekly Cataplexy Rate; wks, weeks

1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09

DISEASE CHARACTERISTICS WERE GENERALLY SIMILAR ACROSS GROUPS AT BASELINE

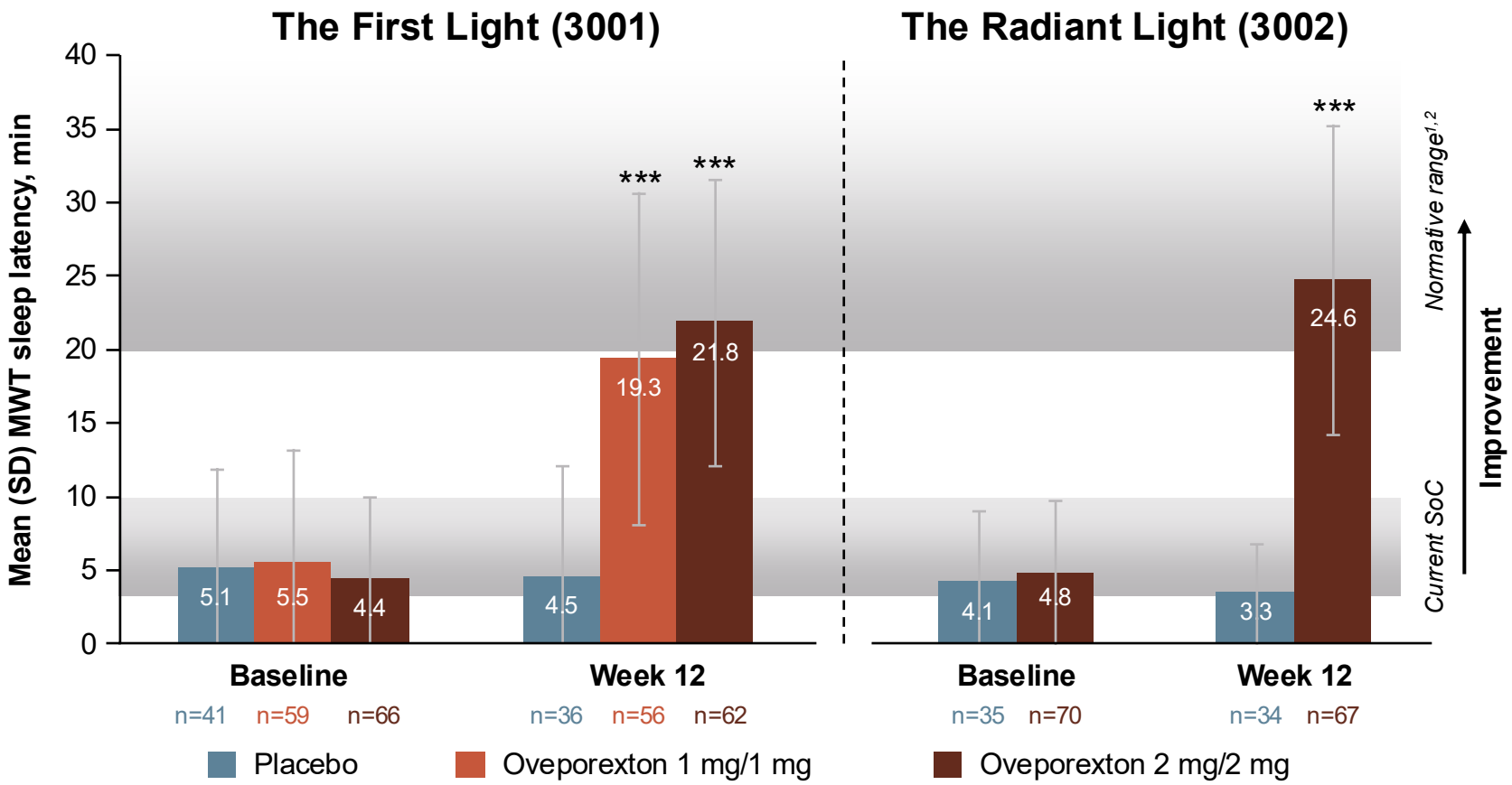
	The FirstLight			The RadiantLight	
	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=61)	Oveporexton 2 mg/2 mg (n=66)	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Mean (SD) age, years	30.9 (12.7)	33.5 (11.8)	29.7 (9.6)	34.0 (13.1)	29.1 (9.6)
Female, n (%)	24 (58.5)	28 (45.9)	46 (69.7)	13 (37.1)	37 (52.9)
Mean (SD) ESS total score	18.2 (3.6)	18.2 (2.6)	19.0 (3.2)	17.9 (3.0)	17.3 (3.4)
Mean (SD) MWT sleep latency, min	5.1 (6.8)	5.5 (7.7)	4.4 (5.5)	4.1 (4.9)	4.8 (4.9)
Median (IQR) WCR	28.5 (16.5-59.5)	21.0 (9.0-45.0)	26.3 (14.5-52.8)	27.0 (19.0-66.5)	21.8 (10.5-37.5)
Mean (SD) NSS-CT total score	31.0 (9.6)	30.4 (8.7)	31.2 (7.3)	31.9 (9.3)	30.7 (9.3)
PGI-S “severe” or “very severe”, n (%)	26 (63.4)	37 (60.7)	47 (71.2)	22 (62.9)	47 (67.1)

ESS, Epworth Sleepiness Scale; IQR, interquartile range; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; PGI-S, Patient Global Impression-Severity; SD, standard deviation; WCR, weekly cataplexy rate

