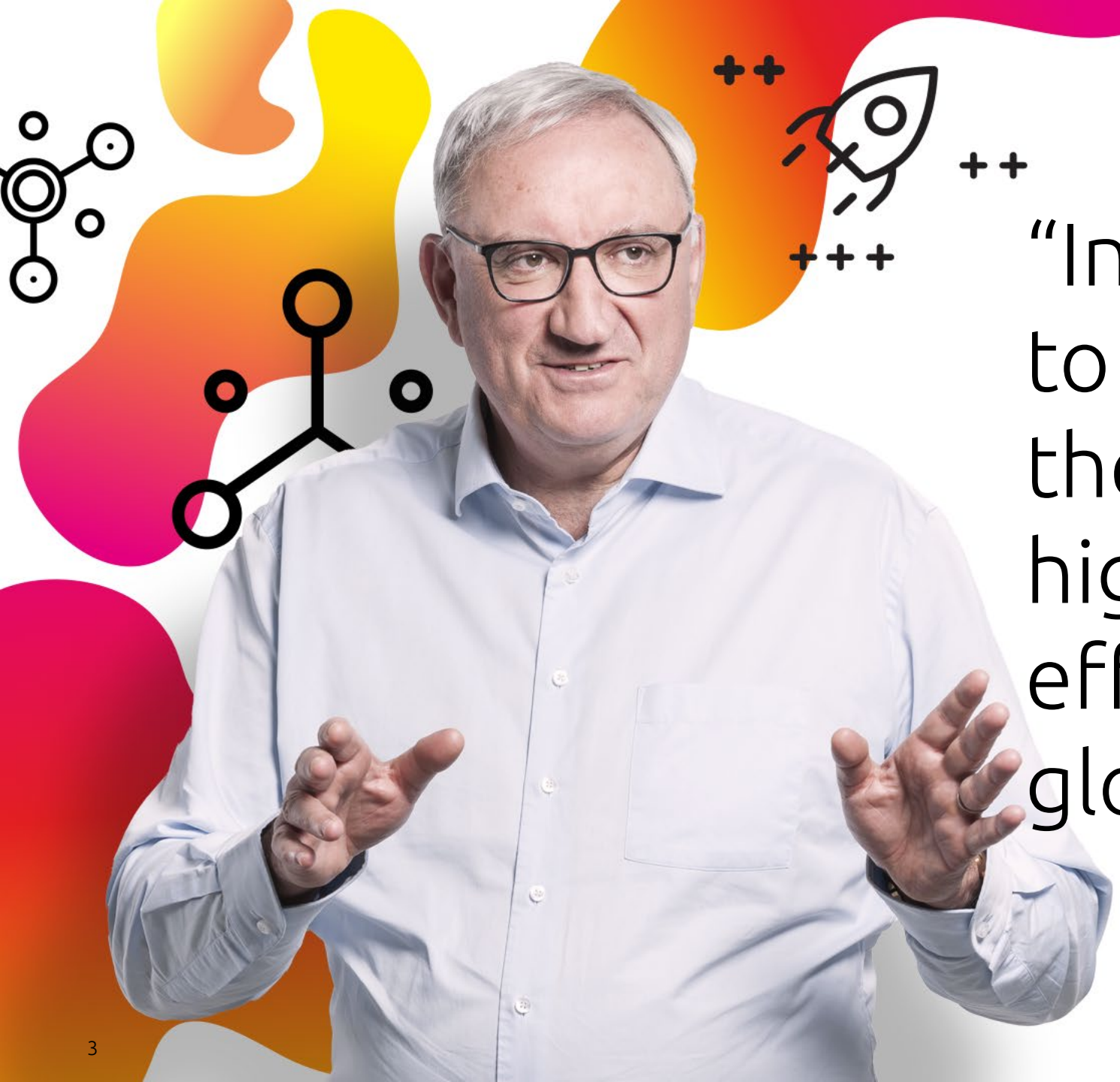
Idorsia – Reaching out for more

Investor webcast – January 2022

The following information contains certain “forward-looking statements”, relating to the company’s business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “are expected to”, “will”, “will continue”, “should”, “would be”, “seeks”, “pending” or “anticipates” or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company’s investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company’s existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.



“In 2022 we are going to see the results of the sustained and highly professional efforts from our global teams”

Jean-Paul Clozel
Chief Executive Officer

Idorsia receives Japanese PMDA approval of PIVLAZ (clazosentan sodium) 150 mg

Clazosentan is only approved in Japan under the tradename PIVLAZ™ and is not yet available. Clazosentan is investigational in all other countries.

idorsia

The Lancet Neurology

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

Emmanuel Mignot, David Mayleben, Ingo Fietze, Damien Leger, Gary Zammit, Claudio L A Bassetti, Scott Pain, Dalma Seboek Kinter, Thomas Roth, on behalf of the investigators

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

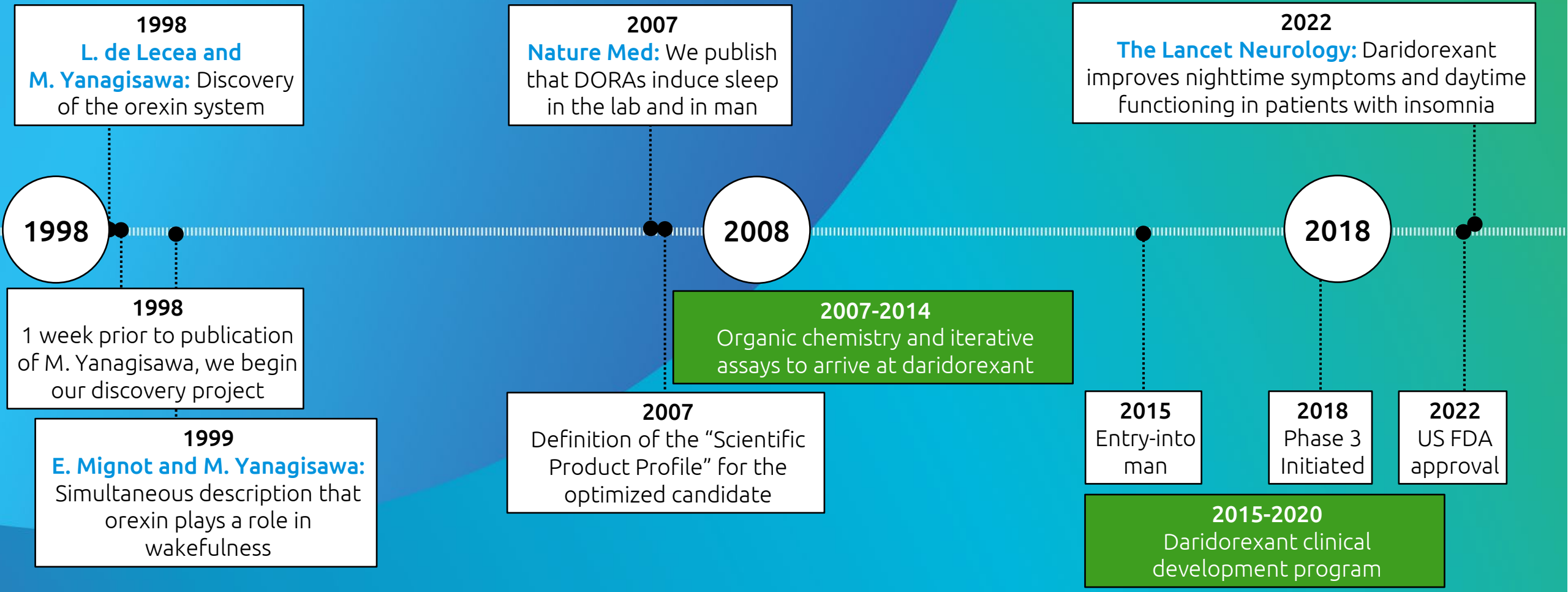
Investor webcast – January 2022

Martine Clozel

Chief Scientific Officer

Daridorexant – The Lancet Neurology

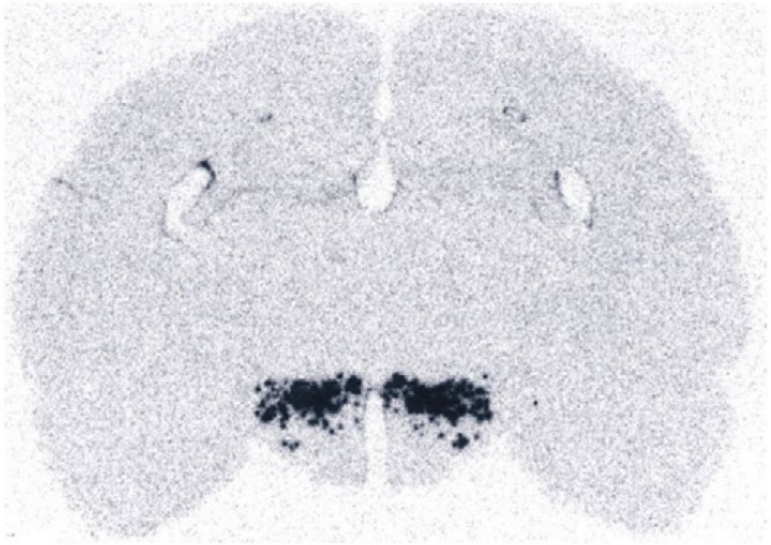
>20 years of drug design



Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

A precision mechanism of action

- Very few cells produce OX



~70’000 Orexin neurons in man

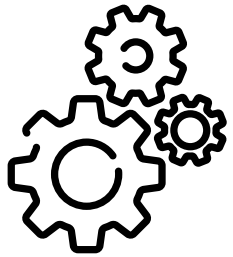
de Lecea L. *Prog Brain Res* 2012; 198: 15–24

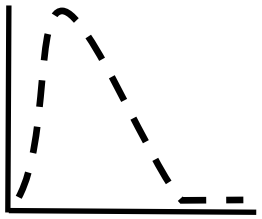
Early learnings on the DORA mechanism

- Induction of sleep
- No change in sleep architecture
- No respiratory depression
- Surmountable sleep if no “pressure to sleep”
- No decrease in muscular strength upon awakening
- Chronic administration without loss of efficacy
- No abuse potential

Brisbare-Roch C, et al. *Nat Med* 2007; 13, 150–155

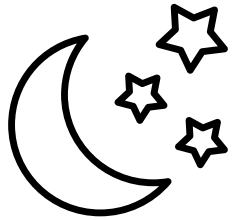
Combine the properties of dual orexin receptor antagonism with an optimal pharmacokinetic profile for insomnia





Precision MOA + Pharmacokinetic profile

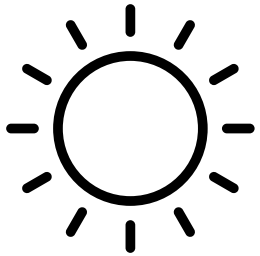
Give patients with insomnia good night's sleep, night after night…



…without next-day carry-over effect

Scientific product profile (SPP) for a next-gen dual orexin receptor antagonist

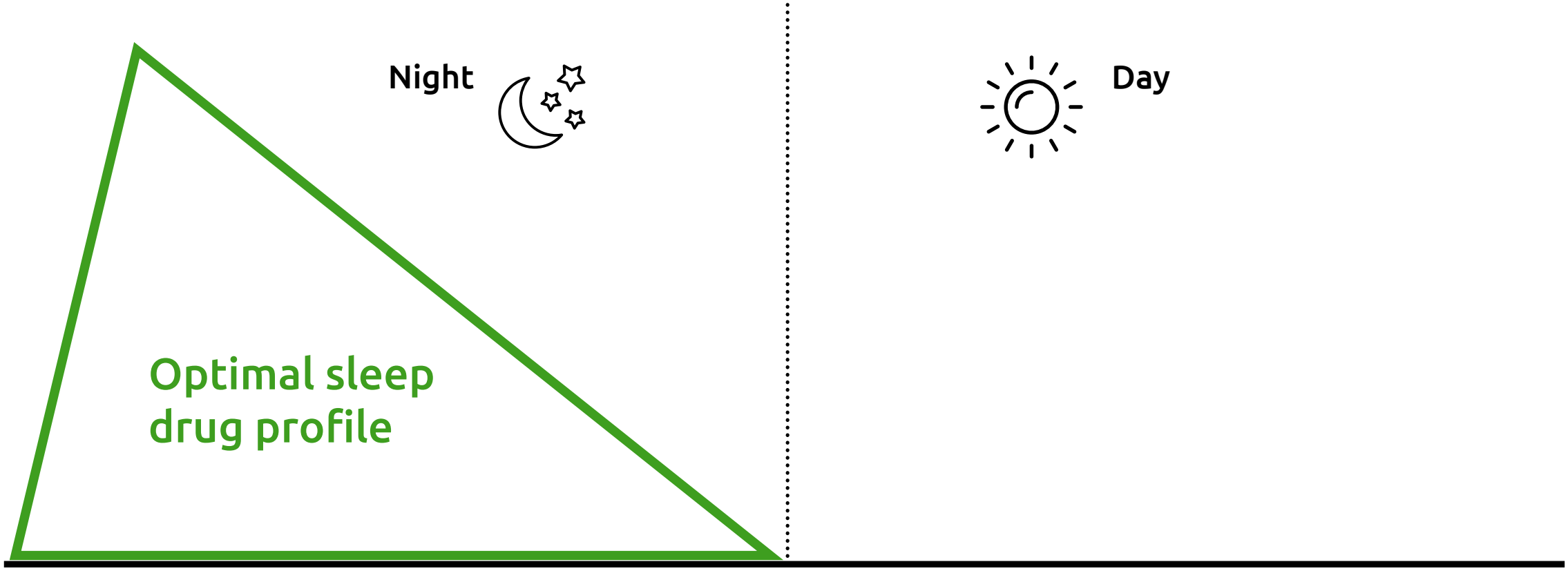
…and improve their daytime functioning.



