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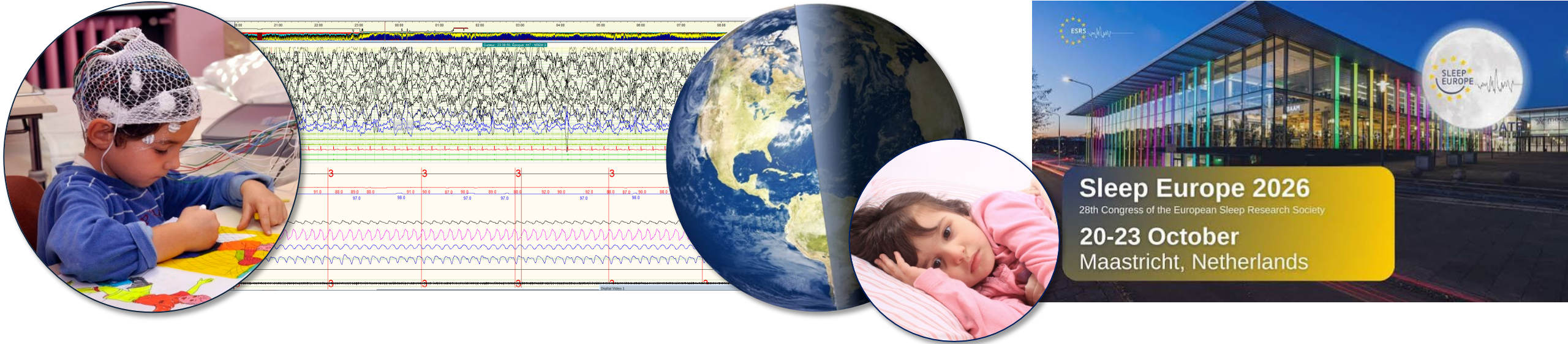
The dual orexin receptor antagonist daridorexant in pediatric insomnia disorder

An Idorsia-sponsored study

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Pediatric insomnia:

Common, persistent with significant clinical consequences

Prevalence (~8-12 %) ^{1,2}
increases from childhood to adolescence and may **persist over time** ³

Adult **insomnia disorder** criteria apply in pediatrics, irrespective of comorbidities ⁴

Insomnia disorder has been linked to ^{5,6}:





Pediatric insomnia

In neurodevelopmental disorders

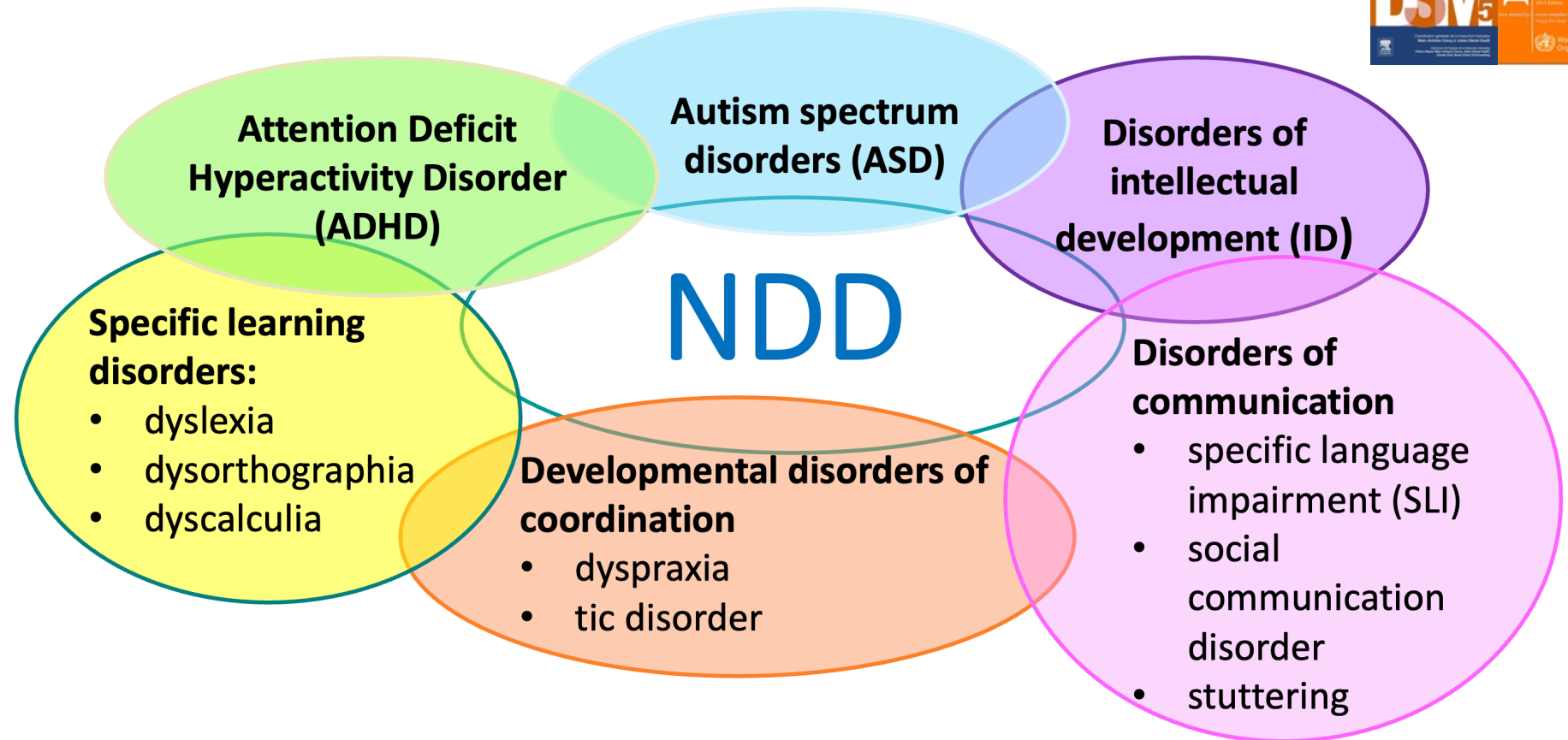


NDDs affect 1 in 6–8 children worldwide ¹

Insomnia symptoms are even **more prevalent in NDDs** ^{2–4}:

- **ASD (50-80 %)**
- **ADHD (25-75 %)**

Insomnia **worsens NDD core symptoms and comorbidities** ^{5–7}



NDD, neurodevelopmental disorders.

1. Zablotsky B, et al. *Pediatrics*. 2019;144; 2. Reynolds A M, et al. *Pediatric Clinics of North America*. 2011;58:685-98; 3. Reynolds AM, et al. *Sleep*. 2023;46; 4. Cortese S, et al. *JAACAP*. 2009;48:894-908; 5. Kim H, et al. *European Child & Adolescent Psychiatry*. 2024;33:1539-49; 6. Yavuz-Kodat E, et al. *J Clin Med*. 2020;9; 7. Becker SP, et al. *JAACAP*. 2019;58:433-42.



