Summary of Two Pivotal Trials and the Extension Study for the Dual Orexin Receptor Antagonist (DORA) Daridorexant

Safety and Efficacy of Daridorexant in Patients with Insomnia Disorder:

Results From Two Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 3 trials and the 40-Week Extension Study[1,2]

- **Key results from the two pivotal phase 3 studies (NCT03545191 and NCT03575104) designed to evaluate the safety and efficacy of the insomnia drug, daridorexant, will be summarized in this report; in addition, this report includes the results of a 40-week extension study (NCT03679884) of the two pivotal trials**
- **The clinical development plan for daridorexant was to conduct a pair of distinct clinical trials with the same trial designs for 3 months; only the doses of medication differed between the trials**
- **An extension study from these two pivotal trials was conducted such that some subjects from these 3-month trials continued treatment or placebo for an additional 9 months, providing 1 year of data in total**
- **These studies were sponsored by Idorsia Pharmaceuticals Ltd. These pivotal studies were cited in the New Drug Application (NDA) to the US Food and Drug Administration (FDA), and approval of daridorexant was granted January 7, 2022**
- **In addition to these two phase 3 studies and their extension study, the PAUSe study, a single substudy within the pair of trials, investigated patient preferences for insomnia medications, which is published (https://pubmed.ncbi.nlm.nih.gov/36054921/)[3]**

What Is Insomnia?

Insomnia is defined as dissatisfaction with sleep quantity or quality associated with at least 1 of the following symptoms—**difficulty initiating sleep or difficulty maintaining sleep**—and is characterized by frequent occurrences of awakening, or by problems returning to sleep after awakening. Insomnia is associated with significant distress and **impaired daytime functioning.**[4]

Common Complaints

Difficulty falling asleep (sleep initiation)

Inability to return to sleep after waking (sleep maintenance)

Nonrestorative sleep

Daytime somnolence, fatigue, and reduced energy (impaired daytime functioning)

Mood alteration

Cognitive impairment

Drugs used for sleep may be necessary for some patients with insomnia, but many approved treatments are associated with side effects or challenges:

- Often does not help with sleep

- Effectiveness decreases with prolonged use
- Patients can become dependent on use of the drug
- No data measuring impact on daytime impairment
- Slowing of cognition

What Is Daridorexant?

- Daridorexant is a dual orexin receptor antagonist (DORA) designed with pharmacokinetic and pharmacodynamic properties to improve sleep onset and sleep maintenance in patients with insomnia
  - Unlike the first two DORAs that entered the US market with half-lives ranging from 12-19 hours, the terminal half-life of daridorexant is 8 hours
- Following the results of the two pivotal clinical trials, the FDA approved daridorexant 50 mg and 25 mg for the treatment of adult patients with insomnia characterized by difficulty with sleep onset or sleep maintenance
  - Patients with mild to moderate hepatic impairment or taking CYP3A4 inhibitors or inducers should be treated with daridorexant 25 mg

How Were These Studies Done?

- Study 1 and study 2 were international, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials conducted to assess the efficacy and safety of daridorexant in patients with insomnia
  - These studies were identical in design except for the dose of daridorexant
  - Study 1 was designed to compare daridorexant 50 mg (higher dose) and 25 mg (lower dose) with placebo, whereas study 2 was designed to compare daridorexant 25 mg (higher dose) and 10 mg (lower dose) with placebo
- The extension study was an international, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the long-term safety of daridorexant
  - This study was designed to compare daridorexant 10 mg, 25 mg, and 50 mg with placebo