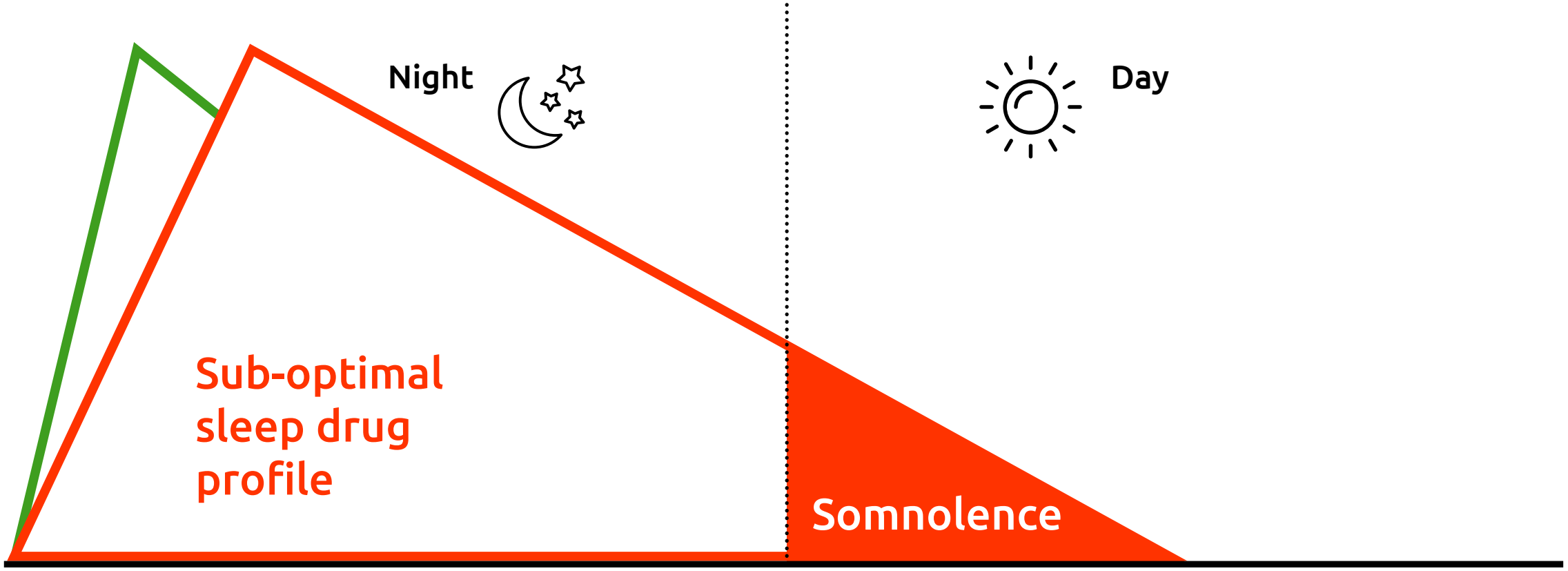
Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

idorsia

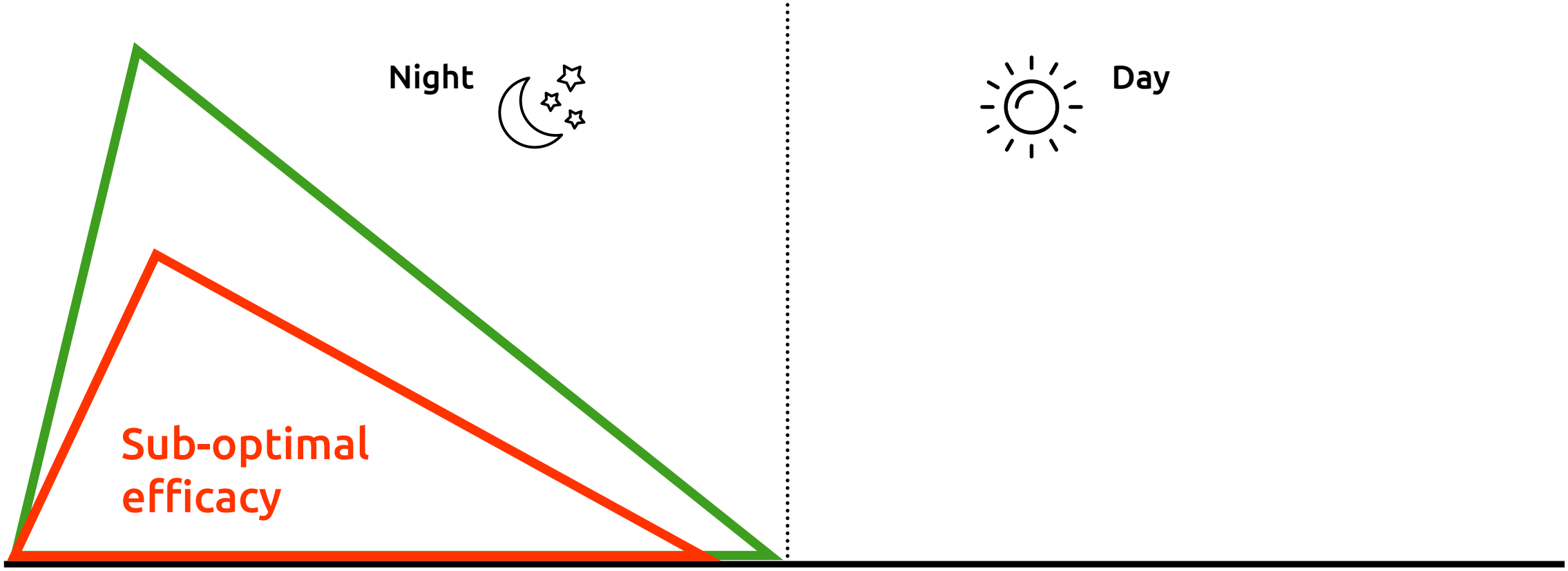
What was our concept?



Duration too long results in next-day somnolence

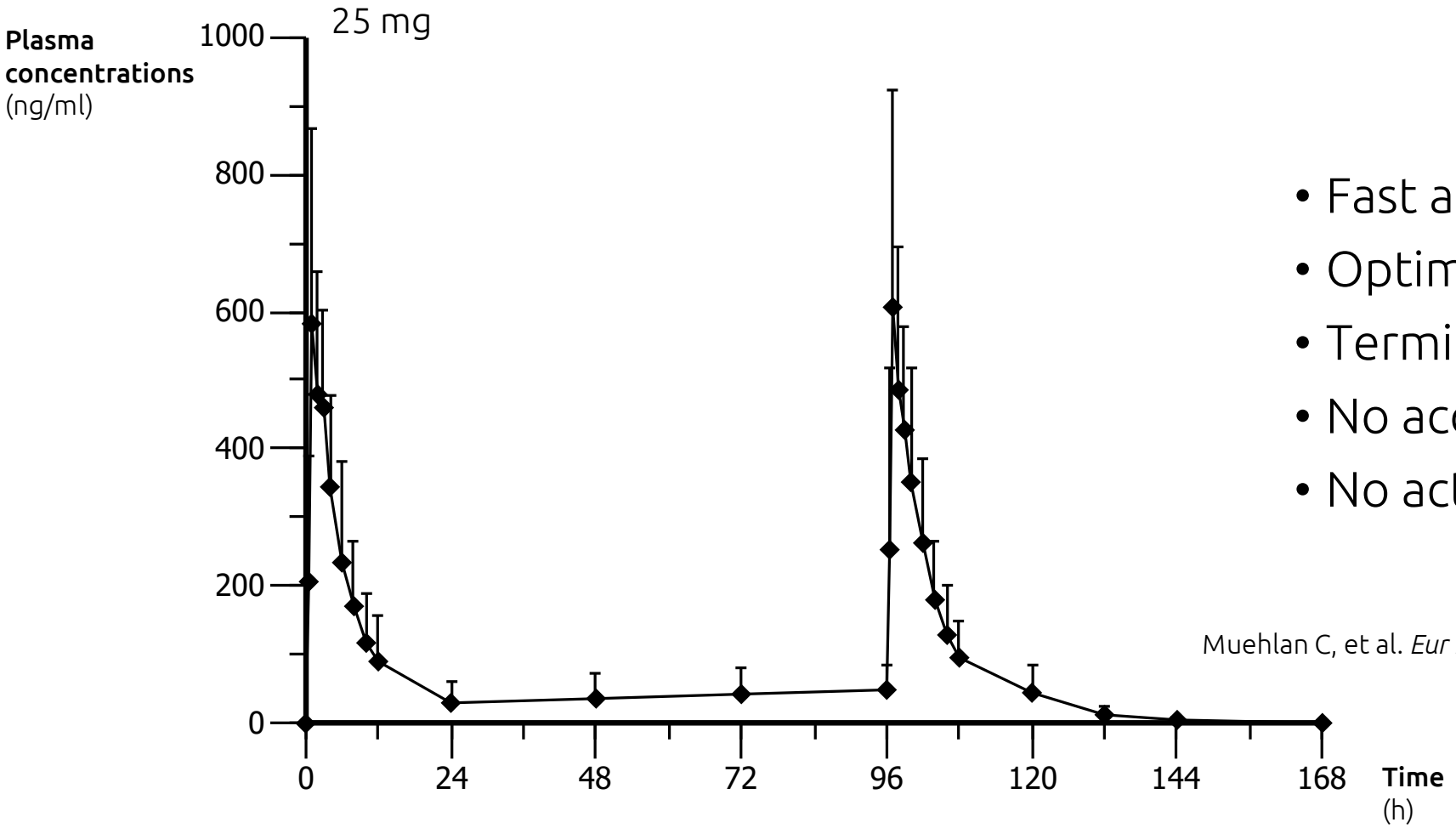


Reducing dose to remove next-day somnolence results in low efficacy



Different by design – next generation DORA

Optimized pharmacokinetic profile

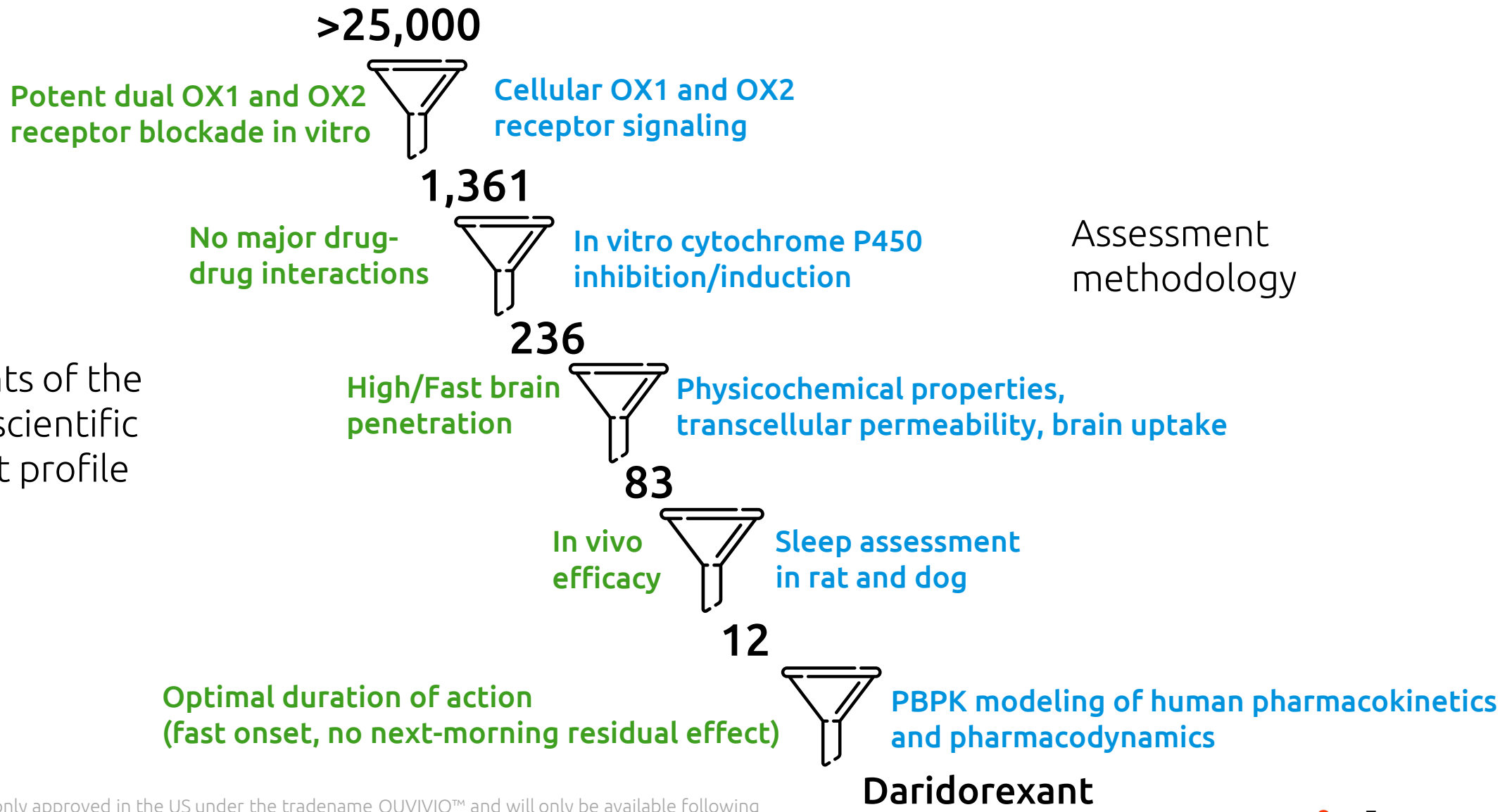


- Fast absorption
- Optimal decline after peak
- Terminal half-life (8 h)
- No accumulation over time
- No active metabolites