Current treatment options do not fully address the needs of children and families



First-line care ¹⁻³

- **Sleep hygiene** progressing to **behavioral interventions** are recommended first-line
- CBT-I access remains **limited** and may be **impractical** for some patients and families



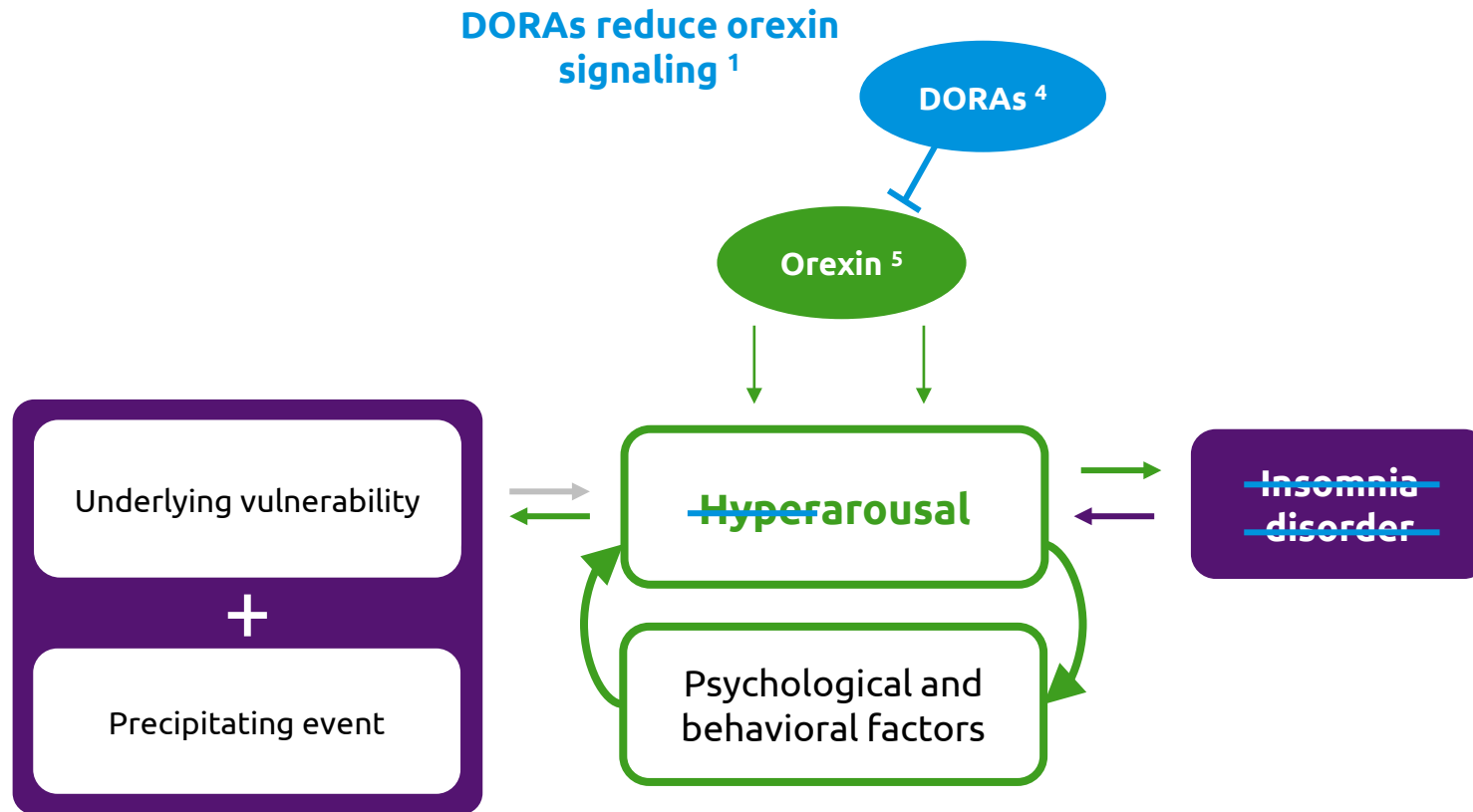
Pharmacological options ⁴

- EU approved options is **limited** to PR-melatonin in specific pediatric populations (ASD, neurogenetic disorders, ADHD) ⁴
- **No** FDA-approved medications for pediatric insomnia

Substantial **unmet need** for safe and effective treatments for pediatric insomnia



Orexin is a central regulator of wakefulness and a rational therapeutic target in insomnia disorder ¹⁻⁶



NDD and pediatric insomnia relevance:

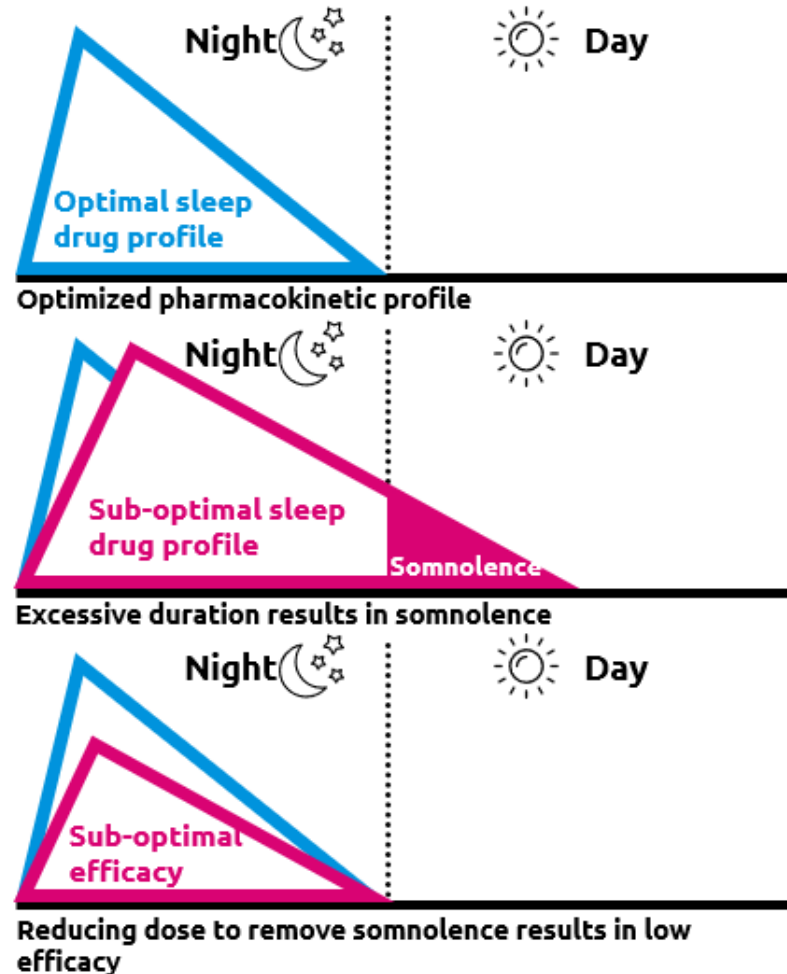
- Orexin modulates wakefulness and arousal ^{1,2}
- Dysregulated orexin signaling may contribute to hyperarousal in NDDs ¹
- Early clinical data in adult patients with NDD support further investigation of DORAs ³

DORA, dual orexin receptor agonist; NDD, neurodevelopmental disorder.

