The dual orexin receptor antagonist daridorexant in pediatric insomnia disorder

Carmen M. Schröder[1,2,3], Akinyemi Ajayi[4], Oliviero Bruni[5], Yves Dauvilliers[6,7], Ingo Fietze[8], Katharina Lederer[8], Judith Owens[9], Adela Fraile Pereda[10], Fabio Pizza[11,12], Martine Clozel[13], Chiara De Stefani[13], Michael Meinel[13], Emanuele Noseda[13], Cedric Vaillant[13], Daniel L. Coury[14]

[1]Strasbourg University Hospitals, Department of Child and Adolescent Psychiatry, Strasbourg, France, [2] CNRS UPR 3212, Team "Sleep, Clock, Light and Neuropsychiatry", Institute of Cellular and Integrative Neurosciences, Strasbourg, Strasbourg, France, [3] Strasbourg University, Excellence Center for Autism and Neurodevelopmental Disorders, Strasbourg, France, [4] Central Florida Pediatric Sleep Disorders Institute, Winter Park, Florida, United States, [5] Sapienza University, Department of Human Neurosciences, Rome, Italy, [6] Gui-de-Chauliac Hospital, Department of Neurology, Sleep-Wake Disorders Center, Montpellier, France, [7] University of Montpellier, Institute of Neurosciences of Montpellier, INSERM, Montpellier, France, [8] Advanced Sleep Research GmbH, Berlin, Germany, [9] Boston Children's Hospital, Boston, United States, [10] Hospital Clínico San Carlos (IdISCC), Department of Neurophysiology, Institute of Neuroscience, Madrid, Spain, [11] IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy, [12] University of Bologna, Department of Biomedical and Neuromotor Sciences (DIBINEM), Bologna, Italy, [13] Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland, [14] Nationwide Children's Hospital, Columbus, Ohio, United States

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Introduction

- Insomnia prevalence increases from childhood to adolescence and may persist over time[1]
- It affects children with and without neurodevelopmental disorders (NDDs - incl. ASD/ADHD) and may exacerbate NDD symptoms[2]
- Pharmacologic treatment options are limited, often used off-label, and supported by little pediatric evidence[3]
- Daridorexant is an equipotent antagonist of both orexin receptors (OX_1 and OX_2), blocking the hyperactive wake signaling, a key cause of insomnia disorder

Study objective

To characterize the dose-response of daridorexant in paediatric insomnia patients

Methods

- Double-blind, randomized, placebo-controlled, parallel-group, **Phase 2 dose-finding study** in participants aged ≥10 to <18 years (N = 166) at 32 sites in 6 countries across US and Europe
- **Once-daily daridorexant (10, 25, 50 mg) or placebo for 14 days**, stratified by NDD status. The treatment period was preceded by a 10-28 day screening period and followed by a 5-15 day safety follow-up period
- **Key inclusion criteria:** Age: ≥10 to <18 years, ICSD or DSM-5 insomnia disorder, SDSC: Score >16 on the Difficulty Initiating or Maintaining Sleep domain. NDD subgroup: documented history of NDD according to DSM-5; or SRS T-score ≥ 55 AND/OR CBCL-ADHD Problems Scale score ≥ 65 at Screening
- **Key exclusion criteria:** Daytime napping, suicidal ideation, sleep-wake disorders, acute/unstable medical conditions, body weight <25 kg, CBT-I ≤ 1 month at screening, treatment with sleep medication
- **Primary endpoint:** Change from baseline to Day 1 in Total Sleep Time (TST), as measured by polysomnography (PSG)
- **Other endpoints:** Change from baseline to Week 2: subjective (s)TST, visual analogue scales (VAS) for sleep quality and morning sleepiness

Results

Table 1. Baseline characteristics in the overall study population.

n (%) or mean (SD)	Placebo	10 mg	25 mg	50 mg	Total
Female	23 (56%)	17 (43%)	22 (52%)	22 (52%)	84 (51%)
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)

Table 2. Baseline insomnia disorder characteristics were balanced across treatment groups.

Mean (SD)	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)
Nighttime sleep variables					
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

Overall, 96% of children had difficulty falling asleep, 89% maintaining sleep, and 75% suffered from early awakenings. In almost the totality (96%) sleep led to distress.

Figure 1. Daridorexant significantly increased objective TST in a dose-dependent manner at Day 1 (49.6 min with daridorexant 50 mg vs. 20.1 min with placebo (LSM difference +29.6 min [95% CI 5.4, 53.7], p=0.0166).

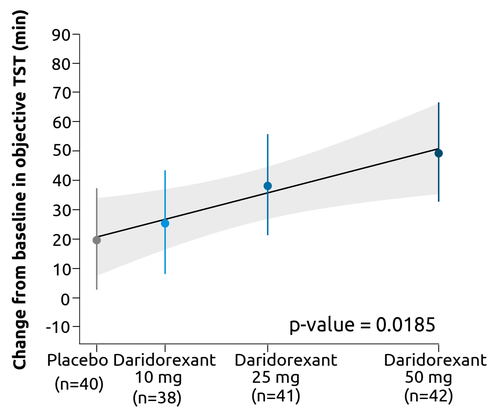
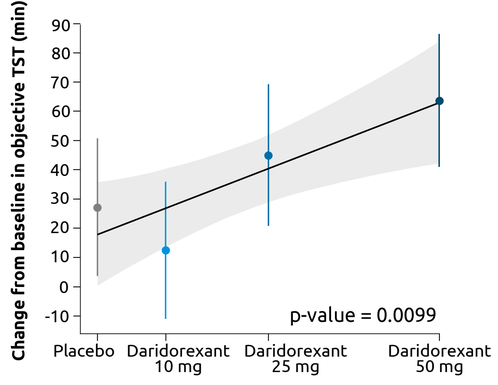