Muehlan C, et al. *Eur Neuropsychopharmacol* 2019; 29(7):847-857

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

The desired product profile



Assessment methodology

Elements of the target scientific product profile

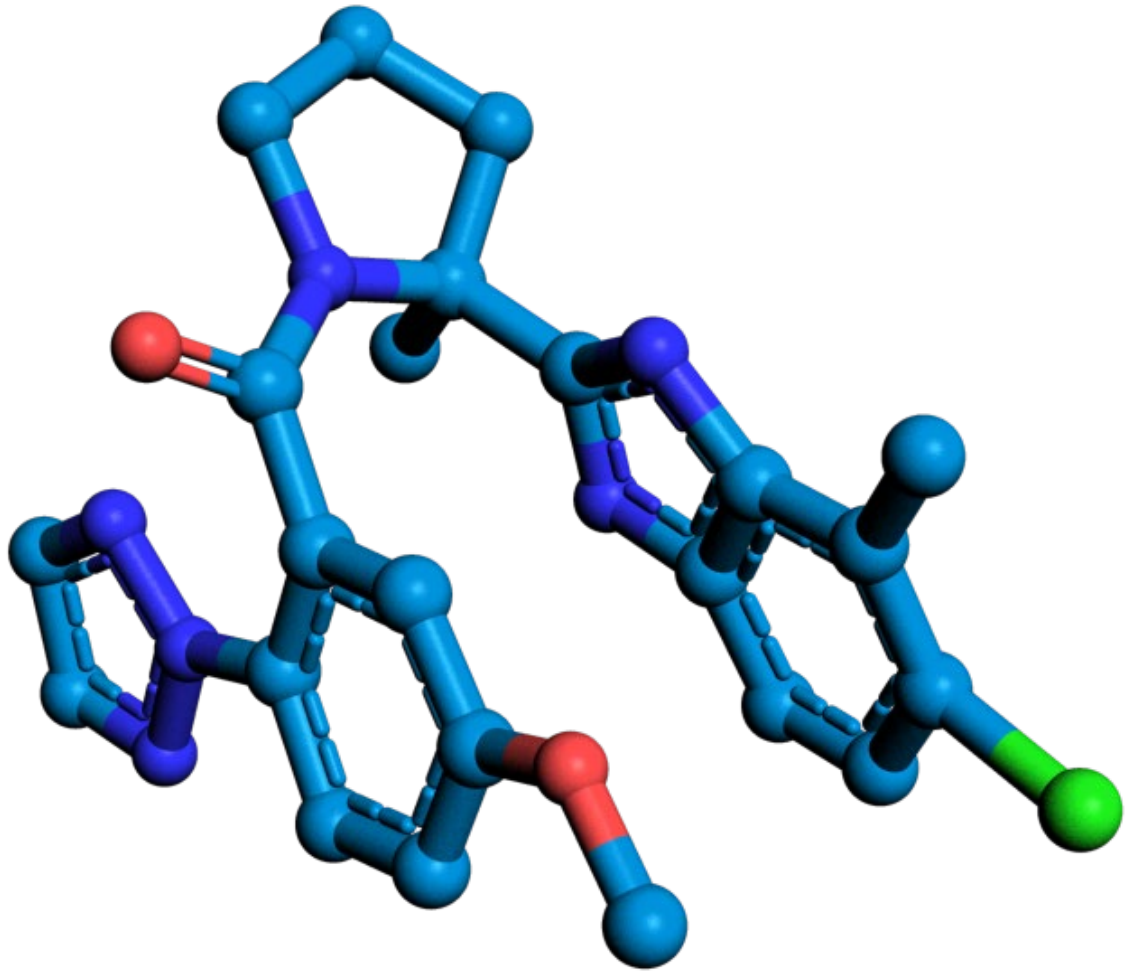
Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

The results of > 20 years of drug design

Preclinical characteristics of daridorexant

- Equipotent antagonism of both orexin receptors OX1 and OX2
- High brain penetration
- Rapid absorption and modeled duration of action of 8 hours
- Very safe in toxicology, no teratogenic or carcinogenic potential

- Chronic efficacy
- Preserves muscular strength and memory, upon awakening
- No abuse potential



Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

The Lancet Neurology

Articles

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

*Emmanuel Mignot, David Mayleben, Ingo Fietze, Damien Leger, Gary Zammit, Claudio L A Bassetti, Scott Pain, Dalma Seboek Kinter, Thomas Roth, on behalf of the investigators**

Summary

Background Daytime functioning is impaired in people with insomnia disorder. Currently available dual orexin receptor antagonists have shown efficacy in insomnia disorder, but do not address all aspects of this disease. We aimed to assess safety and efficacy of daridorexant, a novel orexin receptor antagonist, on night-time and daytime symptoms of insomnia.

Lancet Neurol 2022; 21: 125–39

See Comment page 104

*Investigators are listed in the appendix (p 3)

Stanford Center for Sleep

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Guy Braunstein

Head of Global Clinical Development

Daridorexant – The Lancet Neurology

Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials

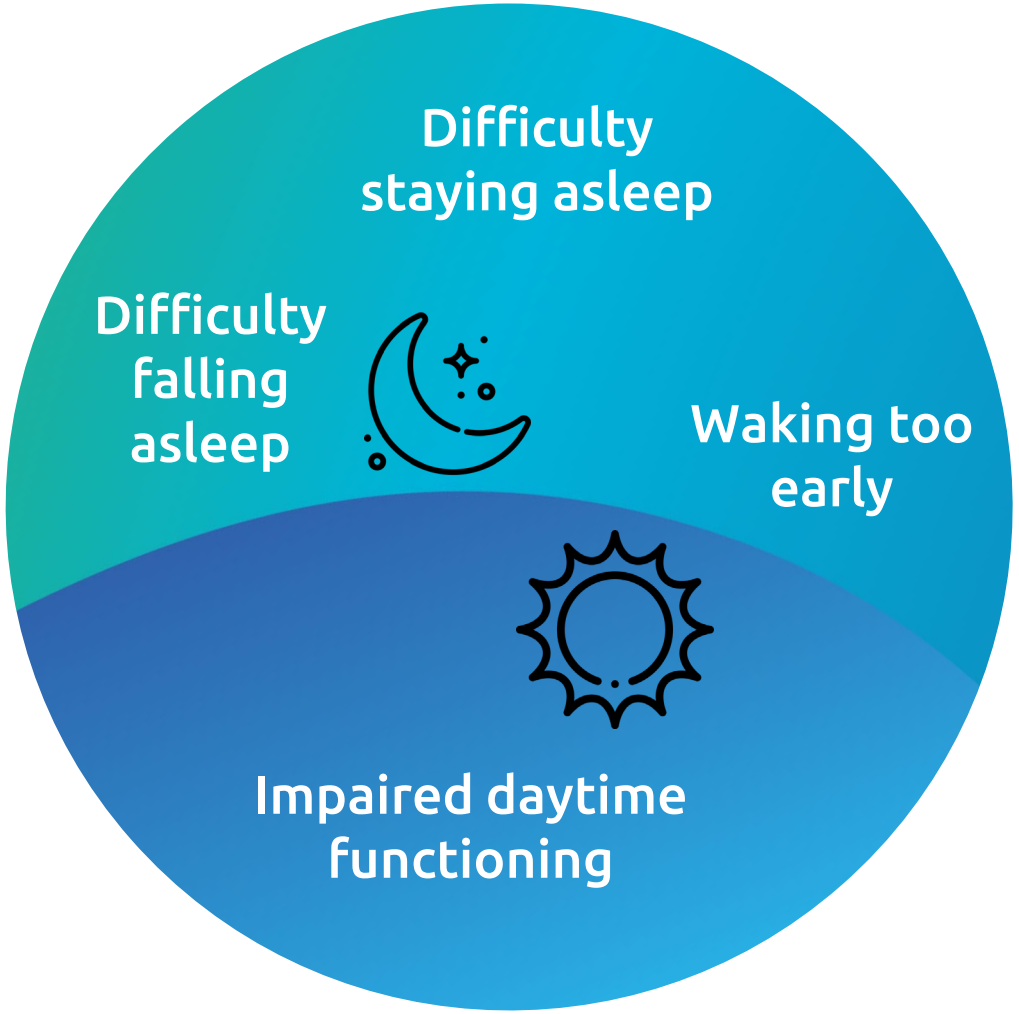
*Emmanuel Mignot, David Mayleben, Ingo Fietze, Damien Leger, Gary Zammit, Claudio L A Bassetti, Scott Pain, Dalma Seboek Kinter, Thomas Roth, on behalf of the investigators**

Interpretation **Daridorexant 25 mg and 50 mg improved sleep outcomes, and daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder, with a favourable safety profile.**

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Insomnia: A disease of the night and the day



- Insomnia is primarily a **subjective patient experience**
- Aligned with **DSM-5** definition, insomnia affects both **night** and **day**
- Patient input: **daytime symptoms** and **total sleep time** are the **major concerns**
- Daytime symptoms have been **largely ignored** by insomnia drug development

Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5®)

Designing the Phase 3 Program

Pharmacokinetic and pharmacodynamic characterization

What we knew from Phase 2

- Dose-response
- Effect on night parameters
- Covering the full night: effect on WASO increased quarter on quarter
- No sleepiness in the morning
- Early signals of daytime improvement

Open questions

- Which dose provides best balance of good night and good day – without morning sleepiness?
- How to measure daytime functioning? Lack of adequate instrument

- Dose
- Effect during the night
- Effect on the morning
- Effect during the day
- Safety with long-term treatment
- Maintained effect with chronic treatment

WASO, wake after sleep onset

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

How to measure daytime functioning?

Developing and validating the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)

Literature review

- The best starting point: DISS – Daytime Insomnia Symptom Scale*

The development

- Qualitative patient interviews
- Reflect the patient voice

The psychometric validation

- IDSIQ quantitative analysis
  - Healthy participants
  - Insomnia patients

The final IDSIQ instrument

- FDA validated
- Meaningful change defined

*Buysse, D.J. et al. *Sleep Med.* 2007; 8(3): 198–208

Published in a peer-reviewed journal

Hudgens S, et al. *Patient.* 2021; 14, 249–268

idorsia

Subjective assessment of daytime functioning

Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)

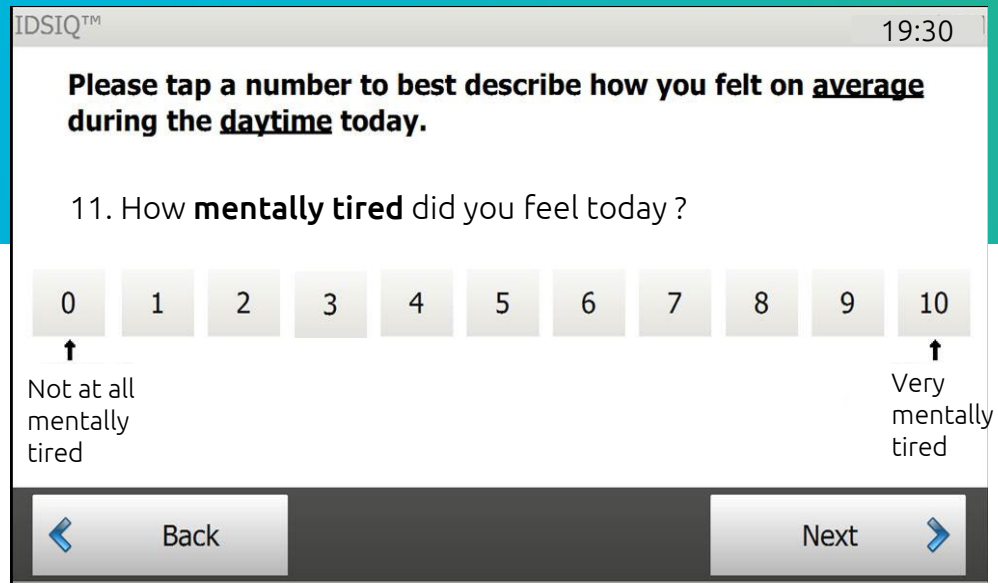
Measures
Item 1. How **clear-headed** did you feel today?
Item 2. How well were you able to **concentrate** today?
Item 3. How **forgetful** did you feel today?
Item 4. How **worried** did you feel today?
Item 5. How **frustrated** by your lack of sleep did you feel today?
Item 6. How **irritable** did you feel today?
Item 7. How **stressed** did you feel today?
Item 8. How **energetic** did you feel today?
Item 9. How **much of an effort** was it to perform daily activities (i.e. reading, cleaning, work, school) today?
Item 10. How **refreshed** did you feel today?
Item 11. How **mentally tired** did you feel today?
Item 12. How **physically tired** did you feel today?
Item 13. How **sleepy** did you feel today?
Item 14. How **awake** did you feel today?