1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09

PRIMARY ENDPOINT: MWT AT WEEK 121

OVEPOREXTON IMPROVED SLEEP LATENCY ON MWT AT WEEK 12 WITH MOST PATIENTS IN NORMATIVE RANGE



The Maintenance of Wakefulness Test (MWT):

Daytime polysomnographic procedure which quantifies wake tendency by measuring ability to remain awake during soporific circumstances (sleepiness condition such as dark quiet room)

*** Indicates significance of $p<0.001$ for LS mean difference from placebo in change from BL at Week 12

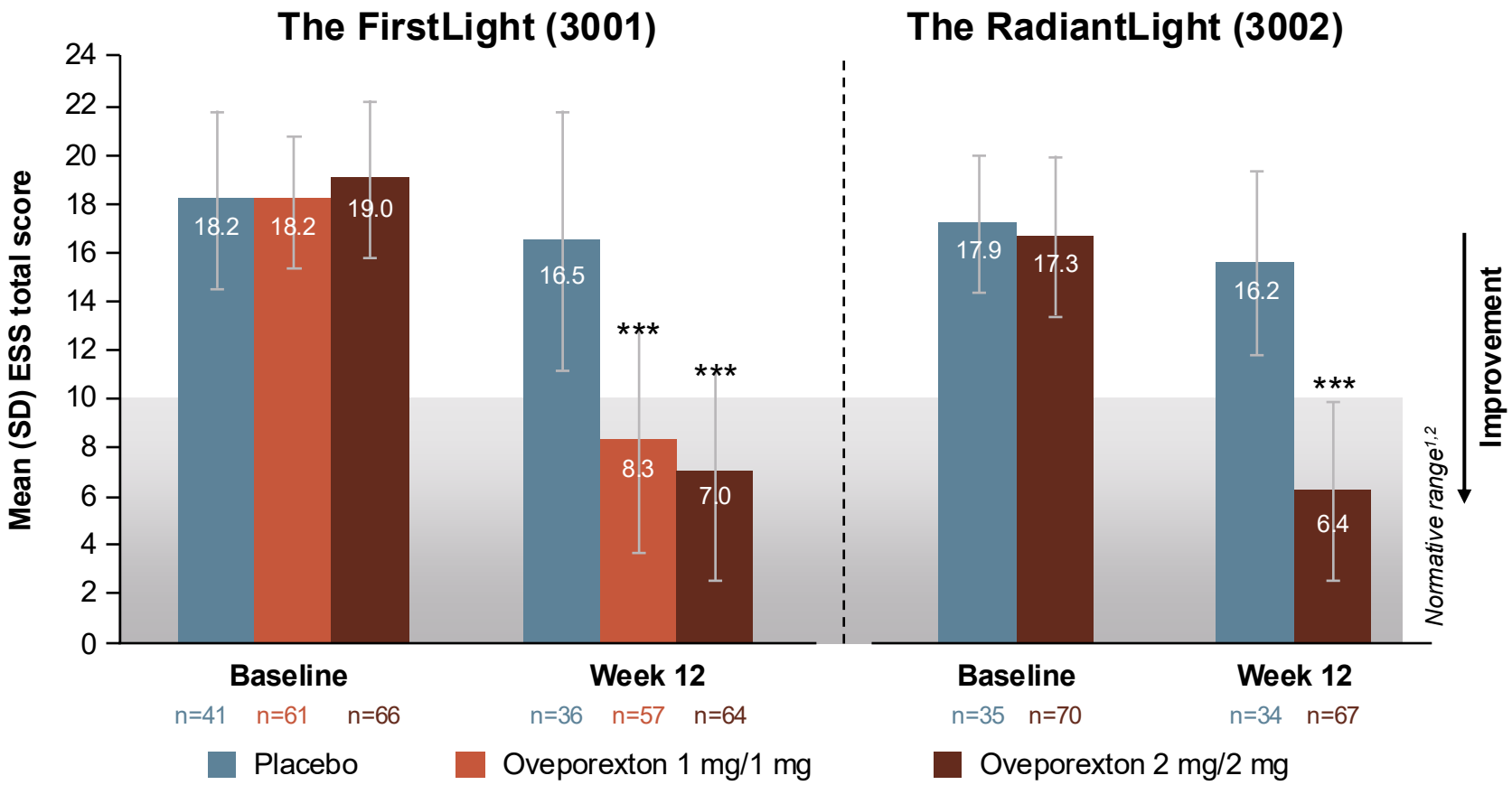
The analysis used a linear mixed effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity

BL, baseline; LS, least squares; MWT, Maintenance of Wakefulness Test; SD, standard deviation; SoC: standard of care

1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09; 2. Doghramji K, et al. Electroencephalogr Clin Neurophysiol. 1997;103:554-62

SECONDARY ENDPOINT: ESS AT 12 WEEKS[1]

OVEPOREXTON IMPROVED SUBJECTIVE SLEEPINESS AT 12 WEEKS WITH MOST PATIENTS WITHIN NORMATIVE RANGE



The Epworth Sleepiness Scale (ESS):

Short self-assessment to identify how likely to fall asleep during daytime, measured by eight questions. Total score range 0-24 (each question 0-3). Scores ≤10 reflect normal levels of daytime sleepiness, and scores over 10 reflect excessive daytime sleepiness

The analysis used a linear mixed effects model for repeated measures with placebo-based multiple imputation. P-values have been adjusted for multiplicity