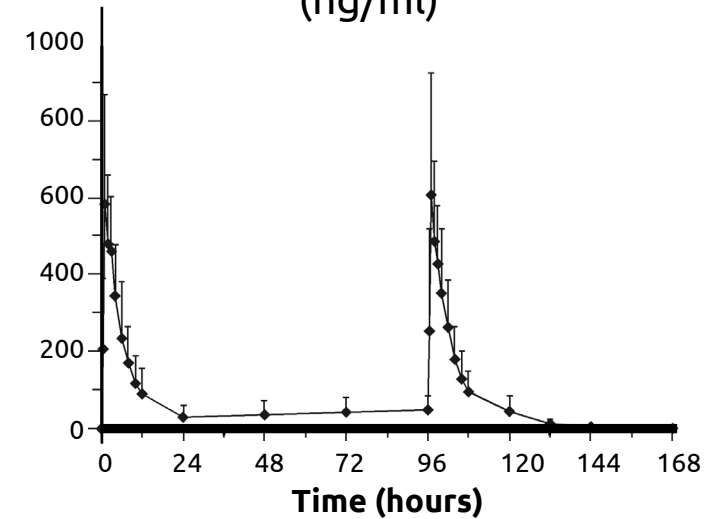
1. Knez R, et al. *Neuropsychiatr Dis Treat*. 2022;18:2683-2702; 2. Hyndych A, et al. *PLOS Mental Health*. 2025;2(12):e0000531; 3. Grassi G, et al. *Compr Psychiatry*. 2026;148:152700; 4. Riemann D, et al. *Sleep Med Rev*. 2010; 14:19-31; 5. Palagini L, et al. *J Sleep Res*. 2023; 32:e13825; 6. Levenson JC, et al. *Chest*. 2015; 147:1179-92.



Daridorexant: Optimized PK profile designed to balance nighttime efficacy and daytime functioning



Daridorexant plasma concentrations³
(ng/ml)



- Fast absorption²
- Rapid decline²
- Optimal terminal half-life (8 h)^{1,2}
- No accumulation over time²
- No active metabolite²



Daridorexant 50 mg is effective and well-tolerated in adults with insomnia disorder

Multicentre, randomized, double-blind, placebo-controlled, phase 3 trial ¹

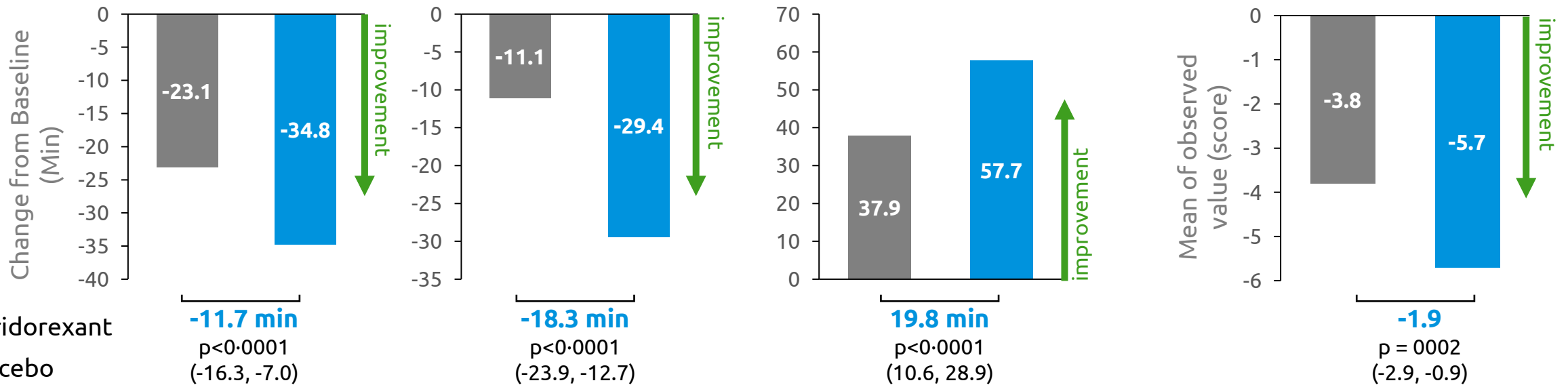
Month 3:

Sleep latency

WASO

sTST

**Daytime functioning
(IDSIQ[®] Sleepiness)**



Daridorexant 50 mg demonstrated significant improvements vs PBO,¹ which persisted up to 12 months of treatment ²⁻⁴



Adverse events with daridorexant 50 mg were **comparable with placebo**, and **rates of somnolence were minimal** for up to 12 months of treatment ^{1,2}

*Subjective total sleep time as recorded in a sleep diary. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; PBO, placebo.

1. Mignot E, et al. *Lancet Neurol.* 2022;21:125–39; 2. Kunz D, et al. *CNS Drugs.* 2023;37:93–106; 3. Phillips-Beyer A, et al. *Pharmaceut Med.* 2024; 38:133–44; 4. Phillips-Beyer A, et al. *Pharmaceut Med.* 2023;37:291–303.