"Alert/cognition" domain score (0-60)

"Mood" domain score (0-40)

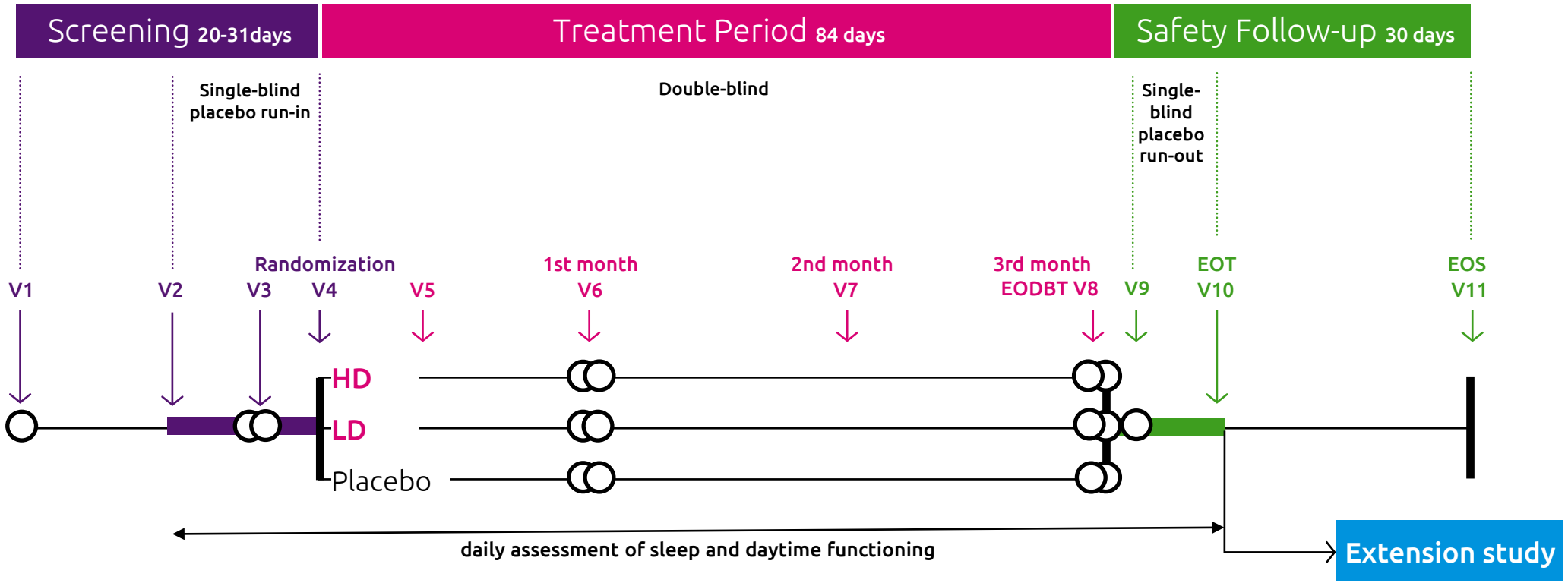
"Sleepiness" domain score (0-40)

Items are ranked on a numeric rating scale from 0-10



Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Two Phase 3 studies – similar design



V = site visit

= 1 polysomnography night

= 2 consecutive polysomnography nights

EODBT = End of double-blind treatment
EOT = End-of-Treatment
EOS = End-of-Study
HD = High dose, 50 mg (study 1) or 25 mg (study 2)
LD = Low dose, 25 mg (study 1) or 10 mg (study 2)

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Key assessments

Objective sleep assessment

Objective measures of night parameters by **polysomnography (PSG)** in the sleep lab

Patient oriented outcome daily recorded

Subjective measures of night parameters by the **sleep diary questionnaire (SDQ)**

Assessment of impact of insomnia during the day by the **insomnia daytime symptoms and impact questionnaire (IDSIQ)**

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Sleep diary questionnaire (SDQ)

Daily recording

Morning questionnaire

- 10 questions related to medication, quantification of sleep, awakenings
- 3 visual analog scales related to quality and deepness of sleep and sleepiness in the morning

→ **Total sleep time**
Secondary endpoint

Evening questionnaire

- 2 questions related to napping
- 2 visual analog scales related to alertness and ability to perform

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Primary and secondary endpoints

Study-wise type 1 error controlled at 0.05 (across 16 comparisons to placebo)

Two primary endpoints (night)

- Wake after sleep onset by PSG
- Latency to persistent sleep by PSG

Two studies / three doses

- Study 1: 50 mg / 25 mg vs. placebo
- Study 2: 25 mg / 10 mg vs. placebo

Two secondary endpoints (night and day patients' feeling)

- Subjective total sleep time by SDQ
- Sleepiness score during the day by IDSIQ

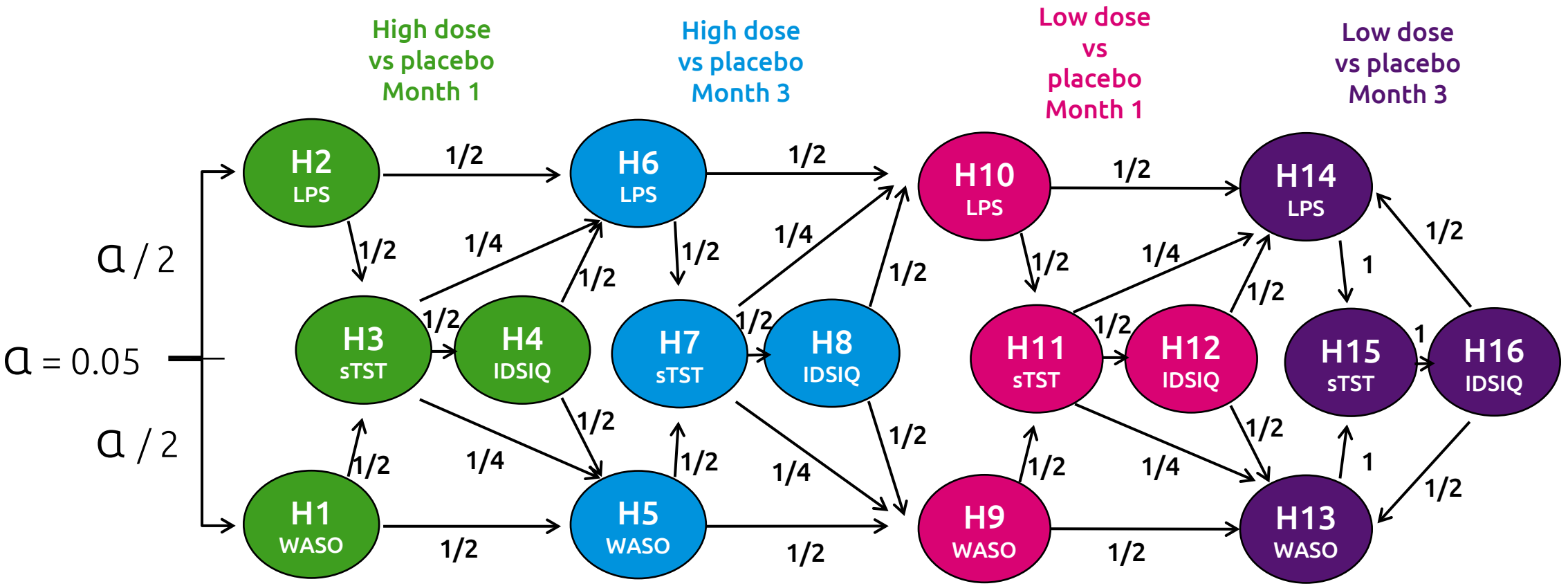
Two assessment time points

- Month 1
- Month 3

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

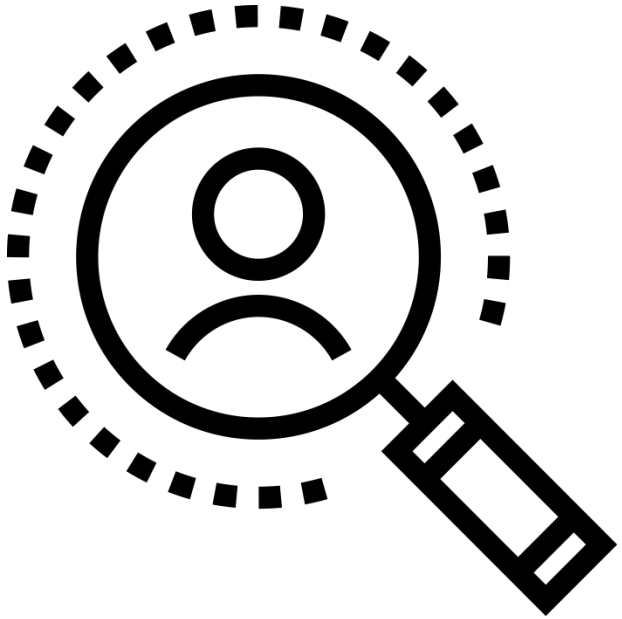
Statistical design and hypothesis testing

Type I error controlled across 16 endpoint measures



Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Exploratory endpoints



- TST and percentage in **each sleep phase** (PSG)
- Morning VAS for **depth and quality of sleep**
- Changes in **Insomnia Severity Index** (ISI) score
- Changes in **other IDSIQ domain scores**
- Evening VAS for **daytime ability to function** and **daytime alertness**
- **Adverse events**
- **Withdrawal**
- **Rebound**

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Patient demographics

	Study 1			Study 2		
	Dari 50 mg (n = 310)	Dari 25 mg (n = 310)	Placebo (n = 310)	Dari 25 mg (n = 309)	Dari 10 mg (n = 307)	Placebo (n = 308)
Sex						
Female	199 (64%)	215 (69%)	210 (68%)	218 (71%)	215 (70%)	205 (67%)
Male	111 (36%)	95 (31%)	100 (32%)	91 (29%)	92 (30%)	103 (33%)
Age at screening, years – mean (SD)	55.5 (15.3)	55.8 (15.3)	55.1 (15.4)	56.3 (14.4)	57.1 (14.0)	56.7 (14.1)
Age group, years						
<65	189 (61%)	189 (61%)	188 (61%)	188 (61%)	186 (61%)	187 (61%)
≥65	121 (39%)	121 (39%)	122 (39%)	121 (39%)	121 (39%)	121 (39%)
Race						
White	274 (88%)	287 (93%)	278 (90%)	271 (88%)	273 (89%)	267 (87%)
Black or African American	30 (10%)	19 (6%)	28 (9%)	26 (8%)	16 (5%)	29 (9%)
Asian	4 (1%)	3 (1%)	2 (1%)	11 (4%)	14 (5%)	10 (3%)
Other	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	2 (1%)
Geographical location						
USA	97 (31%)	99 (32%)	104 (34%)	108 (35%)	103 (34%)	114 (37%)
Non-USA	213 (69%)	211 (68%)	206 (66%)	201 (65%)	204 (66%)	194 (63%)
Body-mass index, kg/m²	26.3 (4.3)	26.6 (4.4)	26.4 (4.1)	26.1 (4.2)	26.0 (4.3)	26.2 (4.3)
<25.0	127 (41%)	122 (39%)	118 (38%)	135 (44%)	146 (48%)	135 (44%)
25·0 to ≤30	128 (41%)	125 (40%)	135 (44%)	120 (39%)	114 (37%)	119 (39%)
>30	55 (18%)	63 (20%)	57 (18%)	54 (17%)	47 (15%)	54 (18%)

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Patient baseline characteristics

Stringent selection criteria results in patient population with chronic insomnia

	Study 1			Study 2		
	Dari 50 mg (n = 310)	Dari 25 mg (n = 310)	Placebo (n = 310)	Dari 25 mg (n = 309)	Dari 10 mg (n = 307)	Placebo (n = 308)
Time since insomnia diagnosis, years	10.7 (10.7)	10.2 (10.1)	11.0 (10.5)	11.7 (11.9)	12.1 (12.0)	10.5 (10.5)
Night-time efficacy variables						
WASO, min	95.5 (37.8)	97.9 (38.8)	102.5 (40.8)	106.0 (49.1)	104.6 (46.2)	108.1 (48.7)
LPS, min	63.6 (37.4)	67.3 (38.6)	66.5 (39.8)	68.9 (40.5)	67.4 (41.7)	71.8 (46.1)
Self-reported total sleep time, min	313.2 (57.6)	309.8 (60.1)	315.9 (53.1)	308.5 (52.8)	308.4 (51.4)	307.6 (51.5)
Total sleep time, min	328.3 (50.2)	322.5 (55.1)	318.6 (54.4)	312.6 (68.8)	316.2 (63.5)	307.4 (69.0)
Insomnia Severity Index score	19.3 (4.0)	19.0 (4.3)	19.2 (4.0)	19.5 (4.0)	19.9 (3.8)	19.6 (4.1)
IDSIQ sleepiness domain score	22.5 (7.2)	22.1 (6.9)	22.3 (6.9)	22.2 (6.2)	22.7 (6.3)	22.6 (5.8)

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Comprehensive set of results published

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Results

Between June 4, 2018, and Feb 25, 2020, 3326 participants were screened for inclusion in study 1, of whom 930 were randomly assigned to receive daridorexant 25 mg (n=310), daridorexant 50 mg (n=310), or placebo (n=310). Between May 29, 2018, and May 14, 2020, 3683 participants were screened for inclusion in study 2…

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mignot E, Mayleben D, Fietze I, et al. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. *Lancet Neurol* 2022; **21:** 125–39.