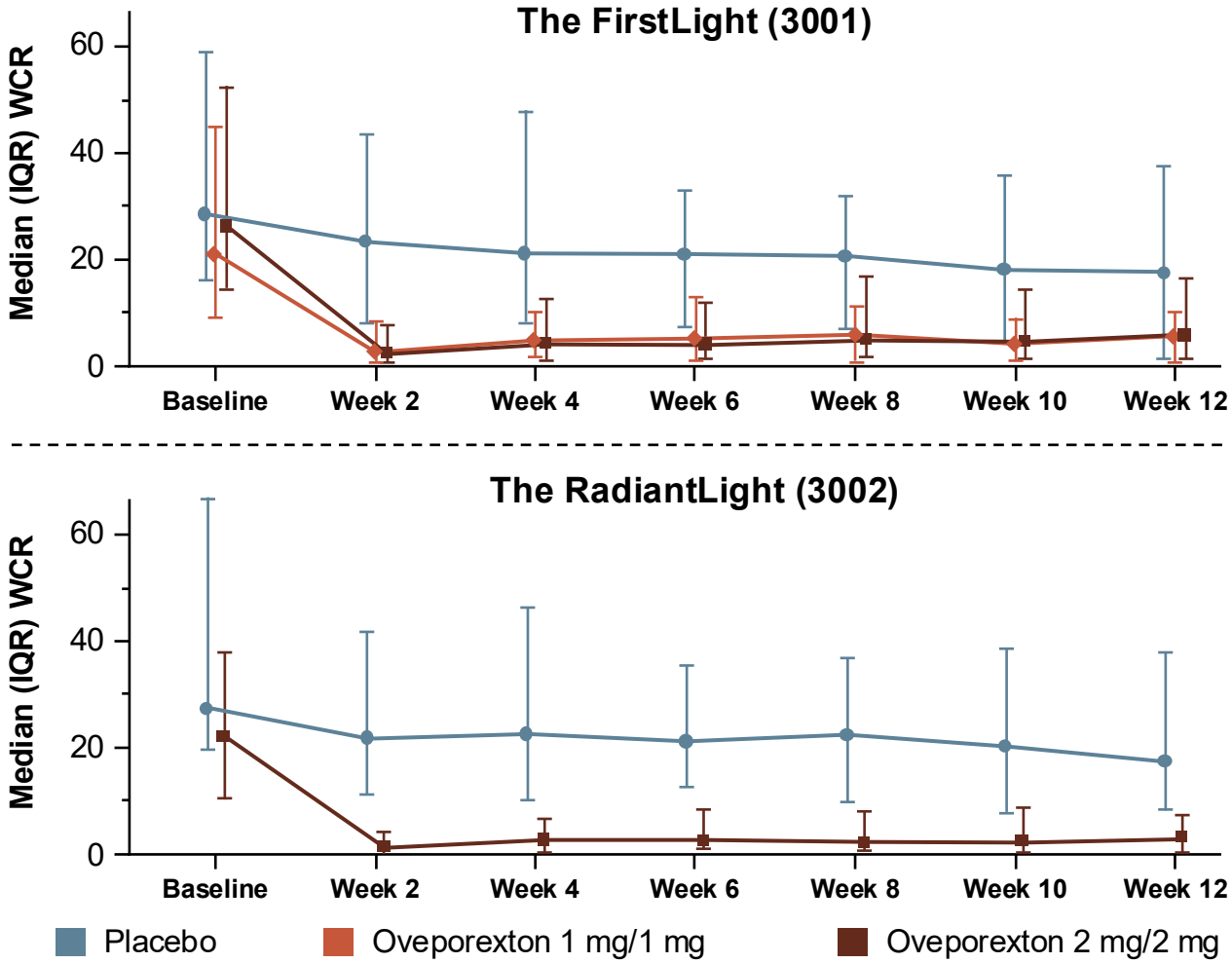
*** indicates significance of $p<0.001$ for LS mean difference from placebo in change from BL at Week 12.

BL, baseline; LS, least squares; ESS, Epworth Sleepiness scale; SD, standard deviation.

1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09; 2. Johns MW. Sleep 1991;14:540-5

SECONDARY ENDPOINT: WCR AT 12 WEEKS

OVEPOREXTON DEMONSTRATED RAPID REDUCTION IN CATAPLEXY, SUSTAINED OVER 12 WEEKS



Weekly Cataplexy Rate (WCR):

The number of cataplexy events per week

- **Reduction in median WCR from baseline sustained** over the entire duration of the study
  - 79% 1 mg/1 mg (The First Light)
  - 83% 2 mg/2 mg (The First Light)
  - 89% 2 mg/2 mg (The Radiant Light)