Figure 2. Daridorexant increased in a dose-dependent manner objective TST at Day 1 **in NDD subgroup** (63.8 min with daridorexant 50 mg vs. 27.2 min with placebo, LSM difference +36.3 min [95% CI 3.1, 69.5], p=0.0311)



For all figures: Data are presented as least-square means ± 95% confidence intervals. Grey area represents the 95% confidence interval of the dose-response curve. CI, confidence interval; SD, standard deviation

Figure 3. Daridorexant 50 mg showed the largest numerical improvement vs. placebo in sTST at Week 2 (68.8 min vs. 29.7 min with placebo, LSM difference +39.2 min [95% CI 0.6, 77.7]).

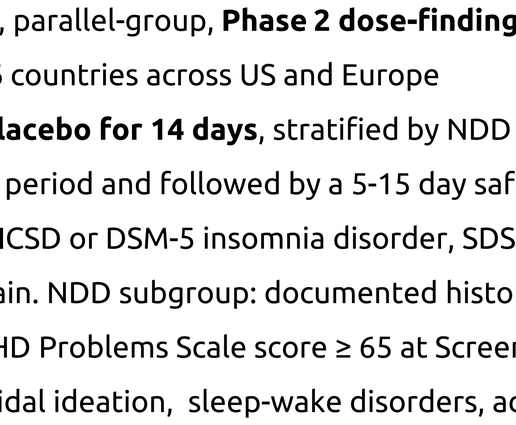


Figure 4. Daridorexant 50 mg showed the largest numerical improvement vs. placebo in VAS quality of sleep at Week 2.

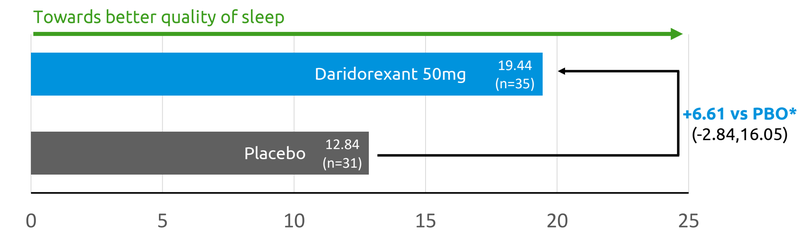
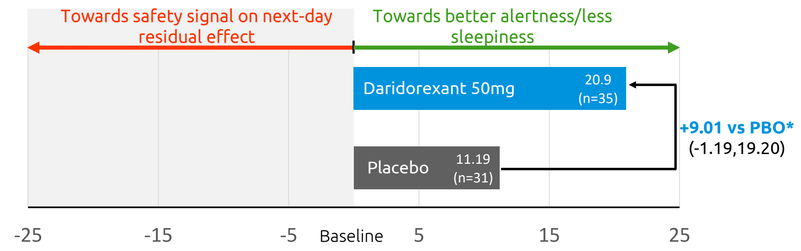


Figure 5. Daridorexant 50mg reduced VAS morning sleepiness at Week 2.



Safety . Daridorexant was well tolerated across all doses with similar safety profile across treatment groups. There were 10 (24.4%), 11 (27.5%), 7 (16.7%) and 10 (23.8%) patients with ≥1 adverse event in the placebo, daridorexant 10, 25, and 50 mg arms respectively.

Conclusions

- In children with insomnia disorder, daridorexant induced a statistically-significant dose-dependent improvement in objective total sleep time from baseline to Day 1
- 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

References

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Disclosures

The study was funded by Idorsia Pharmaceuticals Ltd. **CS** reports consulting fees from Medice and Biocodex, honoraria from Neurim Pharmaceuticals, Biocodex, Salmon, Medice, and InfectoPharm, expert testimony fees from Biocodex, meeting support from Neurim, Medice, and Biocodex, and service on advisory board for Neurim, Medice, and Biocodex. **OB** reports consulting fees from Neurim and Fidia Farmaceutici, honoraria and meeting support from Neurim Pharmaceuticals. **YD** reports institutional funding from Idorsia Pharmaceuticals Ltd, serving on advisory boards for Avadel, Bioprojet, Centessa, Harmony Biosciences, Idorsia, Jazz Pharmaceuticals, Pharmanocia, and Takeda, and serving as a member of a Data Safety Monitoring Board for Idorsia Pharmaceuticals Ltd. **IF** reports receiving honoraria for lectures from Idorsia Pharmaceuticals and Procter & Gamble, reimbursement of travel expenses from Idorsia Pharmaceuticals, and serves as Director of the German Sleep Foundation. **JO** reports receiving consulting fees from AGB Pharma, expert testimony fees from Dovel and Luner LLP, royalties from Wolters Kluwer and service as a member of an Independent Data Monitoring Committee for Idorsia Pharmaceuticals. **FP** reports honoraria for presentations from Bioproject, meeting support from Bioproject, and participation on an advisory board for Takeda. **MC**, **CDS**, **MM**, **EN** and **CV** are employees of Idorsia Pharmaceuticals Ltd. **DC** reports receiving payment for participation on a Data Safety Monitoring Board or Advisory Board from AMO Pharma, MapLight, MaraBiosciences, and Scioto Biosciences. **AA**, **KL**, **AFP**, **FP**, and **IF** were investigators of the study.

Poster presented at the Sleep Europe Congress 2026