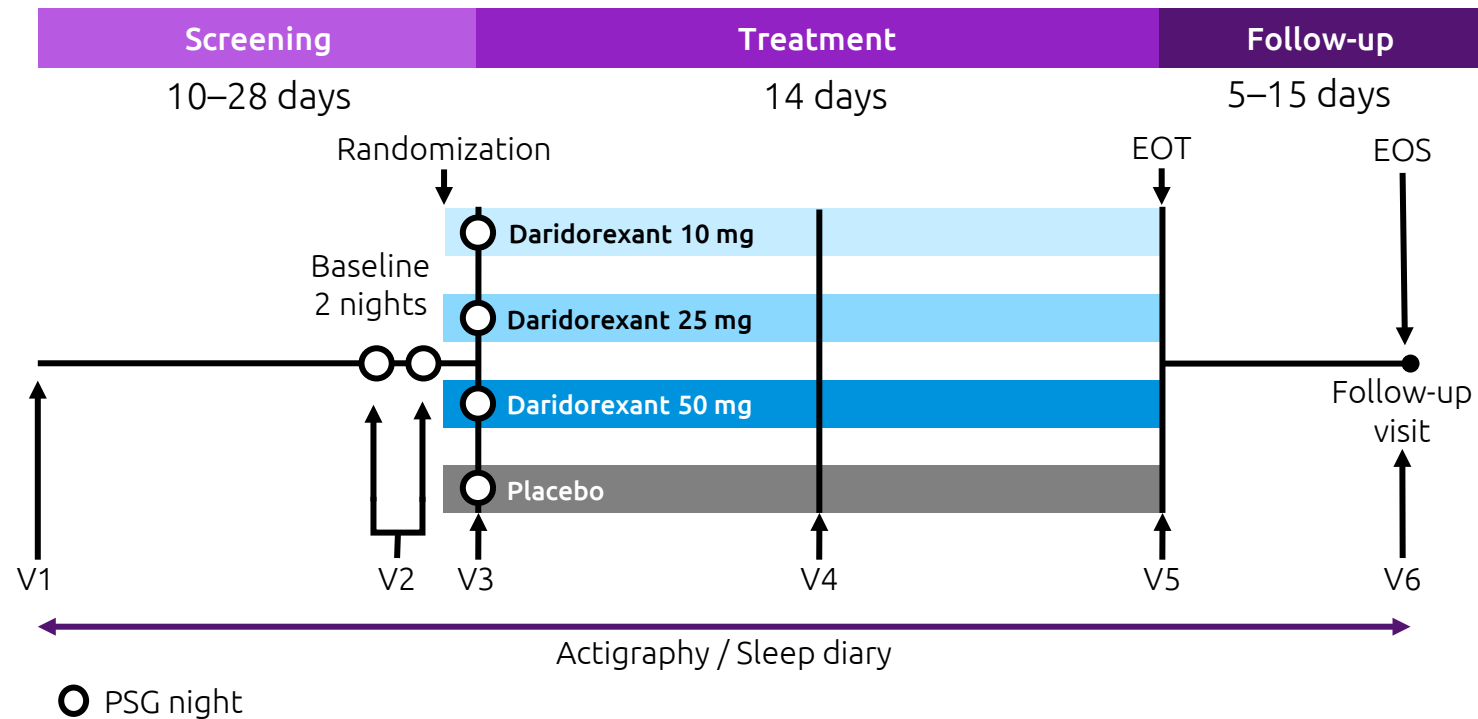


Characterizing daridorexant dose-response in pediatric insomnia patients



Double-blind, randomized, placebo-controlled, parallel-group, **Phase 2 dose-finding study** with 32 sites in 6 countries across US and Europe including **participants aged ≥ 10 to < 18 years (N = 166)** to characterize **daridorexant dose-response on TST** by PSG from baseline to Day 1

Study design



* The Day 1 PSG night started at approximately the same time as the baseline PSG nights and had approximately the same duration.

EOS, end of study; EOT, end of treatment; TST, total sleep time; V, visit.

1. Coloma P, et al. *BMJ Open*. 2026;16:e099888; 2. NCT05423717. Available at: <https://clinicaltrials.gov/study/NCT05423717>. Accessed August 2026.



Patient subgroups based on NDD status and neurodevelopmental traits^{1,2}

No-NDD Group	NDD Group	
n = 79	n = 37	n = 50
Insomnia disorder without associated NDD	Insomnia disorder associated with subthreshold ASD or ADHD traits	Insomnia disorder associated with NDD
<ul style="list-style-type: none">SRS T-score < 55 points ANDCBCL-ADHD Problems Scale score of < 65 at Screening	<ul style="list-style-type: none">No history of a diagnosis of NDDSRS T-score ≥ 55 AND/OR CBCL-ADHD Problems Scale score ≥ 65 at ScreeningPresence of a diagnosis of NDD at Screening	

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CBCL, Child Behavior Checklist; NDD, Neurodevelopmental disorders; SRS, Social Responsiveness Scale.

1. Coloma P, et al. *BMJ Open*. 2026;16:e099888; 2. NCT05423717. Available at: <https://clinicaltrials.gov/study/NCT05423717>. Accessed March 2026.



Key eligibility criteria and endpoints

✓ Key inclusion criteria

Age: ≥10 to <18 years

Insomnia disorder: In accordance with ICSD or DSM-5

SDSC: Score >16 on the Difficulty Initiating or Maintaining Sleep domain

Group 3: Documented history of NDD according to DSM-5

✗ Key exclusion criteria

Daytime napping: (≥1 h/day on ≥3 weekdays/week)

Suicidal ideation/attempt

Sleep-wake disorders: incl. sleep-related breathing disorders, periodic limb movement arousal

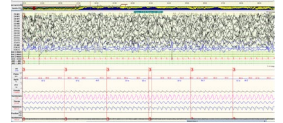
Acute/unstable medical conditions

Body weight <25 kg

Special therapy: CBT-I ≤ 1 month screening, treatment with sleep medication



Primary endpoint:
Change from baseline to Day 1* in PSG TST



Other key sleep-related endpoints presented:

- Change from baseline[†] to Day 1:
WASO and **LPS**
- Change from baseline[§] to Week 2:
sTST, **VAS sleep quality** and **VAS morning sleepiness**

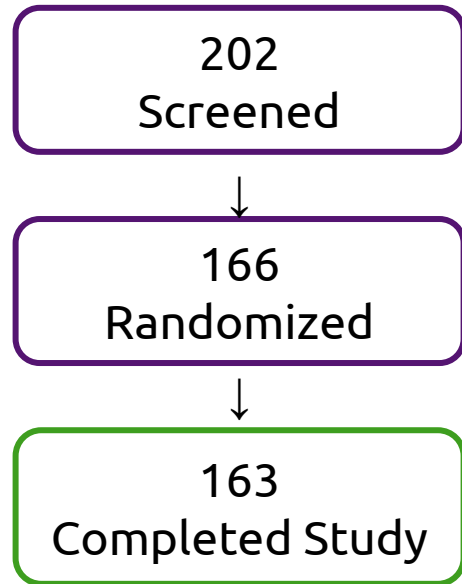
* The Day 1 PSG night started at approximately the same time as the baseline PSG nights and had approximately the same duration. † Baseline is the mean of the 2 PSG nights during the screening period.

§ Baseline, Week 1, and Week 2 are defined as the mean values of the 5 consecutive weekdays preceding Visit 3, Visit 4, and Visit 5; LPS, latency to persistent sleep; NDD, neurodevelopmental disorders; PSG, polysomnography; sLSO, subjective latency to sleep onset; TST, total sleep time; VAS, Visual Analog Scale; WASO, wake after sleep onset.