IQR, interquartile range; WCR, weekly cataplexy rate,

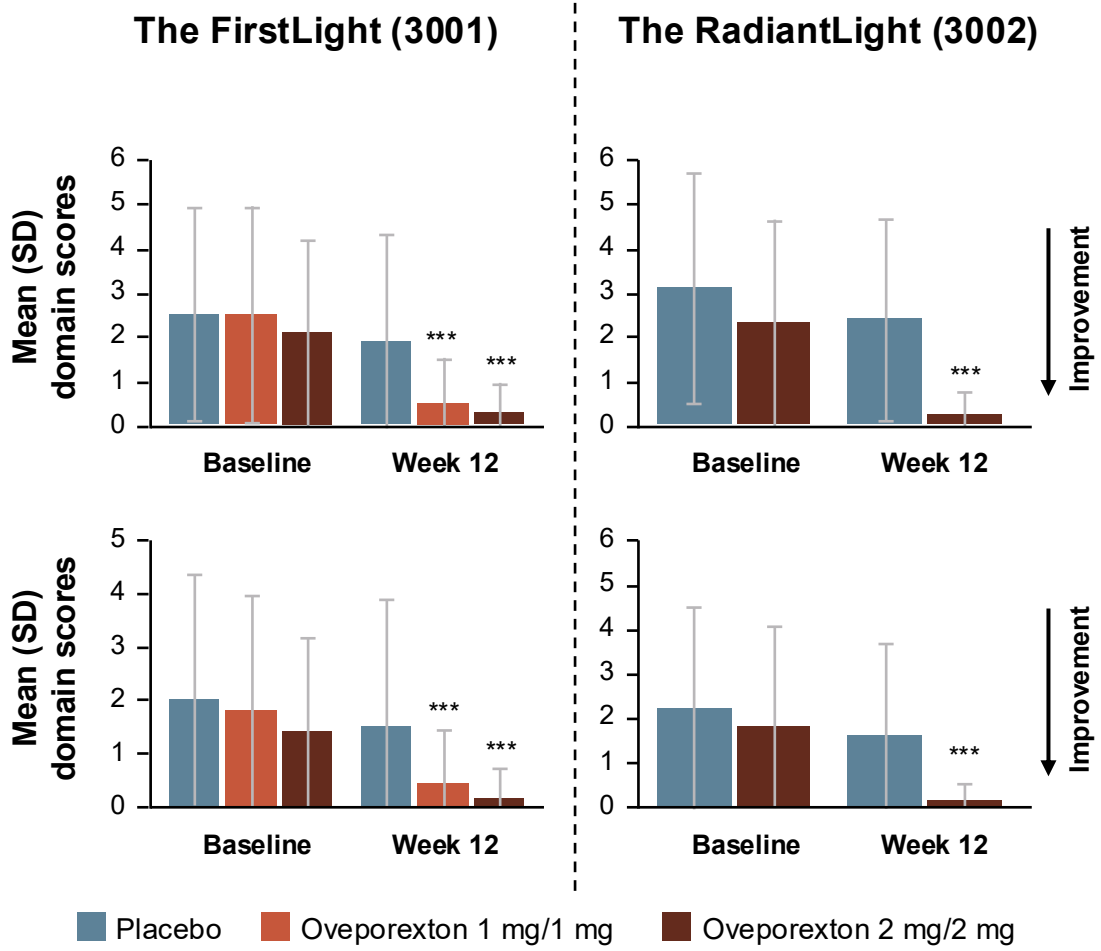
1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09

SECONDARY ENDPOINT: NSS-CT

OVEPOREXTON IMPROVED NIGHTTIME SYMPTOMS AT WEEK 12

Hallucinations
How frequently do you have hallucinations when falling asleep or waking up? (score 0-6)

Sleep paralysis
How frequently do you experience sleep paralysis when falling asleep or waking up? (score 0-6)



Narcolepsy Severity Scale for Clinical Trials (NSS-CT):

Validated, self-administered, 15-item scale evaluating severity, frequency and impact of 5 narcolepsy symptoms (sleepiness, cataplexy, sleep paralysis, hallucinations and disrupted nocturnal sleep)

LS mean difference from placebo, p-value: ***Nominal p<0.001; SD, standard deviation.

LS, least squares; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; SD, standard deviation.

1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09

SECONDARY ENDPOINT: SAFETY

OVEPOREXTON SHOWED NO TREATMENT RELATED SERIOUS TEAEs. MOST COMMON TEAEs WERE INSOMNIA AND URINARY FREQUENCY AND URGENCY

	The FirstLight (3001)			The RadiantLight (3002)	
	Placebo (n=41)	Oveporexton 1 mg/1 mg (n=60)	Oveporexton 2 mg/2 mg (n=66)	Placebo (n=35)	Oveporexton 2 mg/2 mg (n=70)
Any TEAE, n (%)	22 (53.7)	52 (86.7)	59 (89.4)	15 (42.9)	60 (85.7)
Mild	14 (34.1)	26 (43.3)	34 (51.5)	9 (25.7)	38 (54.3)
Moderate	7 (17.1)	24 (40.0)	23 (34.8)	5 (14.3)	20 (28.6)
Severe	1 (2.4)	2 (3.3)	2 (3.0)	1 (2.9)	2 (2.9)
Serious TEAE, n (%)	0	1 (1.7)	1 (1.5)	0	0
TEAEs leading to study drug discontinuation, n (%)	1 (2.4)	3 (5.0)	0	0	2 (2.9)
Most frequent TEAEs, n (%)					
Urinary frequency	3 (7.3)	32 (53.3)	36 (54.5)	1 (2.9)	43 (61.4)
Insomnia	0	32 (53.3)	38 (57.6)	1 (2.9)	40 (57.1)
Urinary urgency	1 (2.4)	9 (15.0)	12 (18.2)	0	10 (14.3)
Nasopharyngitis	6 (14.6)	6 (10.0)	10 (15.2)	0	0
Headache	5 (12.2)	4 (6.7)	10 (15.2)	2 (5.7)	3 (4.3)
Salivary hypersecretion	0	5 (8.3)	4 (6.1)	0	5 (7.1)

Most TEAEs were mild to moderate in severity, and most started within 1-2 days of treatment and were transient

TEAEs, treatment emergent adverse events.