In the following slides we present **Study 1**, **25 mg** and **50 mg**, efficacy results

In **Study 2**, **10 mg** did not provide benefit while **25 mg** was consistent between the two studies

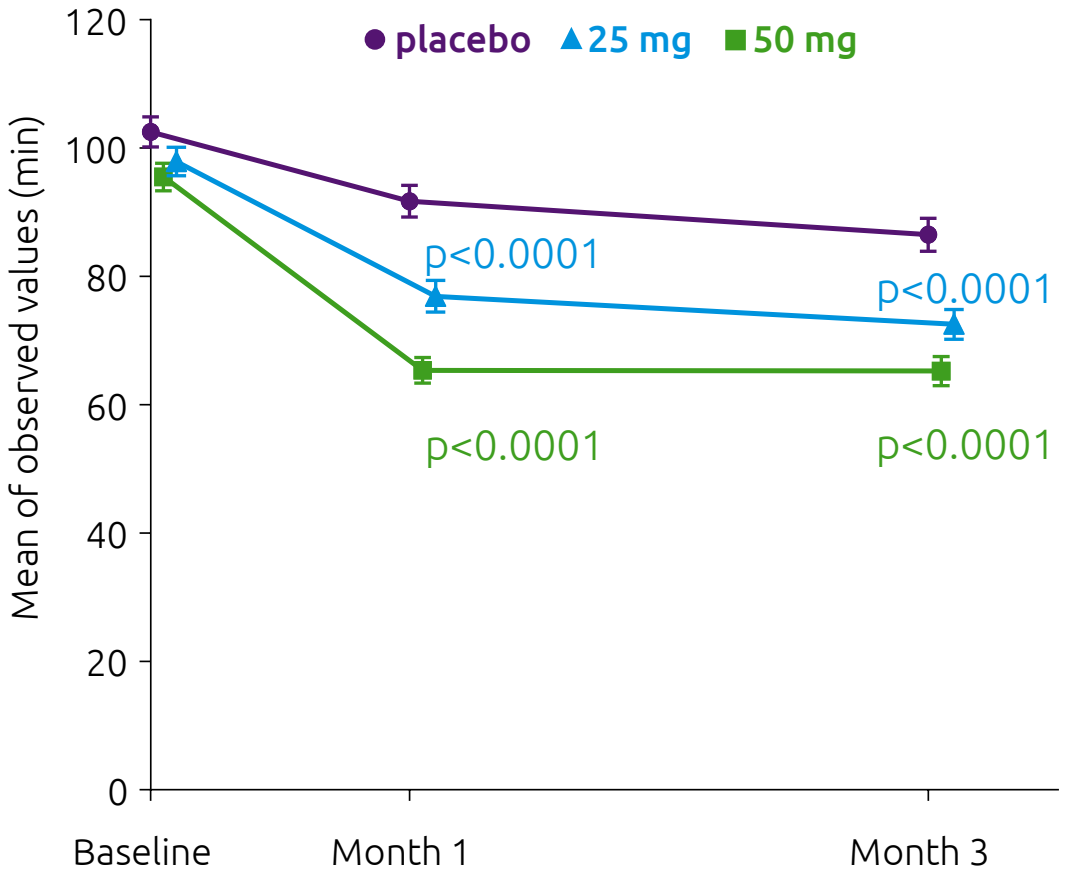
Safety data from both studies will be presented

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

idorsia

1º endpoint: Wake after sleep onset (WASO)

A measure of sleep maintenance



Daridorexant 25 mg and 50 mg significantly improved WASO compared to placebo at months 1 and 3

LSM change from baseline (95% CI)

	Month 1	Month 3
Placebo	**–6.2** (–9.9 to –2.5)	**–11.1** (–15.1 to –7.1)
Daridorexant 25 mg	**–18.4** (–22.1 to –14.7)	**–23.0** (–27.0 to –19.0)
LSM difference compared with placebo (95% CI)	**–12.2** (–17.4 to –7.0)	**–11.9** (–17.5 to –6.2)
Daridorexant 50 mg	**–29.0** (–32.7 to –25.3)	**–29.4** (–33.4 to –25.4)
LSM difference compared with placebo (95% CI)	**–22.8** (–28.0 to –17.6)	**–18.3** (–23.9 to –12.7)

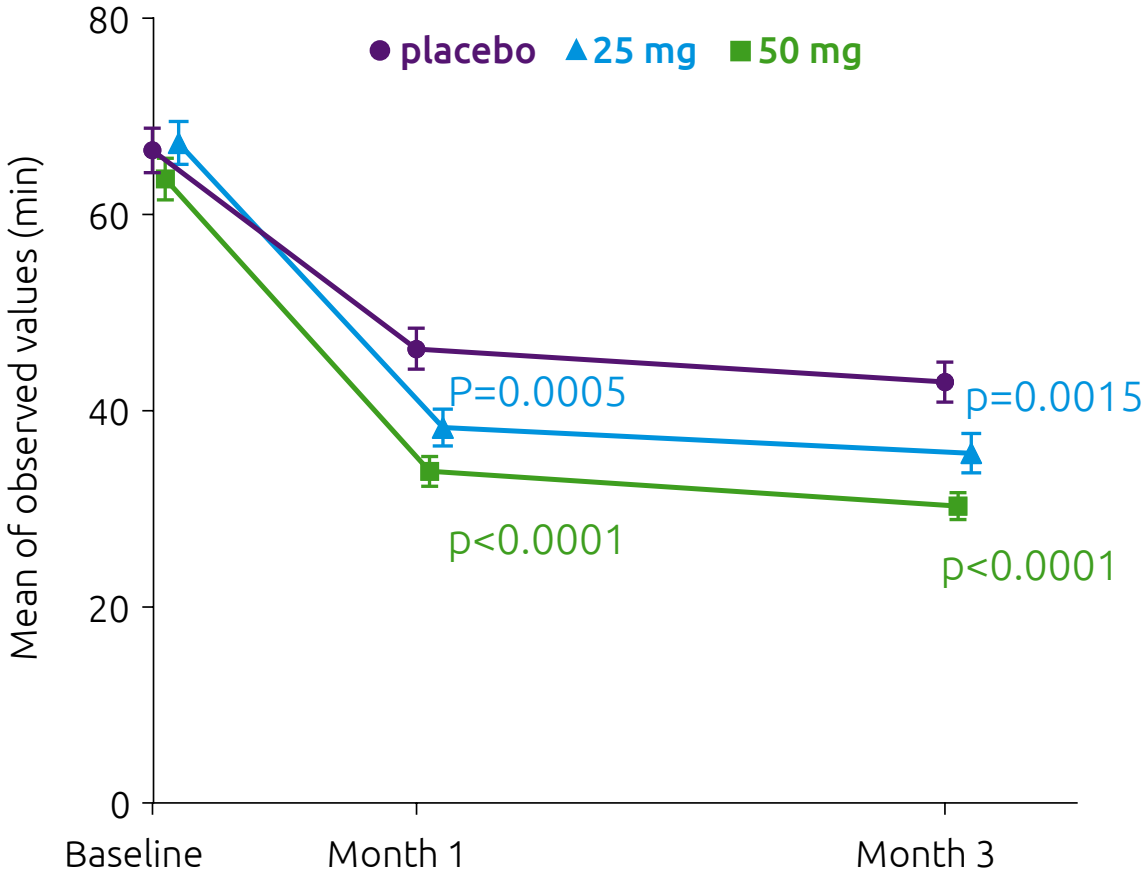
CI = confidence interval; LSM = least squares mean

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

1º endpoint: Latency to persistent sleep (LPS)

A measure of sleep onset



Daridorexant 25 mg and 50 mg **significantly improved LPS** compared to placebo at months 1 and 3

LSM change from baseline (95% CI)

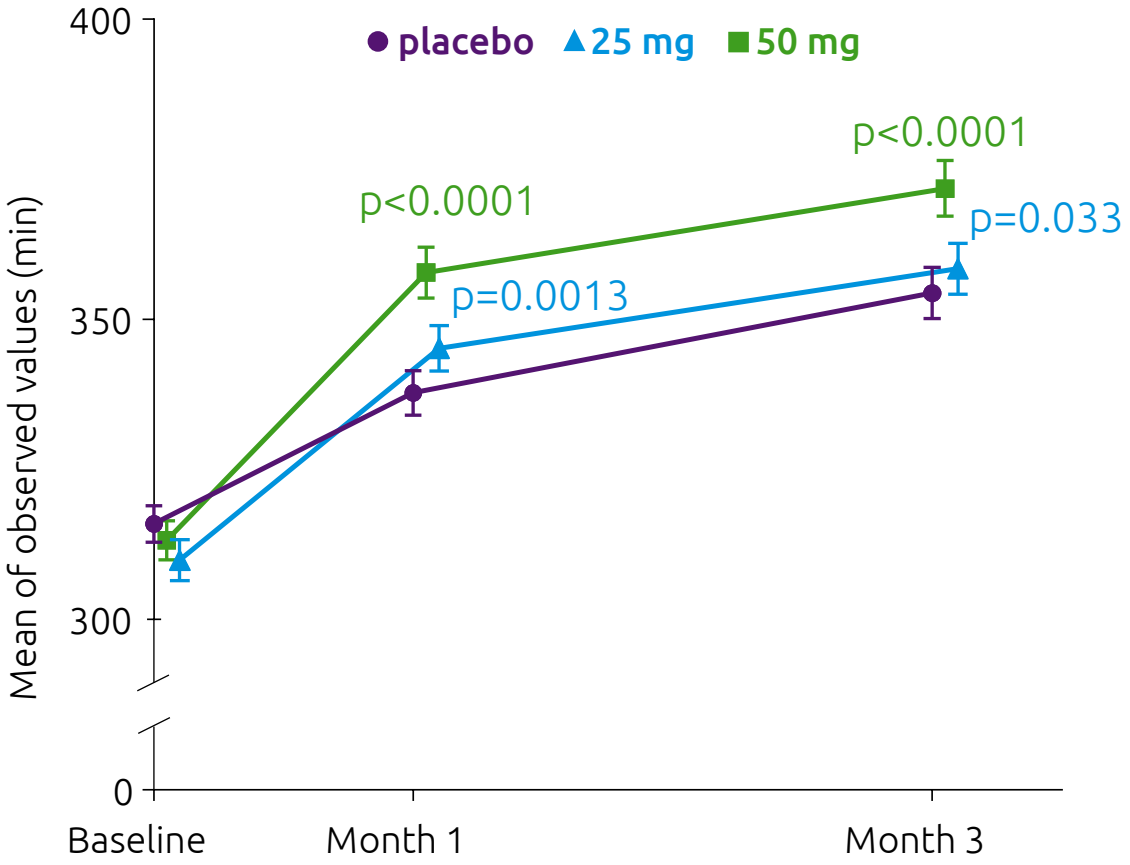
	Month 1	Month 3
Placebo	**–19.9** (–23.2 to –16.5)	**–23.1** (–26.5 to –19.8)
Daridorexant 25 mg	**–28.2** (–31.5 to –24.8)	**–30.7** (–34.0 to –27.4)
LSM difference compared with placebo (95% CI)	**–8.3** (–13.0 to –3.6)	**–7.6** (–12.3 to –2.9)
Daridorexant 50 mg	**–31.2** (–34.5 to –27.9)	**–34.8** (–38.1 to –31.5)
LSM difference compared with placebo (95% CI)	**–11.4** (–16.0 to –6.7)	**–11.7** (–16.3 to –7.0)