Patient Disposition: Excellent patient retention throughout the 14-day study

163 of 166 randomized patients completed the study (98.2 %)



Study completion by treatment arm

	Placebo	Daridorexant		
		10 mg	25 mg	50 mg
Randomized, N	41	41	42	42
Completed, n	40	40	41	42
Rate, %	97.6	97.6	97.6	100

Only 3 discontinuations overall

- Withdrawal by patient (n = 1)
- Withdrawal by caregiver (n = 1)
- Lost to follow-up (n = 1)

Study retention exceeded 97 % in every treatment group



Baseline demographics in the overall study population

n (%) or mean (SD)	Placebo n = 41	Daridorexant 10 mg n = 40	Daridorexant 25 mg n = 42	Daridorexant 50 mg n = 42	All patients n = 165
Sex					
Female	23 (56)	17 (43)	22 (52)	22 (52)	84 (51)
Male	18 (44)	23 (58)	20 (48)	20 (48)	81 (49)
Age (years)	14.1 (2.1)	13.2 (2.6)	14.7 (1.9)	13.5 (2.2)	13.9 (2.3)
Distribution					
10-11 years	6 (15)	16 (40)	3 (7)	9 (21)	34 (21)
12-17 years	35 (85)	24 (60)	39 (93)	33 (79)	131 (79)
Body weight (kg)	62.0 (16.4)	55.7 (16.8)	65.2 (19.3)	62.7 (21.8)	61.5 (18.9)



Baseline disease characteristics were balanced across treatment groups

	Placebo n = 41	Daridorexant 10 mg n = 40	Daridorexant 25 mg n = 42	Daridorexant 50 mg n = 42	All patients n = 165
Time since insomnia diagnosis – years	3.6 (3.1)	4.8 (3.7)	4.2 (3.6)	3.7 (3.3)	4.1 (3.4)
Sleep symptoms [n (%)]					
Difficulty initiating sleep	39 (95.1)	38 (95.0)	41 (97.6)	41 (97.6)	159 (96)
Difficulty maintaining sleep	35 (85.4)	33 (82.5)	38 (90.5)	40 (95.2)	146 (89)
Early morning awakening	29 (70.7)	27 (67.5)	31 (73.8)	37 (88.1)	124 (75)
Sleep disturbances leading to distress	39 (95.1)	38 (95.0)	40 (95.2)	41 (97.6)	158 (96)
Nighttime sleep variables [mean (SD)]					
PSG-total sleep time, min	413.6 (55.9)	416.1 (58.0)	399.4 (87.3)	383.9 (79.0)	403.1 (72.1)
PSG-latency to persistent sleep*, min	29.1 (3.1)	30.1 (2.6)	35.3 (3.2)	35.4 (3.4)	32.4 (3.1)
PSG-wake after sleep onset, min	45.5 (38.0)	40.9 (38.1)	38.6 (28.5)	55.1 (52.3)	45.1 (40.3)
Subjective total sleep time, min [†]	428.5 (120.9)	404.4 (96.2)	392.8 (117.4)	389.4 (98.7)	403.7 (108.6)
NDD Group [n]	21	22	21	23	87

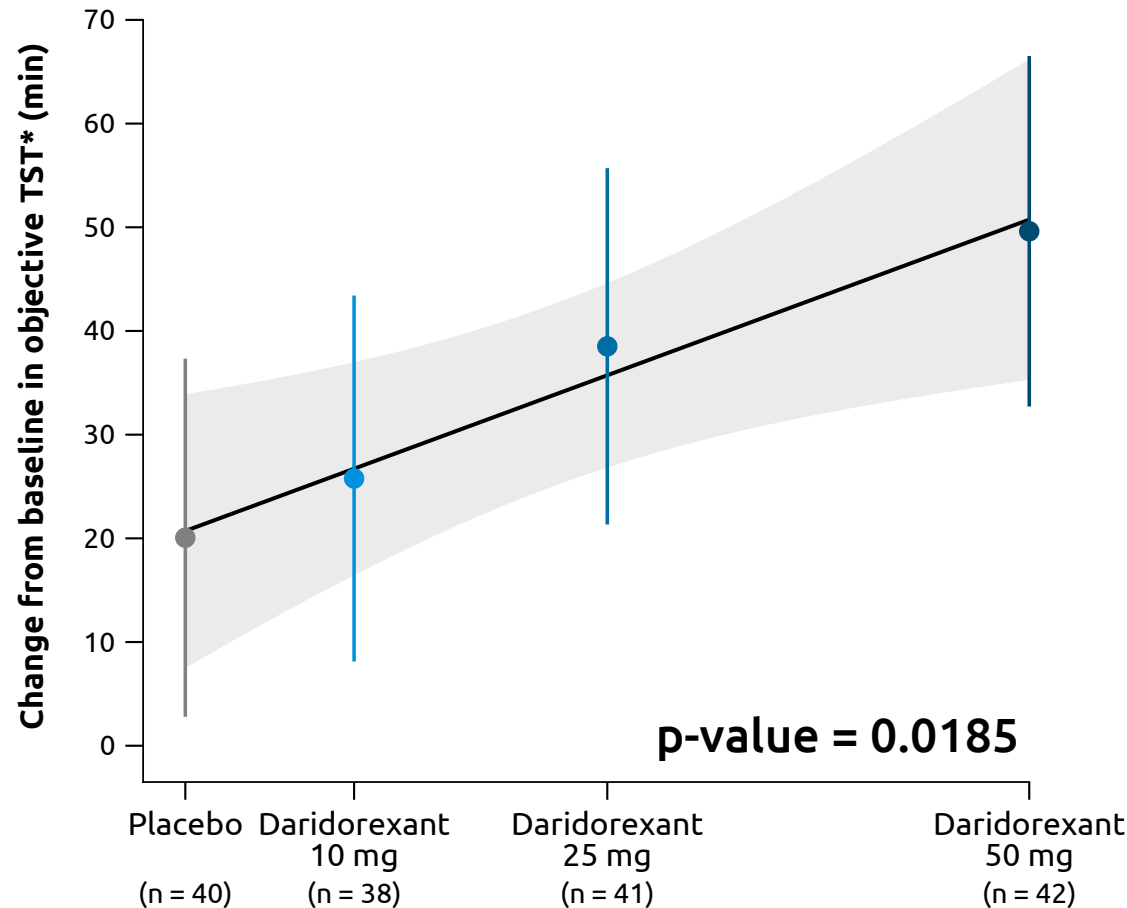
* Data are geometric mean (SD). The calculation of the geometric mean and standard deviation is performed with the imputation of 0.5 min for zero values of latency to persistent sleep. Percentages may not sum to 100 due to rounding.

† Data for the subjective total sleep time, as reported by the caregiver, are shown for 155 patients (94%). NDD, neurodevelopmental disorders; PSG, polysomnography; SD, standard deviation; VAS, Visual Analog Scale.