1. Dauvilliers Y, et al. World Sleep Congress 2025. Abstract Session O-09.

PHASE 2/3 TRIALS OF OX2R AGONIST FOR NT1 TREATMENT

KEY PHASE 2/3 TRIALS OF OX2R AGONISTS FOR NT1

Drug Name	Phase	Trial ID	Main Objectives	Status
Oveporexton (TAK-861)	3	NCT06505031 (RadiantLight)	• To assess the effect on wakefulness measured by the MWT, and EDS via ESS total score, and cataplexy using the WCR[1]	Completed
	3	NCT06470828 (FirstLight)	• To assess the effect on wakefulness measured by the MWT, and EDS via ESS total score, and cataplexy using the WCR[1]	Completed
	3	RadiantLight/ FirstLight	• The trials include ongoing long-term extension studies to assess durability of benefit and rare adverse effects[2]	Ongoing
	2b	NCT05687903	• To assess the effect on wakefulness measured by the MWT, and EDS via ESS total score, and cataplexy using the WCR	Completed
Alixorexton (ALKS 2680)	2	NCT06358950 (Vibrance-1)	• To assess the effect on wakefulness measured by the MWT, and EDS via ESS total score, and cataplexy using the WCR	Completed
			• Participants in the double-blind portion of the study were eligible to continue to a 7-week open-label safety extension portion of the study, followed by a long-term safety study[3]	Ongoing
ORX750	2a	NCT06752668 (CRYSTAL-1)	• Evaluate the safety, tolerability, efficacy, and pharmacokinetics of multiple doses of ORX750 for the first time in participants with NT1, NT2, and IH[4]	Ongoing
	2	NCT07096674	• Long-term extension study of the safety and efficacy of ORX750 in participants with NT1/2 or IH who completed a sponsored ORX750 Trial	Ongoing

EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OX2R orexin 2 receptor; WCR, weekly cataplexy rate

1. Takeda Pharmaceutical Company. Press release, 14 July 2025. Available here (accessed 04 March 2026); 2. touchNEUROLOGY. *Oveporexton phase 3 data signal new hope for narcolepsy type 1 treatment*. 15 September 2025. Available here (accessed 04 March 2026); 3. FirstWord Pharma. *Alkermes Presents Detailed Positive Results from Vibrance-1 Phase 2 Study of Alixorexton in Patients with Narcolepsy Type 1 at World Sleep Congress 2025.* 08 September 2025. Available here (accessed 04 March 2026); 4. Dauvilliers Y, et al. SLEEP 2025. Poster P-51.423

VIBRANCE-1 PHASE 2 STUDY DESIGN: ALIXOREXTON

Inclusion criteria:

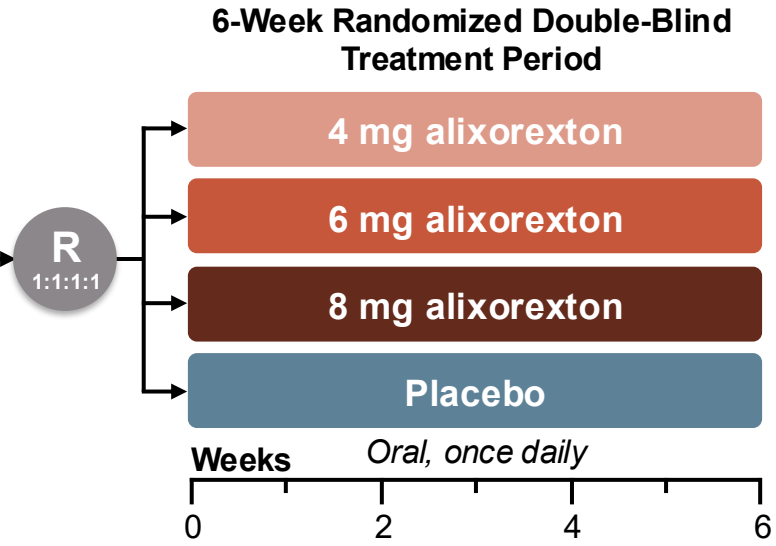
NT1 patients (ICSD-3-TR) with residual EDS and cataplexy

- 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 MWT from baseline to 6 weeks

Optional open-label extensions
7 Weeks

Patients receive alixorexton (adjusted dosing[a])

Safety follow-up
2 Weeks

ALKS 2680-301
Phase 2/3 long-term extension study

Secondary endpoint:

- Change in ESS from baseline to 6 weeks
- WCR at Week 6
- TEAEs, vital signs, laboratory parameters