Study Design

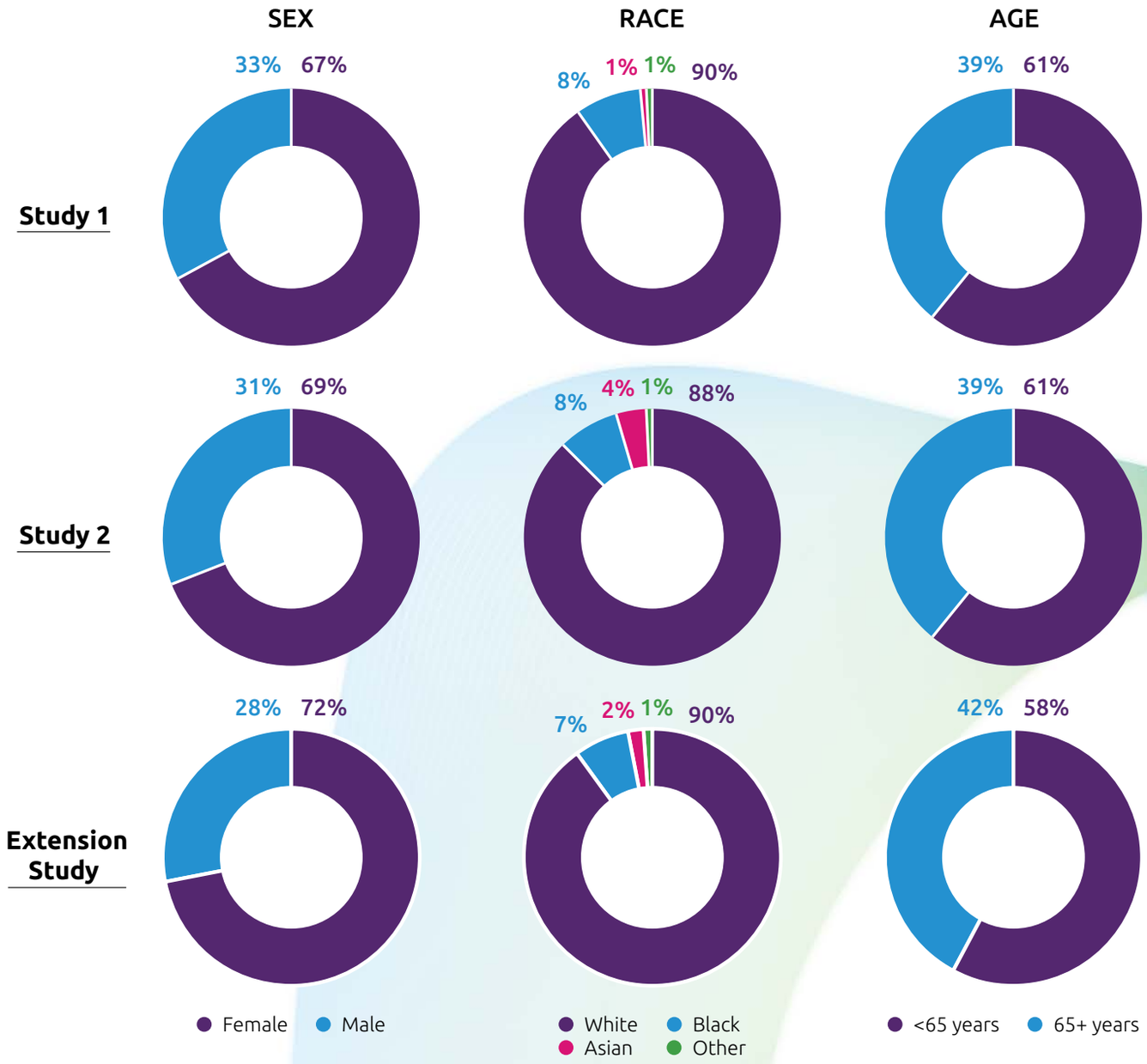
Screening (21-30 days) Single-blind placebo run-in	Study 1 Study 2 (84 days) Treatment period	Study 1 Study 2 (7 days) Run-out period[a]	Extension Study (40 weeks) Treatment Phase Either placebo or daridorexant 10, 25, or 50 mg Double-blind	Extension Study (30 days) Follow-up Phase Placebo, single-blind	Extension Study (30 days) Follow-up Phase No treatment/ No blinding
	Study 1:				
Placebo	Daridorexant 50 mg	Placebo	Daridorexant 50 mg		
Placebo	Daridorexant 25 mg	Placebo	Daridorexant 25 mg		
Placebo	Placebo	Placebo	Placebo		
			Daridorexant 25 mg		
				Run-out	
	Study 2:				
Placebo	Daridorexant 25 mg	Placebo	Daridorexant 25 mg		
Placebo	Daridorexant 10 mg	Placebo	Daridorexant 10 mg		
Placebo	Placebo	Placebo	Placebo		
			Daridorexant 25 mg		

[a]Participants who did not enroll in the extension were followed for an additional 23 days of observation.

Who Took Part in the Studies?