Daridorexant significantly increased objective TST in a dose-dependent manner

Primary endpoint - Change from baseline to Day 1 (measured by PSG)



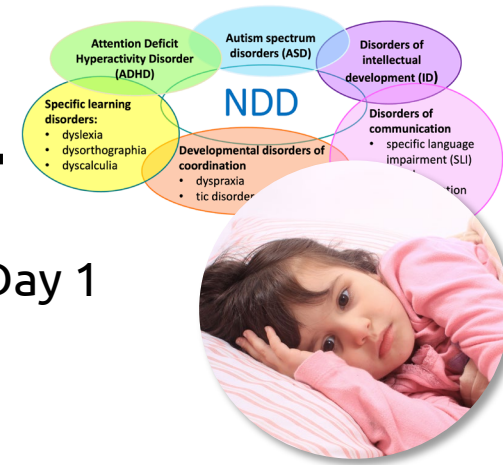
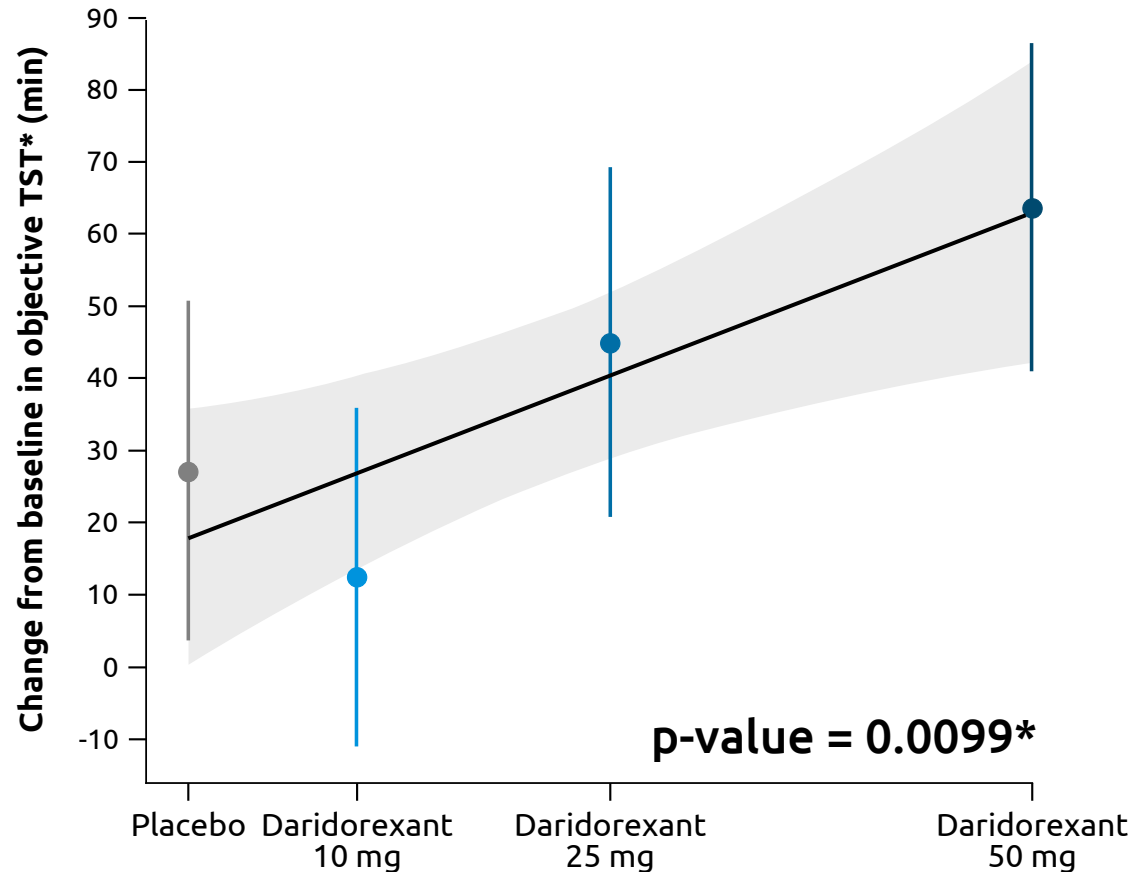
**Daridorexant 50 mg
increased TST 49.6 min
vs. 20.1 min with PBO**
LSM difference +29.6 min
[95% CI 5.4, 53.7], p=0.0166

* Data are presented as least-square means $\pm$ 95% confidence intervals. Grey area represents the 95% confidence interval of the dose-response curve. CI, confidence interval; LSM, least-square mean; PSG, polysomnography; TST, total sleep time.



NDD subgroup: Dose-response observed in objective TST

Exploratory analysis of the primary endpoint - Change from baseline to Day 1

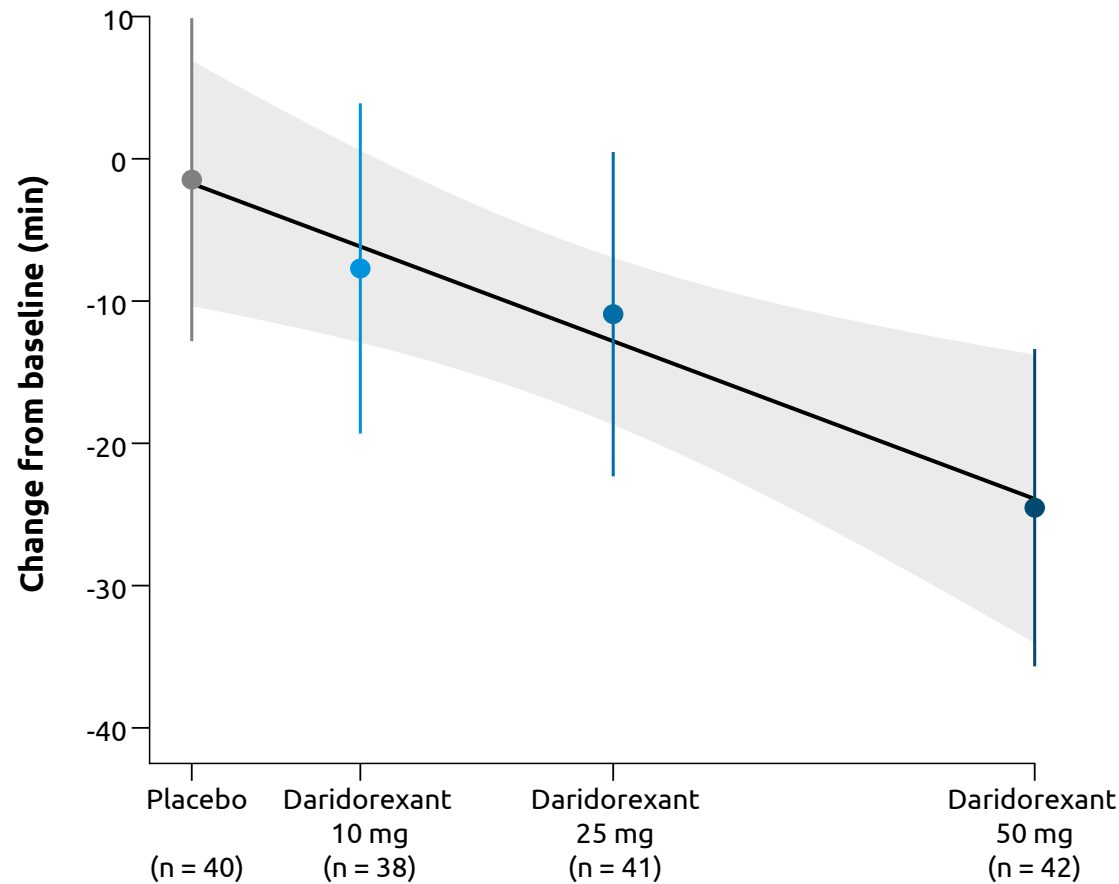


**Daridorexant 50 mg
increased TST 63.8 min
vs. 27.2 min with PBO**
LSM difference +36.3 min
[95% CI 3.1, 69.5], p=0.0311

* Data are presented as least-square means $\pm$ 95% confidence intervals. Data not adjusted for multiple comparisons. Grey area represents the 95% confidence interval of the dose-response curve. CI, confidence interval; LSM, least-square mean; NDD, neurodevelopmental disorder..