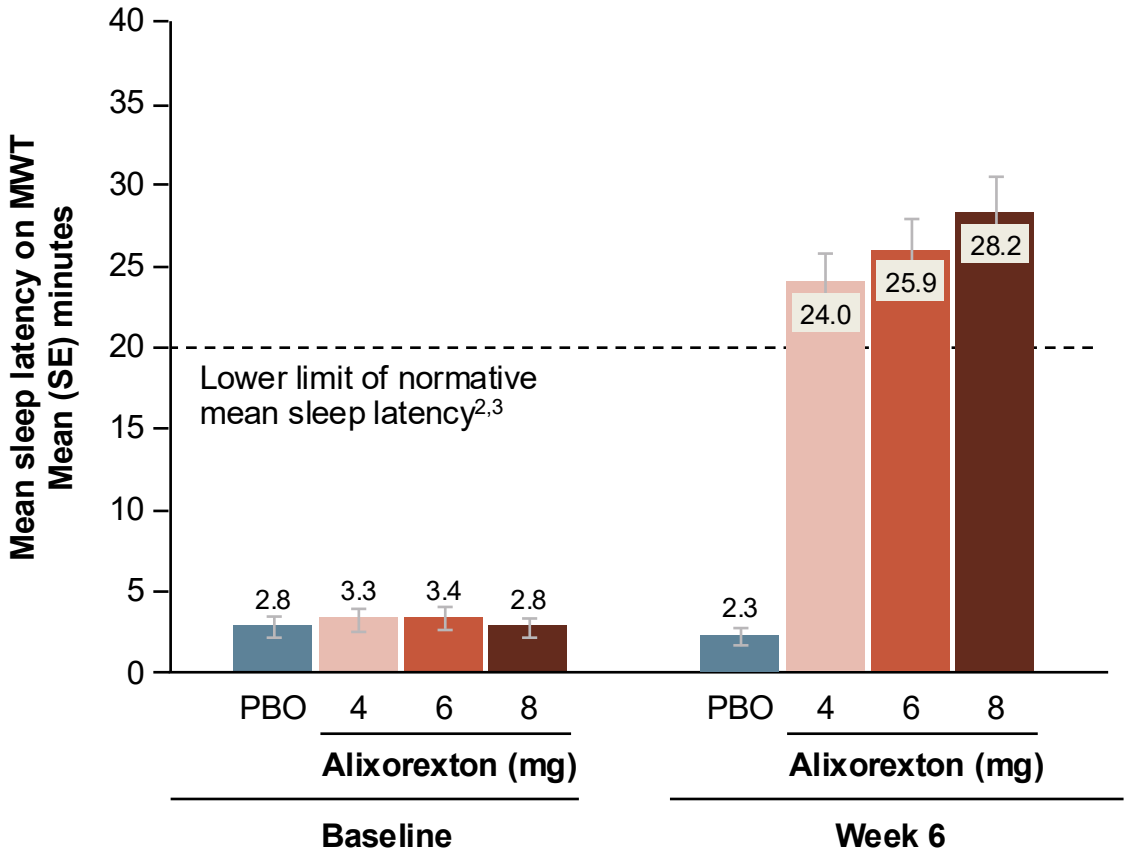
[a] All patients in the open-label extension period start with 6 mg alixorexton. Dose adjustment possible (up or down) during the first 2 weeks of the optional open-label extension period

BMI, body mass index; CSF, cerebrospinal fluid; EDS, Excessive Daytime Sleepiness; ESS, Epworth Sleepiness Scale; HLA, human leukocyte antigen; ICSD-3-TR, International Classification of Sleep Disorders, third edition, text revision; MWT, Maintenance of Wakefulness Test; NT1, narcolepsy type 1; R, randomisation; TEAEs, treatment-emergent adverse events; WCR, weekly cataplexy rate

1 . Plazzi G, et al. World Sleep Congress 2025. Abstract Session O-09

PRIMARY ENDPOINT: MWT[a]

ALIXOREXTON ACHIEVED NORMATIVE WAKEFULNESS WITH ALL DOSES



Primary endpoint analysis at Week 6

Change from baseline at Week 6 (minutes)[b]	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 (95% CI of LSM)	**-0.6** (-4.5, 3.3)	**21.6** (17.7, 25.6)	**23.5** (19.4, 27.6)	**25.5** (21.4, 29.5)
LSM difference vs PBO (95% CI of LSM differences)		**22.2** (17.2, 27.2)	**24.1** (19.0, 29.1)	**26.0** (21.0, 31.0)
P value (adjusted for multiplicity)		**0.01**	**<0.0001**	**<0.0001**

[a] Adapted from Plazzi et al. (2025);[3] study citations[1,2] shown as per the original slide.

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

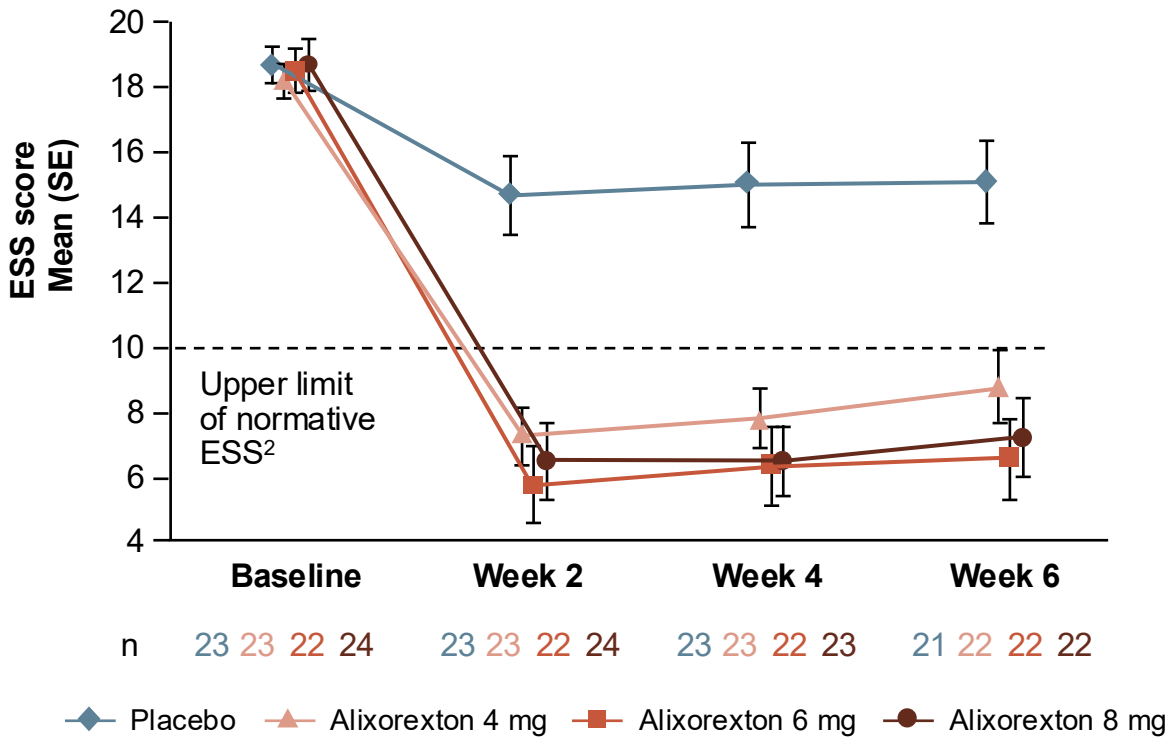
ANCOVA, analysis of covariance; CI, confidence interval; LSM, least squares mean; MWT, Maintenance of Wakefulness Test; PBO, placebo; SE, standard error.