CI = confidence interval; LSM = least squares mean

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

2º endpoint: Subjective Total Sleep Time (sTST)

A measure of how the patient think they slept



Daridorexant 25 mg and 50 mg **significantly improved sTST** compared to placebo at months 1 and 3

LSM change from baseline (95% CI)

	Month 1	Month 3
Placebo	**21.6** (16.1 to 27.0)	**37.9** (31.4 to 44.4)
Daridorexant 25 mg	**34.2** (28.7 to 39.6)	**47.8** (41.3 to 54.3)
LSM difference compared with placebo (95% CI)	**12.6** (5.0 to 20.3)	**9.9** (0.8 to 19.1)
Daridorexant 50 mg	**43.6** (38.2 to 49.1)	**57.7** (51.2 to 64.2)
LSM difference compared with placebo (95% CI)	**22.1** (14.4 to 29.7)	**19.8** (10.6 to 28.9)

CI = confidence interval; LSM = least squares mean

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Further analysis of the night…

Visual Analogue Scale (VAS)

Proportion of sleep time in each stage

The proportion of sleep time spent in **each sleep stage** was preserved across all treatment groups as was sleep continuity at months 1 and 3

Quality of sleep **Depth of sleep**

VAS scores for **depth and quality of sleep** were numerically higher at months 1 and 3 for daridorexant versus placebo

Insomnia Severity Index (ISI)

ISI scores were numerically lower at months 1 and 3 for daridorexant versus placebo

None of these endpoints were statistically tested

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

2º endpoint: IDSIQ sleepiness domain

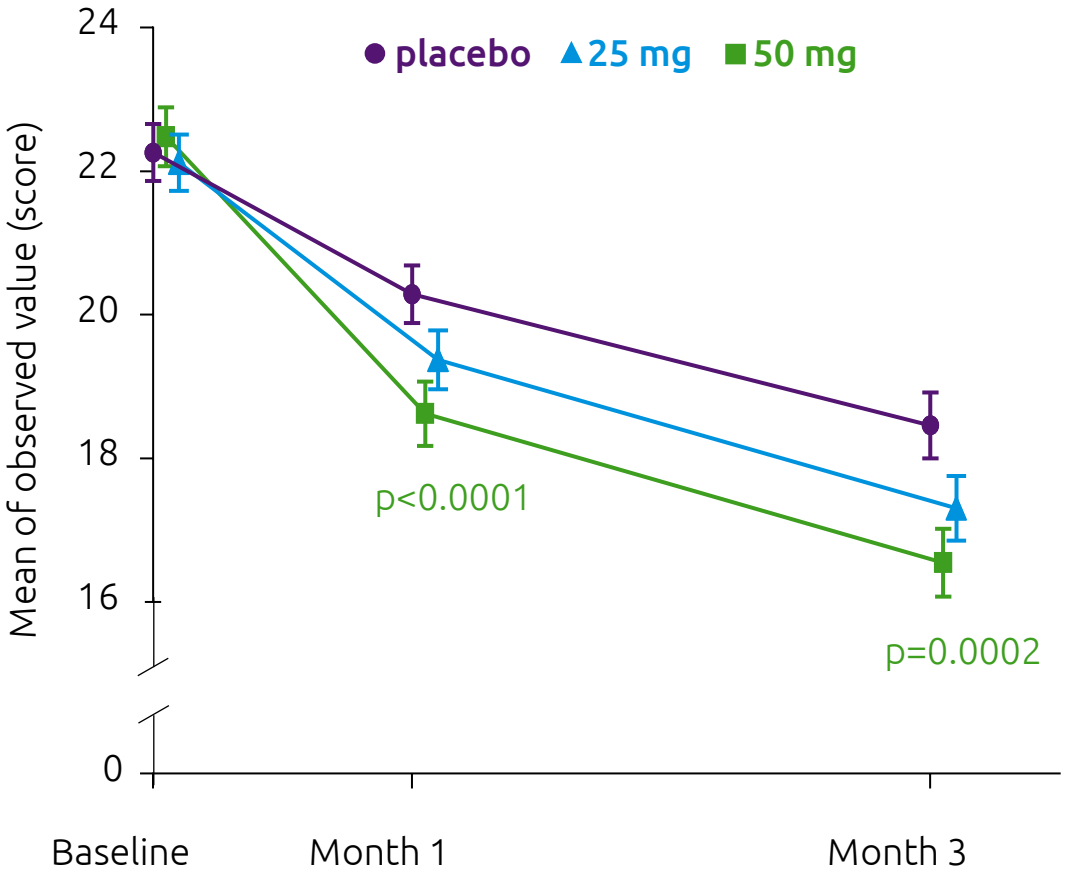
A measure of daytime functioning

How **energetic** did you feel today?

How **mentally tired** did you feel today?

How **physically tired** did you feel today?

How **sleepy** did you feel today?



Daridorexant 50 mg **significantly improved IDSIQ sleepiness domain** score compared to placebo at months 1 and 3

LSM change from baseline (95% CI)

	Month 1	Month 3
Placebo	**–2.0** (–2.6 to –1.5)	**–3.8** (–4.5 to –3.1)
Daridorexant 25 mg	**–2.8** (–3.3 to –2.2)	**–4.8** (–5.5 to –4.1)
LSM difference compared with placebo (95% CI)	**–0.8** (–1.5 to 0.01)	**–1.0** (–2.0 to 0.01)
Daridorexant 50 mg	**–3.8** (–4.3 to –3.2)	**–5.7** (–6.4 to –5.0)
LSM difference compared with placebo (95% CI)	**–1.8** (–2.5 to –1.0)	**–1.9** (–2.9 to –0.9)

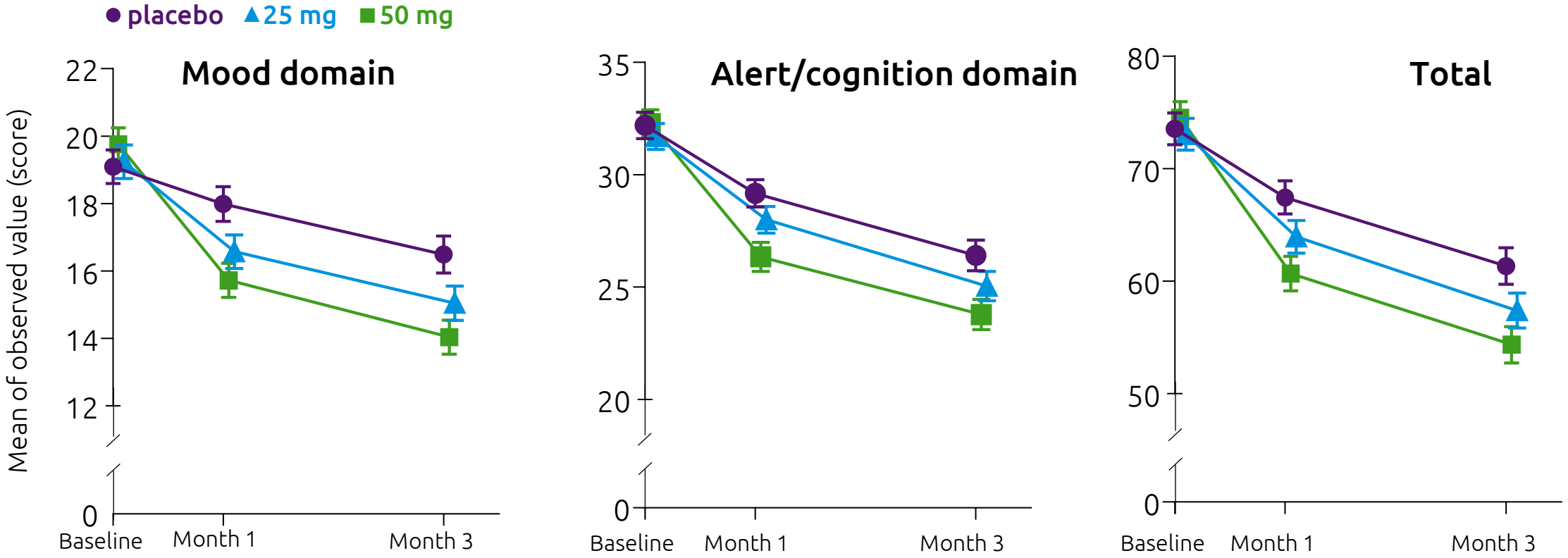
CI = confidence interval; LSM = least squares mean

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Exploratory endpoints: IDSIQ other scores

A measure of daytime functioning



IDSIQ mood domain, alert/cognition domain, and total scores at both timepoints were reduced (improved) (all nominal p-values for daridorexant 50 mg versus placebo ≤0.0005; not adjusted for multiplicity)

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Further analysis of the day…

Visual Analogue Scale (VAS)

Ability to function

Daytime alertness

VAS **scores for ability to function and daytime alertness** were higher at months 1 and 3 for daridorexant versus placebo

Morning sleepiness

VAS **scores for morning sleepiness** showed numerical improvements at months 1 and 3 for daridorexant versus placebo

None of these endpoints were statistically tested

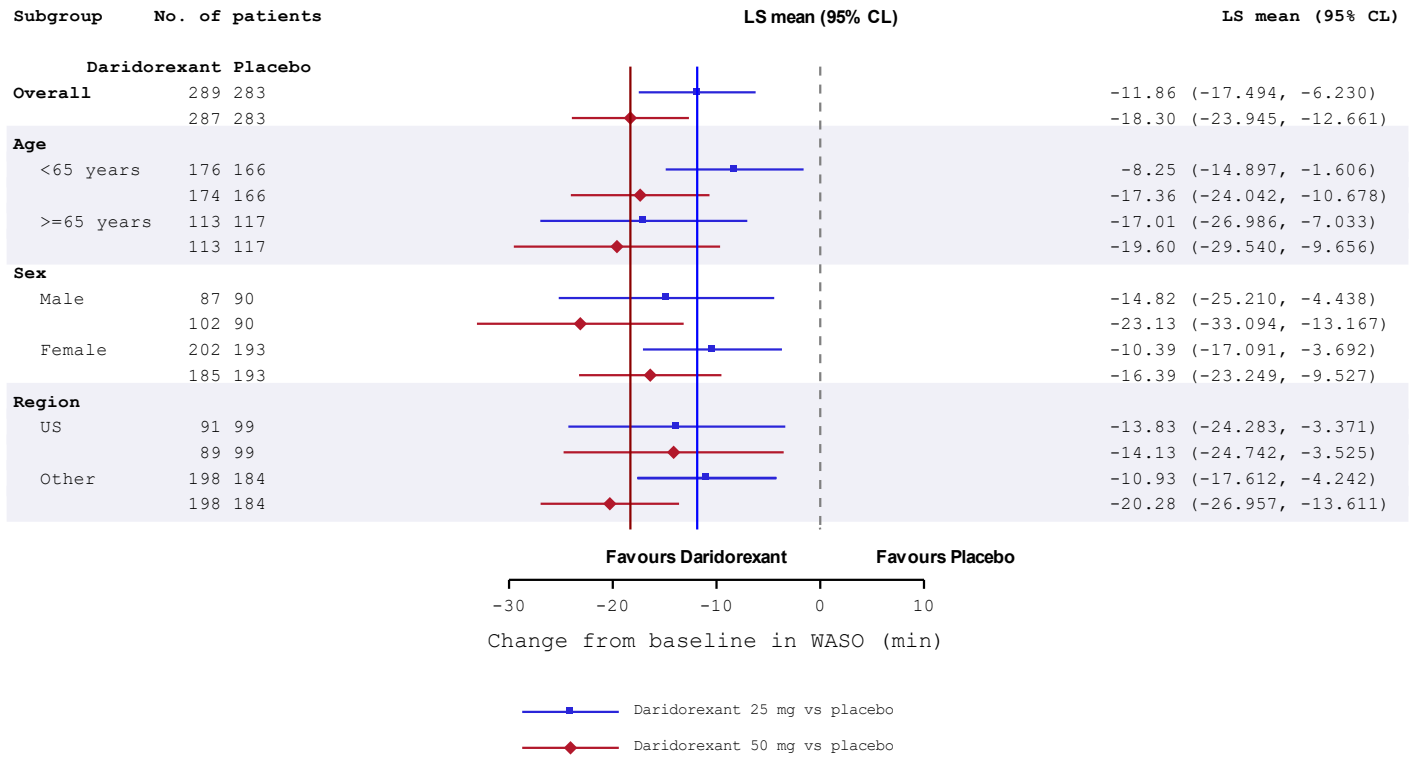
Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Subgroup

The effect of daridorexant on WASO, LPS, self-reported total sleep time, and IDSIQ sleepiness domain score was consistent in adults and older adults and across sex and geographical location