Daridorexant reduced wakefulness at night

Other endpoints - Change from baseline to Day 1 (WASO* measured by PSG)



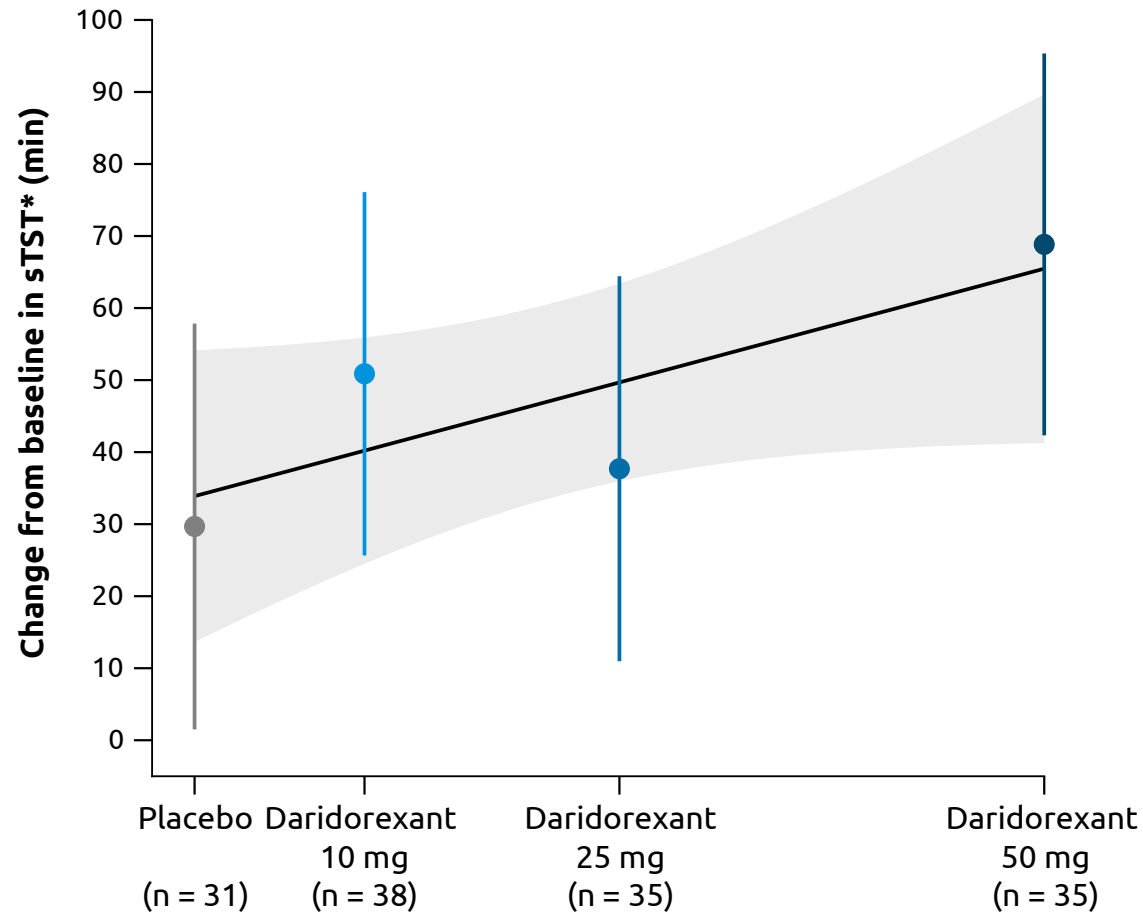
Daridorexant 50 mg reduced WASO
-24.5 min vs. -1.5 min with PBO
 LSM difference -23.1min [95% CI -38.8, -7.3]

* Data are presented as least-square means $\pm$ 95% confidence intervals. Grey area represents the 95% confidence interval of the dose-response curve. CI, confidence interval; LSM, least-square mean; PSG, polysomnography; WASO, wake after sleep onset.



Daridorexant 50 mg showed the largest numerical improvement vs. placebo in subjective duration of sleep

Other endpoints - Change from baseline to Week 2 in sTST (caregiver-reported)



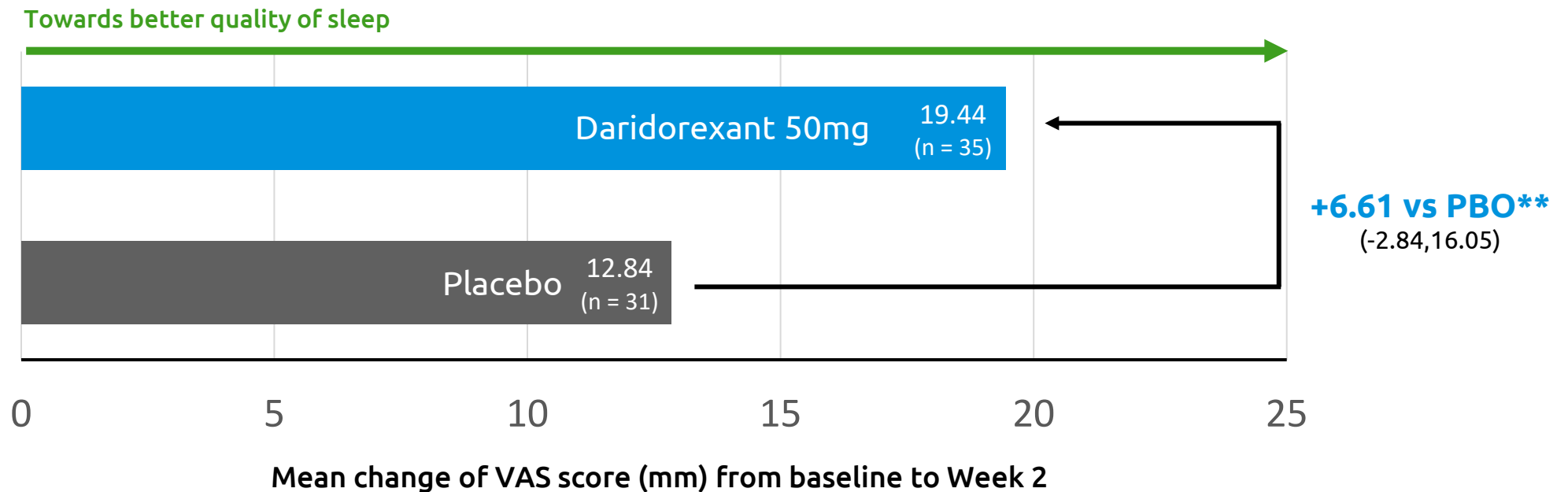
**Daridorexant 50 mg
increased sTST 68.8 min
vs. 29.7 min with PBO**
LSM difference +39.2 min
[95% CI 0.6, 77.7]

* Data are presented as least-square means $\pm$ 95% confidence intervals. Grey area represents the 95% confidence interval of the dose-response curve. CI, confidence interval; LSM, least-square mean; sTST, subjective total sleep time WASO, wake after sleep onset.