1. Krahn LE, et al. J Clin Sleep Med. 2021;17(12):2489-98; 2. Doghramji K, et al. Electroencephalogr Clin Neurophysiol. 1997;103(5):554-62; 3. Plazzi G, et al. World Sleep Congress 2025. Abstract Session O-09

KEY SECONDARY ENDPOINT: ESS[a]

ESS SHOWED ALIXOREXTON ACHIEVED NORMATIVE WAKEFULNESS AT ALL DOSES

Randomised double-blind treatment period



Key secondary endpoint analysis at Week 6

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

[a] Adapted from Plazzi et al. (2025);[2] study citation[1] shown as per the original slide

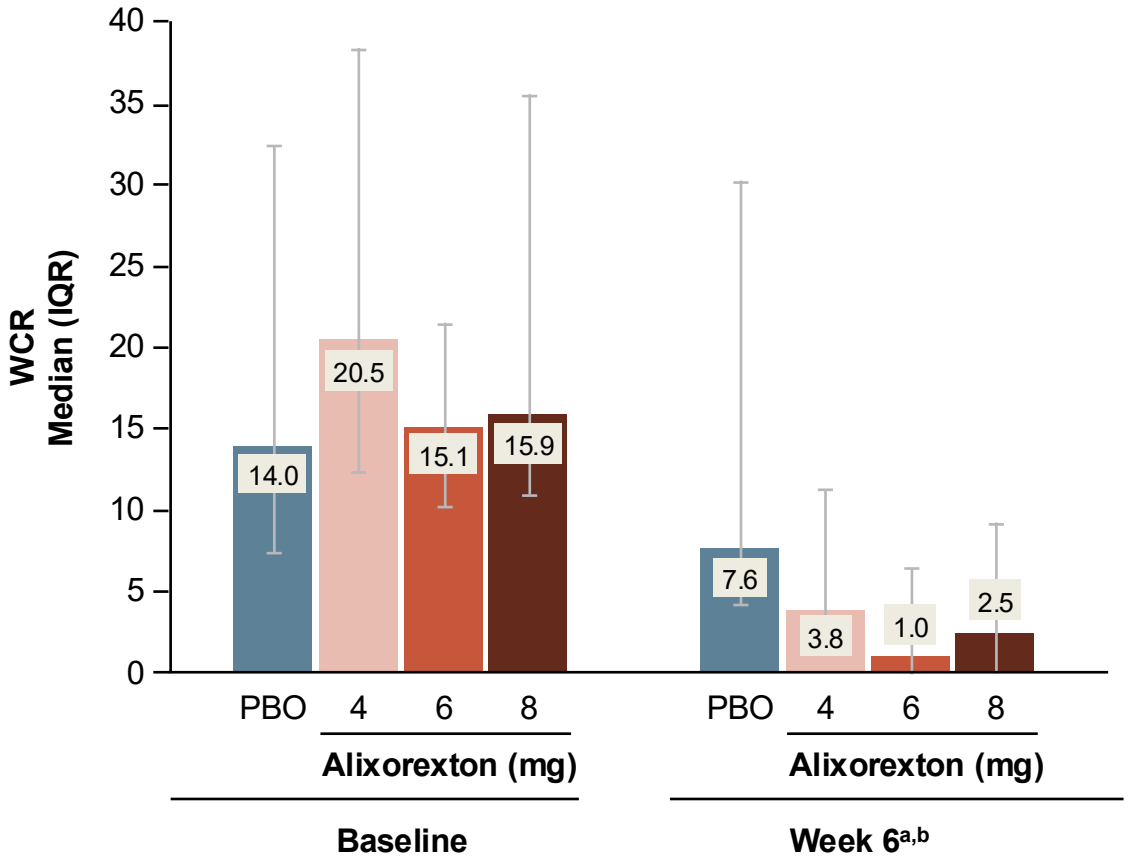
[b] ANCOVA model. Missing data were imputed using multiple imputation

ANCOVA, analysis of covariance; CI, confidence interval; ESS, Epworth Sleepiness Scale; LSM, least squares mean; PBO, placebo; SE, standard error

1. Johns MW. Sleep 1991;14:540-5; 2. Plazzi G, et al. World Sleep Congress 2025. Abstract Session O-09

KEY SECONDARY ENDPOINT: WCR

WCR AT WEEK 6 SHOWED ALIXOREXTON REDUCED CATAPLEXY EVENTS VS 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.