E.g., WASO by subgroup in Study 1 – Month 3



Supplement to: Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Adverse events

In the safety analysis population (n=1847)

	Study 1			Study 2		
	Dari 50 mg (n = 308)	Dari 25 mg (n = 310)	Placebo (n = 309)	Dari 25 mg (n = 308)	Dari 10 mg (n = 306)	Placebo (n = 306)
Participants with ≥1 adverse event*	116 (38%)	117 (38%)	105 (34%)	121 (39%)	117 (38%)	100 (33%)
Adverse events* leading to treatment discontinuation	3 (1%)	7 (2%)	10 (3%)	4 (1%)	6 (2%)	7 (2%)
Participants with ≥1 serious adverse event	3 (1%)	2 (1%)	7 (2%)	3 (1%)	3 (1%)	4 (1%)
Participants with adverse event* (≥2% in any group)						
Nasopharyngitis	20 (6%)	21 (7%)	20 (6%)	13 (4%)	32 (10%)	16 (5%)
Headache	19 (6%)	16 (5%)	12 (4%)	15 (5%)	12 (4%)	11 (4%)
Accidental overdose	8 (3%)	4 (1%)	5 (2%)	4 (1%)	4 (1%)	1 (<1%)
Fatigue	7 (2%)	7 (2%)	2 (1%)	11 (4%)	7 (2%)	2 (1%)
Dizziness	7 (2%)	6 (2%)	2 (1%)	6 (2%)	4 (1%)	4 (1%)
Nausea	7 (2%)	1 (<1%)	3 (1%)	2 (1%)	3 (1%)	3 (1%)
Somnolence	5 (2%)	11 (4%)	6 (2%)	10 (3%)	6 (2%)	4 (1%)
Fall	1 (<1%)	1 (<1%)	8 (3%)	3 (1%)	4 (1%)	3 (1%)
Upper respiratory tract infection	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)	5 (2%)	6 (2%)

Data are n (%). The safety analysis population included all participants who received at least one dose of double-blind treatment. *Adverse events that occurred during the double-blind treatment period in the safety population are included in the table and presented with their preferred terms.

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

idorsia

Adjudicated adverse events

In the safety analysis population (n=1847)

	Study 1			Study 2		
	Dari 50 mg (n = 308)	Dari 25 mg (n = 310)	Placebo (n = 309)	Dari 25 mg (n = 308)	Dari 10 mg (n = 306)	Placebo (n = 306)
Adjudicated adverse events†						
Excessive daytime sleepiness	1 (<1%)	2 (1%)	1 (<1%)	4 (1%)	1 (<1%)	1 (<1%)
Sleep paralysis	1 (<1%)	1 (<1%)	0	2 (1%)	0	0
Hallucinations	0	1 (<1%)	0	1 (<1%)	0	0
Suicidal ideation or self-injury‡	0	0	0	1 (<1%)	1 (<1%)	0

Data are n (%). The safety analysis population included all participants who received at least one dose of double-blind treatment. †Adjudicated adverse events were reported during the double-blind treatment up to 30 days after the end of treatment or date of enrolment into the extension trial and were adjudicated blindly by an independent safety board. ‡Adjudicated adverse events belonging to the category suicidal ideation or self-injury (preferred term: suicidal ideation) were reported in two participants, one in each daridorexant group in study 2; both patients had pre-existing medical conditions (paranoid schizophrenia or depression) and the independent safety board adjudicated both adverse events as potentially related to trial treatment.

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Adverse events by age subgroup in Study 1

	<65 years			≥65 years		
	Dari 50 mg (n = 189)	Dari 25 mg (n = 189)	Placebo (n = 187)	Dari 50 mg (n = 119)	Dari 25 mg (n = 121)	Placebo (n = 122)
Patients with ≥1 adverse event – n (%)	74 (39.2)	78 (41.3)	67 (35.8)	42 (35.3)	39 (32.2)	38 (31.1)
Patients with a given adverse event (≥2% in any group) – n (%)						
Nasopharyngitis	13 (6.9)	19 (10.1)	16 (8.6)	7 (5.9)	2 (1.7)	4 (3.3)
Headache	13 (6.9)	11 (5.8)	7 (3.7)	6 (5.0)	5 (4.1)	5 (4.1)
Accidental overdose	5 (2.6)	3 (1.6)	5 (2.7)	3 (2.5)	1 (0.8)	0
Dizziness	6 (3.2)	2 (1.1)	1 (0.5)	1 (0.8)	4 (3.3)	1 (0.8)
Fatigue	4 (2.1)	3 (1.6)	1 (0.5)	3 (2.5)	4 (3.3)	1 (0.8)
Back pain	5 (2.6)	0	3 (1.6)	1 (0.8)	2 (1.7)	1 (0.8)
Somnolence	4 (2.1)	5 (2.6)	5 (2.7)	1 (0.8)	6 (5.0)	1 (0.8)
Influenza	4 (2.1)	3 (1.6)	3 (1.6)	0	0	2 (1.6)
Nausea	3 (1.6)	1 (0.5)	2 (1.1)	4 (3.4)	0	1 (0.8)
Diarrhoea	1 (0.5)	6 (3.2)	3 (1.6)	1 (0.8)	0	1 (0.8)
Upper abdominal pain	0	0	0	0	3 (2.5)	1 (0.8)
Fall	0	0	4 (2.1)	1 (0.8)	1 (0.8)	4 (3.3)

Includes only those treatment-emergent adverse events that started or worsened during the double-blind study period.

Supplement to: Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Further safety observations

No adverse events suggested that **drug misuse** might have occurred

No withdrawal symptoms were observed during the placebo run-out period, as assessed by adverse events or the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ)

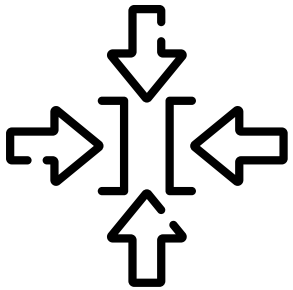
During the placebo run-out period, WASO and LPS were numerically lower, and mean self-reported total sleep time was higher than respective baseline values, indicating **absence of rebound insomnia**

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Strengths and Limitations

Strengths

- Assessed **most components of insomnia** as defined in the DSM-5
  - Both objective nighttime variables and patient reported assessments of night and day symptoms
- **Robust control** for study-wise type I error for all primary and secondary endpoints
- Proportion of **male and female** patients was representative of the general insomnia population
- **Older adult patients** (≥ 65 years) were well represented (~40% of the population)
- Low rate of **missing data**



Limitations

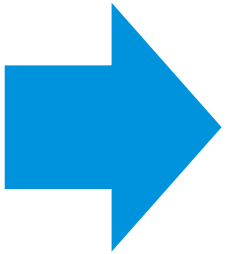
- Patients had **moderate to severe insomnia** and may not be representative of the general insomnia population
- Regarding **race**, randomized population may only partially reflect the insomnia population
- Number of patients with **CBTi experience** was low
- Patients with **comorbidities** were not included
- IDSIQ is a **novel tool** and there is limited experience with its use

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Interpretation and Implications

Daridorexant 25 mg and 50 mg improved sleep outcomes, and daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder, with a favorable safety profile.

- New treatments for insomnia should be directed at **improving both night-time and daytime symptoms**.
- A prerequisite to achieve this goal is that a drug has **no next-morning residual effect** leading to excessive daytime somnolence, yet it adequately induces and maintains sleep.



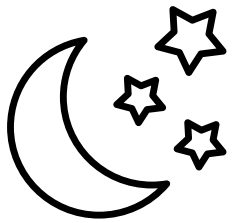
- Daridorexant **50 mg seems to fulfil** those requirements.
- Improvements in **sleep variables** were achieved **without excess sleepiness** the following morning, and improvements in **daytime functioning** were observed.

Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

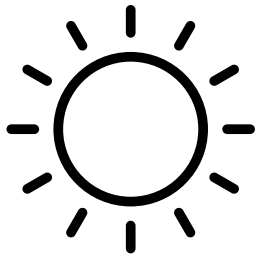
Idorsia conclusion

The daridorexant clinical program provides a wealth of evidence



Comprehensive sleep efficacy perceived by patients (25 mg & 50 mg)

- Fall asleep faster
- Stay asleep longer
- Time in each sleep stage preserved

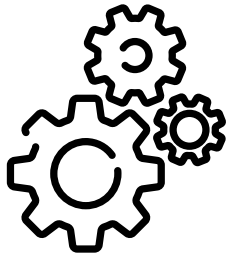


Daytime functioning perceived by patients (50 mg)

- Improved sleepiness
- Consistent effect on mood and alertness / cognition on exploratory endpoints
- Progressive improvement over time

Documented safety

- A low overall incidence of adverse events (AE), comparable between treatment groups
- Most common AEs (>5%): nasopharyngitis and headache
- No evidence of tolerance or dependence
- No rebound insomnia or withdrawal effects



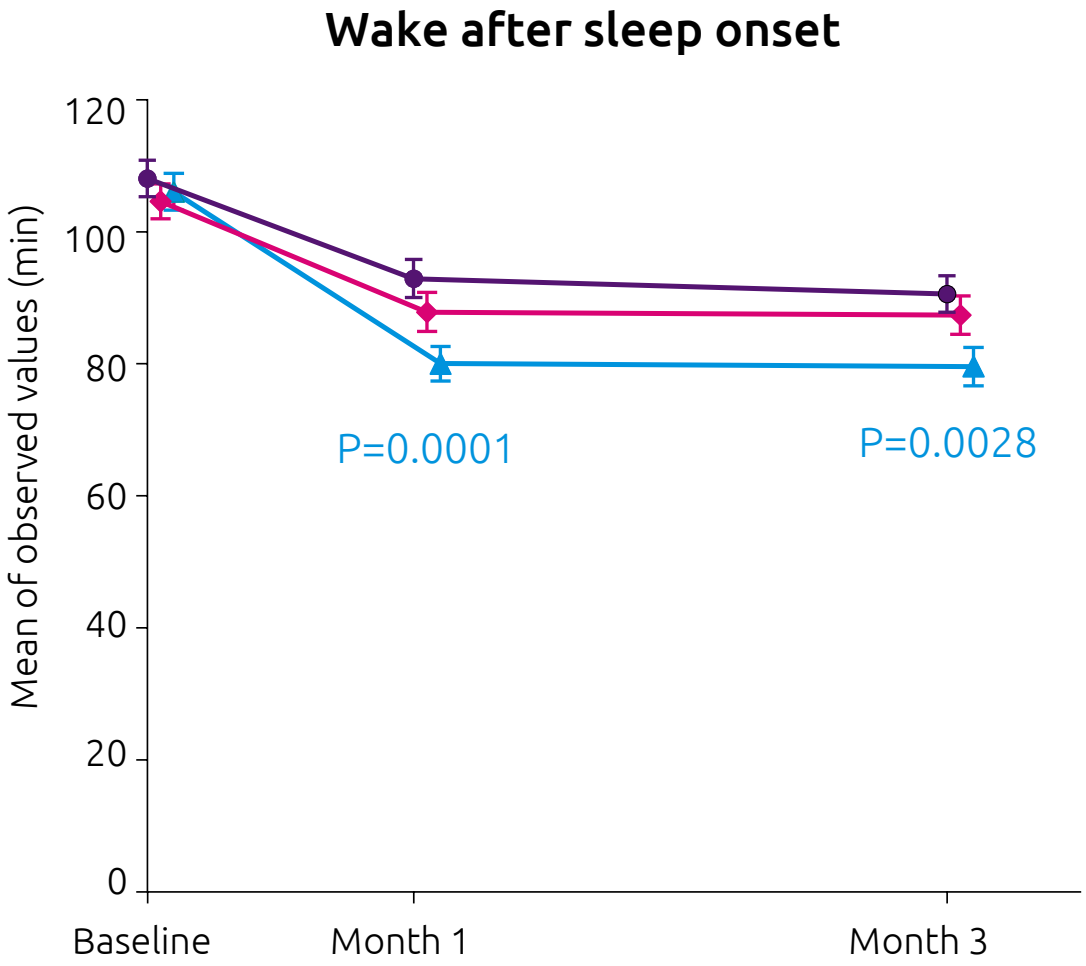
Precision MOA & intrinsic properties of daridorexant