- Most subjects were female (67% in study 1; 69% in study 2; 72% in the extension)

- Most subjects were white (90% in study 1; 88% in study 2; 90% in the extension)
- In the two pivotal studies, 39% of subjects were aged 65 years or older; in the extension study, 42% of subjects were aged 65 years or older



How Were Subjects Chosen?

To participate in the double-blind treatment period, subjects had to give informed consent and fulfill select inclusion criteria

- Be ≥18 years of age
- Meet DSM-5 criteria for insomnia disorder
- Have moderate to severe insomnia according to the Insomnia Severity Index (ISI)
- Have a self-reported history of disturbed sleep

Subjects could not participate if they had any of the following:

- Self-reported daytime napping
- Other sleep disorders
- Acute or unstable psychiatric conditions
- Breathing disorders

How Was Efficacy Measured?

Study 1 and Study 2 Endpoints

Objective primary endpoints

(at 1 month and 3 months, by polysomnography [sleep study])

Latency to persistent sleep (LPS)
The time it takes for a subject to enter consolidated sleep for at least 10 minutes after lying down[5]

Wake after sleep onset (WASO)
The total time a subject is awake after initially falling asleep[5]

Subjective secondary endpoints

(at 1 and 3 months, using an eDiary filled out twice per day by the subject)

Self-reported total sleep time (sTST)
The total sleep time as reported by the subject[5]

Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) Sleepiness domain score
The IDSIQ is a validated patient-reported outcome (PRO) tool consisting of a questionnaire with 14 items to be completed by the subject every evening[6]

Extension Study Endpoints

Primary endpoints

(up to 30 days after treatment end date)

Safety and tolerability
Treatment-emergent adverse events (TEAEs) that occurred

Additional endpoints including Epworth Sleepiness Scale, Visual Analog Scale-assessed morning sleepiness score, Benzodiazepine Withdrawal Symptom Questionnaire, and rebound insomnia were assessed, but are not included in this infographic. Please refer to the full manuscript.

Exploratory endpoints

(at 3 months, 6 months, and 9 months, self-reported)

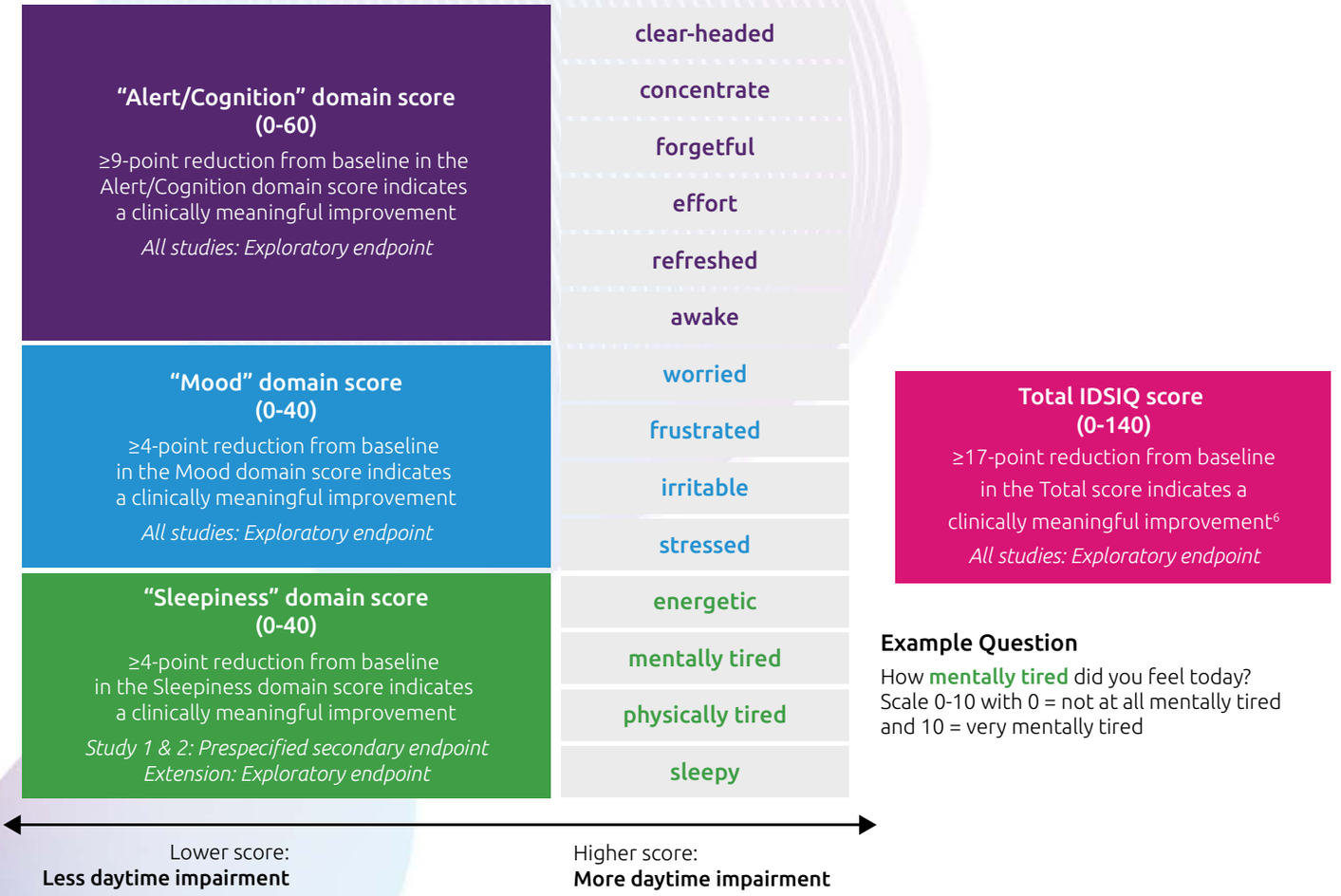
Efficacy results from the extension study were exploratory, results are descriptive only, and no conclusions regarding efficacy can be made