Daridorexant 50 mg improved VAS quality of sleep

Other outcomes - Change from baseline to Week 2 as assessed by the caregiver*



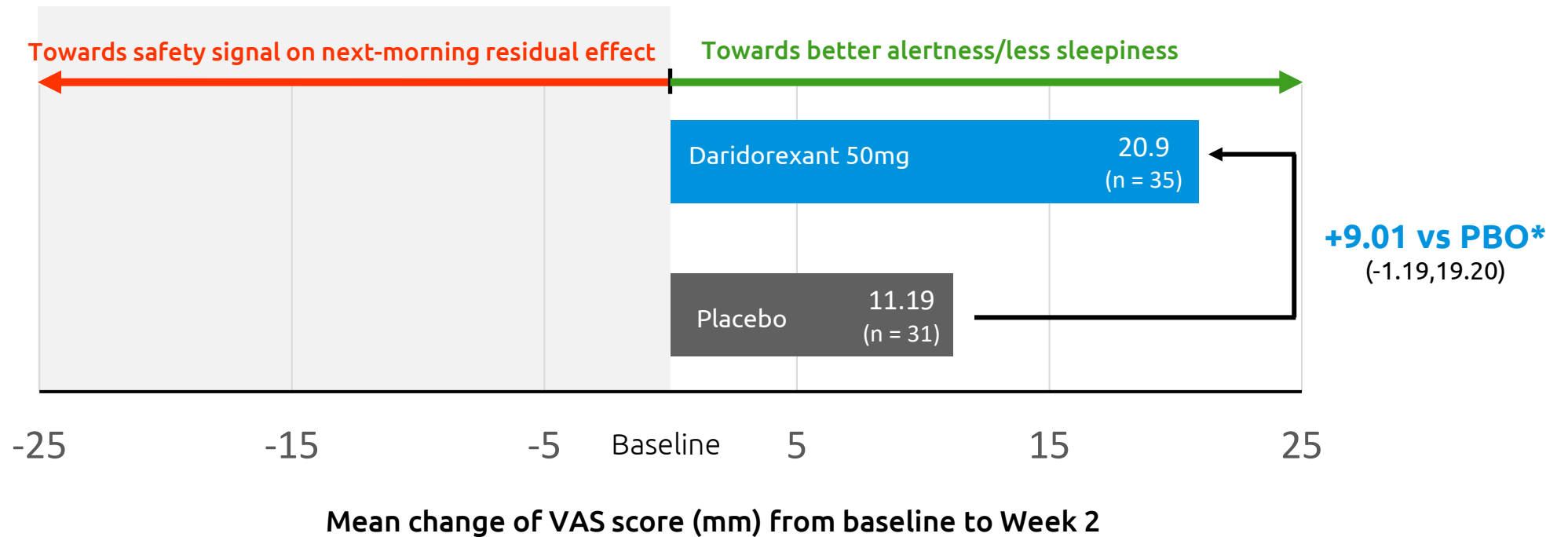
Numerically largest improvements observed for 50 mg daridorexant in quality of sleep

* Caregiver-reported VAS scores. Scores ranging from 0-100. ** LSM (95% Confidence interval. Numerical increase, not statistically significant.



Daridorexant 50mg reduced morning sleepiness

Safety outcomes - Change from baseline to Week 2 as assessed by the caregiver



Largest numerical reduction in morning sleepiness was observed for daridorexant 50 mg

*Caregiver-reported VAS scores. Scores ranging from 0-100. A higher score indicates less morning sleepiness and improved alertness. * LSM (95% Confidence interval. Numerical increase, not statistically significant
VAS, visual morning sleepiness, PBO, Placebo



Daridorexant was well tolerated across all doses, with similar safety profile across treatment groups

Safety outcomes*

n (%)	Placebo (n = 41)	Daridorexant 10 mg (n = 40)	Daridorexant 25 mg (n = 42)	Daridorexant 50 mg (n = 42)
Patients with ≥1 adverse event	10 (24.4)	11 (27.5)	7 (16.7)	10 (23.8)
Patients with ≥1 serious adverse event	1 (2.4) [§]	0	0	0
Patients with adverse events leading to discontinuation of study treatment	0	0	1 (2.4)	0
Treatment-emergent adverse events[†]				
Somnolence	1 (2.4)	2 (5.0)	1 (2.4)	3 (7.1)
Headache	0	3 (7.5)	2 (4.8)	1 (2.4)
Nasopharyngitis	1 (2.4)	2 (5.0)	1 (2.4)	1 (2.4)
Nausea	2 (4.9)	0	0	1 (2.4)
Fatigue	0	2 (5.0)	0	0
Adjudicated adverse events[§]				
Excessive daytime sleepiness, cataplexy [§]	0	2 (5.0%)	0	1 (2.4)
Hallucinations/sleep paralysis	0	0	0	1 (2.4)
Complex sleep behavior	0	0	0	0
Drug abuse	0	0	0	0
Suicidal ideation/self-injury	0	0	0	0



No AEs suggestive of abuse potential or physical dependence

No withdrawal symptoms during follow-up

*Adverse events that occurred during the double-blind treatment period and up to 5 days after the end of treatment in the safety population are included in the table and presented with their preferred terms.

†Adverse events are listed for those that occurred in at least two patients in any study group. §Adjudicated adverse events were reported during the double-blind treatment up to 5 days after the end of treatment and were adjudicated blindly by an independent safety board. §Reported during the safety follow-up period. \$ TEAEs suggestive of narcolepsy-like symptoms ||One 10-year-old female patient experienced a mild, non-serious episode of sleep paralysis on Day 15 upon awakening during the night. No hallucinations were reported, no treatment was required, and the event resolved on Day 19 after the last dose of study treatment on Day 15. The participant completed the study per protocol.



Conclusions: The dual orexin receptor antagonist daridorexant in pediatric insomnia disorder



- **Primary endpoint:** Statistically significant **dose-dependent improvement** in **objective total sleep time** from baseline to Day 1 ($p = 0.0185$)
 - Efficacy was also demonstrated in children with insomnia and **NDDs**
- **Daridorexant 50 mg showed consistent and clinically meaningful improvements** across objective and subjective sleep measures
- **Morning sleepiness was reduced**, with the largest numerical improvement on daridorexant 50 mg
- Daridorexant was **well tolerated across all dose groups**, with a safety profile **consistent with that observed in adults**

These findings support further investigation of daridorexant in pediatric insomnia disorder, particularly those with NDD, given the highest unmet needs

Thank you for your attention !