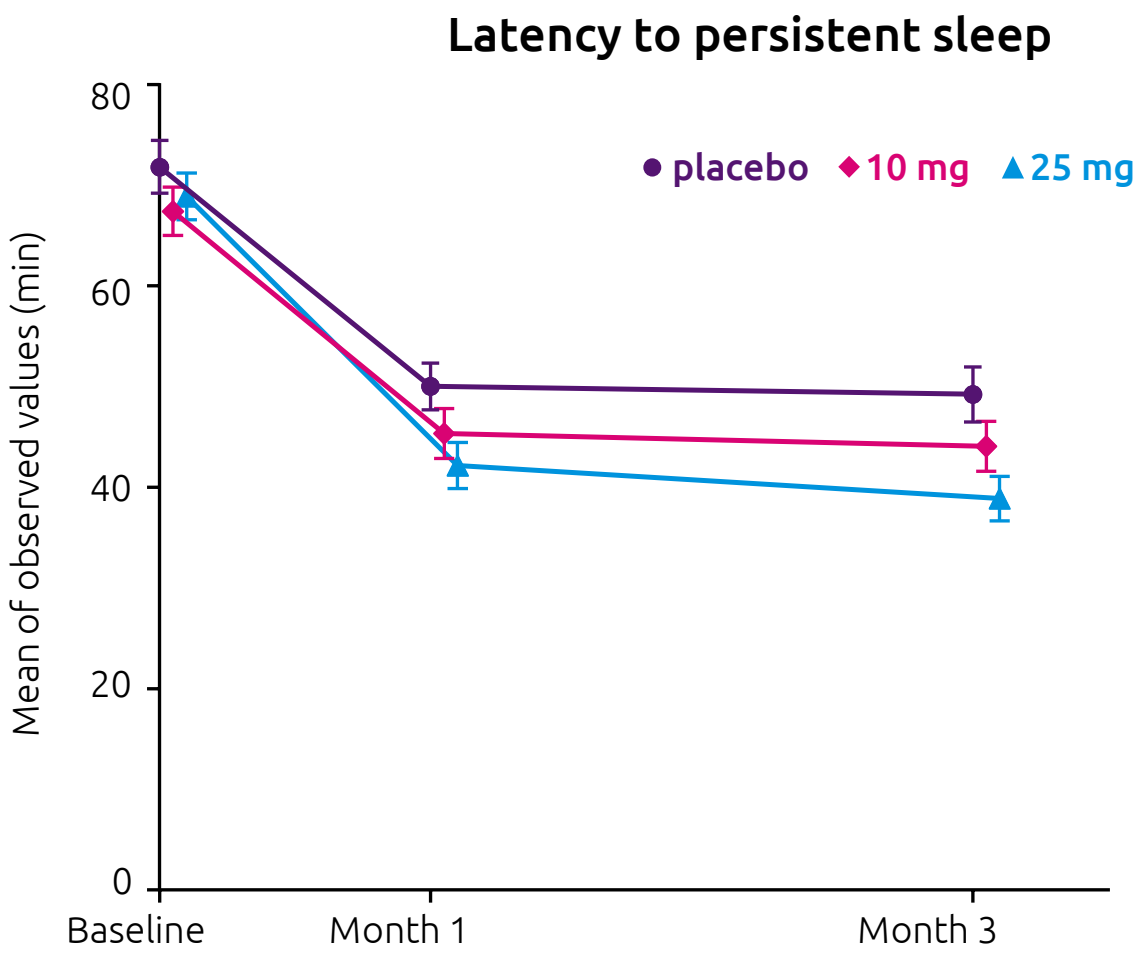
- Targets only the part of the brain that keeps you awake, without broad sedation
- Ideal pharmacological profile

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Appendix

1º endpoints: Objective measures from study 2

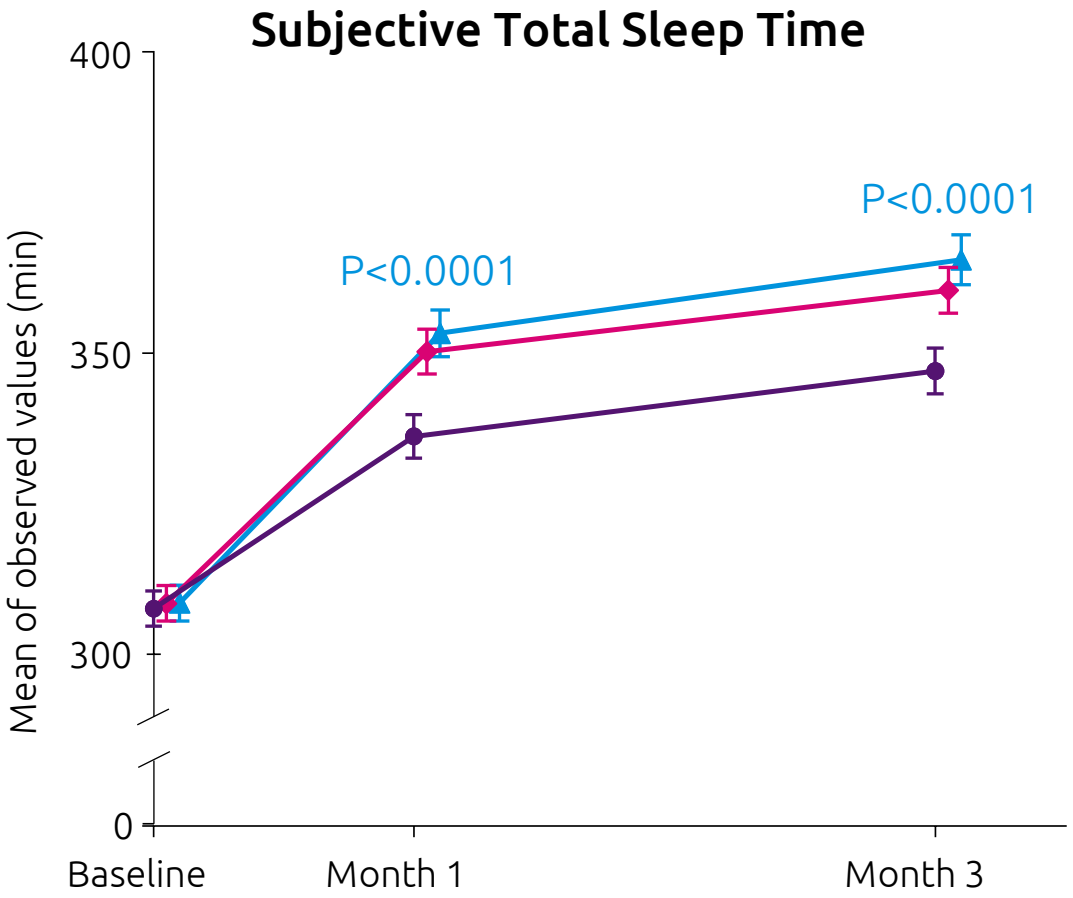


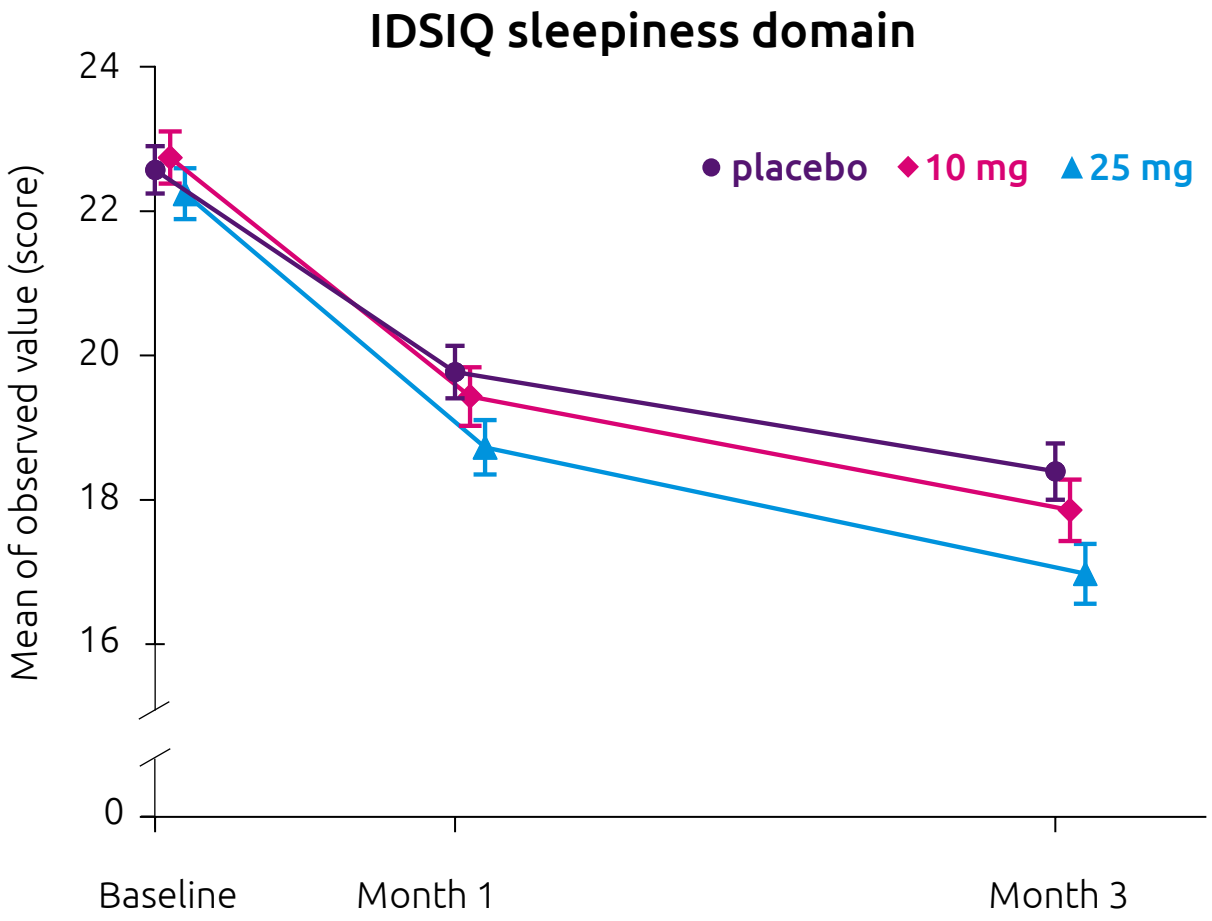


Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

2º endpoints: Subjective measures from study 2

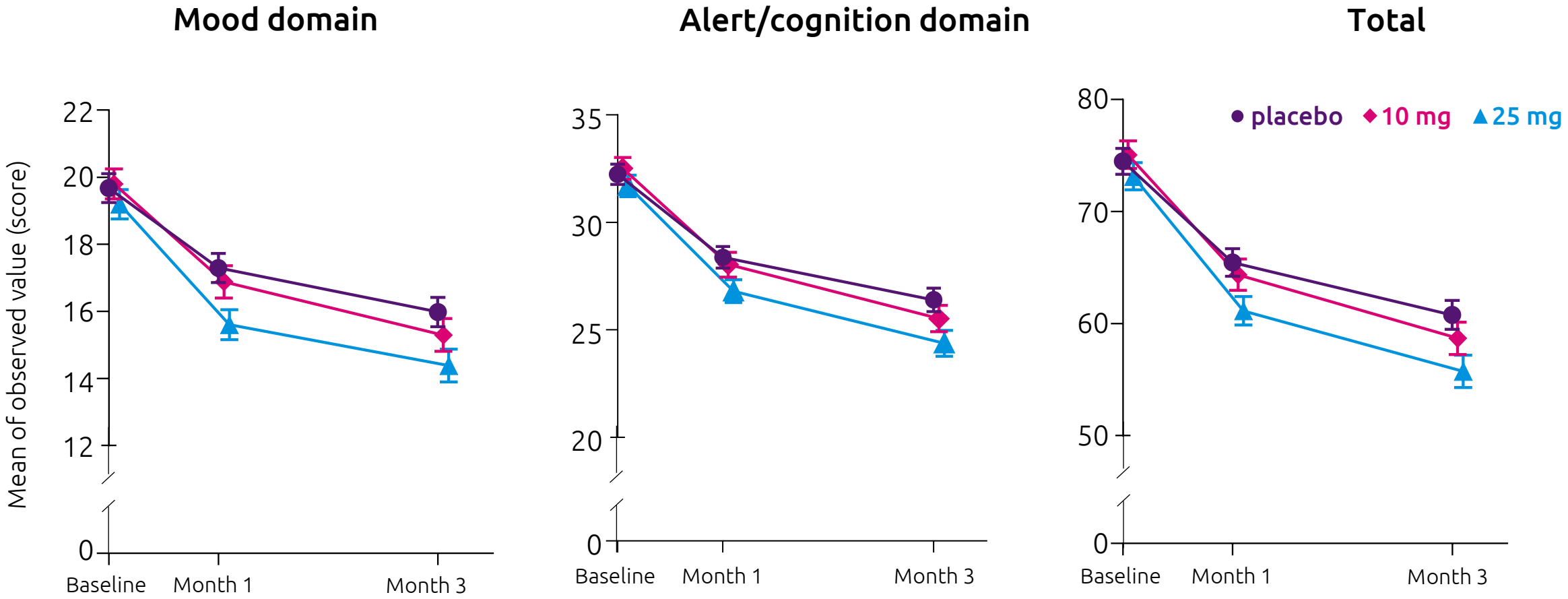




Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39

Daridorexant is only approved in the US under the tradename QUVIVIQ™ and will only be available following scheduling by the US Drug Enforcement Administration. Market authorization is under review in other countries.

Exploratory endpoints: IDSIQ other scores from study 2



Mignot E, et al. *Lancet Neurol* 2022; 21: 125–39