1. Plazzi G, et al. World Sleep Congress 2025. Abstract Session O-09

KEY SECONDARY ENDPOINT: SAFETY

ALIXOREXTON SHOWED NO SERIOUS TEAEs. MOST COMMONLY REPORTED TEAEs OCCURRED WITHIN THE 1ST WEEK OF DOSING

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

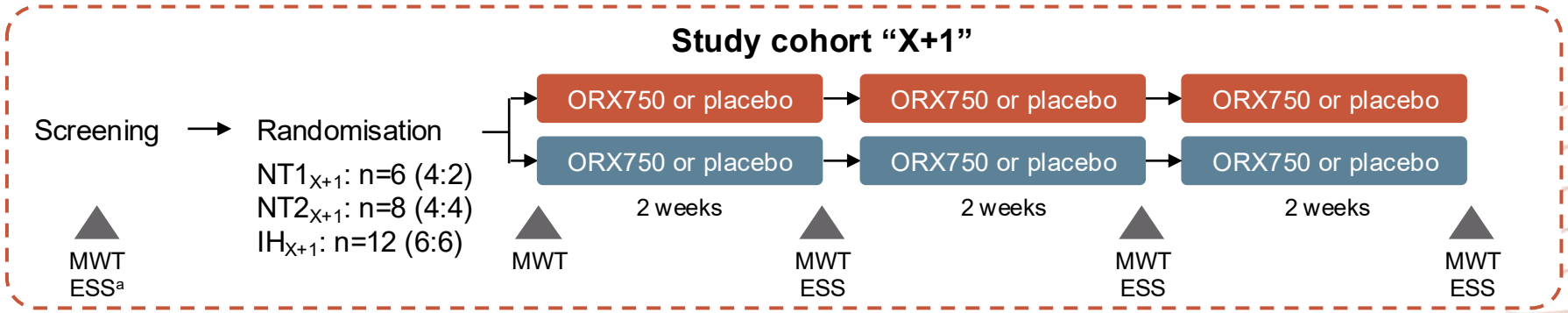
TEAE, treatment-emergent adverse event

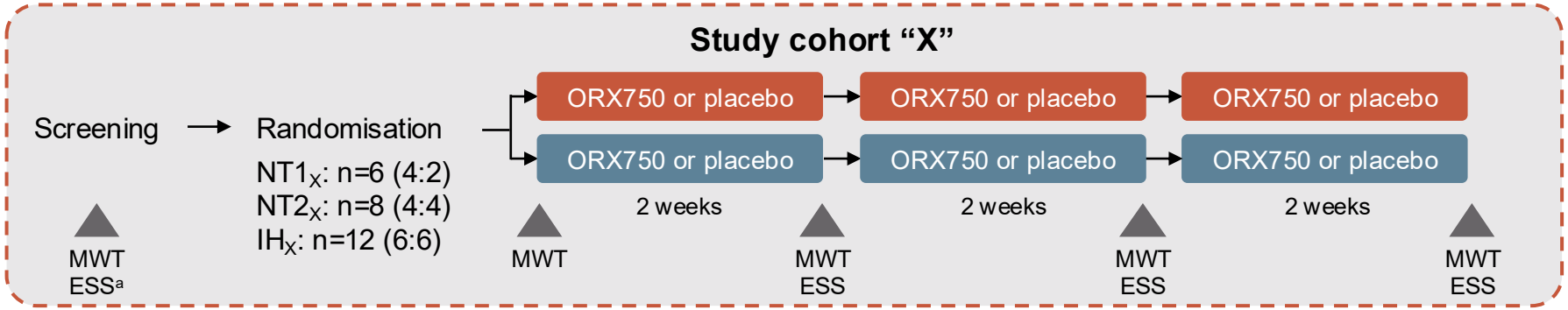
1. Plazzi G, et al. World Sleep Congress 2025. Abstract Session O-09

CRYSTAL-1 PHASE 2A STUDY DESIGN: ORX750

INVESTIGATES MULTIPLE DOSES FOR THE FIRST TIME IN NT1, NT2, AND IH

Data reviewed for each cohort and decision made to escalate or de-escalate for next dose level





Initial dose of 1.0 mg QD (NT1) and 2.0 mg QD (NT2 and IH)

Primary endpoints:

- Safety and tolerability

Secondary endpoints:

- Pharmacokinetic parameters of ORX750
- Efficacy on measures of excessive daytime sleepiness:
  - Objective: Maintenance of Wakefulness Test (MWT)
  - Subjective: Epworth Sleepiness Scale (ESS)

Study design is for illustrative purposes only

[a] Baseline MWT and ESS assessments are conducted after washout of medications used for narcolepsy or IH.

ESS, Epworth Sleepiness Scale; IH, idiopathic hypersomnia; MWT, Maintenance of Wakefulness Test; NT1/2, narcolepsy type 1/2; QD, once daily.

1. Dauvilliers Y, et al. SLEEP 2025. Poster P-51.423

CONCLUSIONS

CONCLUSIONS

- A deeper understanding of hypersomnolence biology remains essential to inform future therapeutic advances
- Improvements in diagnostic precision and clinical management are required to optimise patient outcome
- Treatment strategies should increasingly be individualised and aligned with underlying pathophysiology

COR2ED
THE HEART OF MEDICAL EDUCATION

For more information visit

SLEEP connect®
POWERED BY COR2ED

Connect on
LinkedIn @SLEEP CONNECT

Watch on
YouTube @COR2ED

Email
info@cor2ed.com

Visit us at
https://cor2ed.com/

Follow us on
X @SleepConnect_

Heading to the heart of Independent Medical Education since 2012