sTST

IDSIQ Total and Domain Scores

The items are divided into three domains that cover different aspects of daytime impairment[6]

Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)



Did Daridorexant 50 mg Improve Sleep?

- Daridorexant 50 mg was evaluated only in study 1 and the extension study
- Objective Primary Endpoints: Use of daridorexant 50 mg significantly improved LPS and WASO scores at month 1 and month 3
- Subjective Secondary Endpoint: Use of daridorexant 50 mg significantly improved sTST at month 1 and month 3
- Subjective Exploratory Endpoint-Long-term Use: Use of daridorexant 50 mg resulted in sustained improvement in sTST up to 1 year

Did Daridorexant 50 mg Improve Daytime Impairment?

- Subjective Secondary Endpoint: In study 1, use of daridorexant 50 mg significantly improved the IDSIQ Sleepiness domain scores at month 1 and month 3, and these improvements were considered clinically meaningful at month 3[6]
- Exploratory Endpoints From IDSIQ: Improvements were observed in all exploratory endpoints of the IDSIQ, including the Mood domain score, Alert/cognition domain score, and Total score, at month 1 and month 3 in study 1 with the use of daridorexant 50 mg; however, because these results are exploratory, no conclusions regarding efficacy can be made
- Long-term Exploratory Endpoints From IDSIQ: IDSIQ domain and Total score improvement with the use of daridorexant 50 mg was maintained in the extension study up to 1 year

Did Daridorexant 25 mg Improve Sleep?

- Daridorexant 25 mg was the low-dose treatment in study 1, the high-dose treatment in study 2, and the mid-dose treatment in the extension study
- Objective Primary Endpoints: Use of daridorexant 25 mg significantly improved LPS in study 1 but not in study 2. Daridorexant 25 mg significantly improved WASO in both studies
  - In study 1, use of daridorexant 25 mg significantly improved LPS at month 1 and month 3; however, in study 2, daridorexant 25 mg did not significantly improve LPS at either time point

- In both study 1 and study 2, use of daridorexant 25 mg significantly improved WASO at month 1 and month 3

- Subjective Secondary Endpoint: Use of daridorexant 25 mg significantly improved sTST at month 1 and month 3 in both studies

- Subjective Exploratory Endpoint-Long-term Use: Improvement in sTST with the use of daridorexant 25 mg was maintained in the extension study up to 1 year

Did Daridorexant 25 mg Improve Daytime Impairment?

- Subjective Secondary Endpoint: Use of daridorexant 25 mg did not improve the IDSIQ Sleepiness domain score in either study 1 or 2

- Exploratory Endpoints From IDSIQ: Improvements were observed in all exploratory endpoints of the IDSIQ, including the Mood domain score, Alert/cognition domain score, and Total score, at month 1 and month 3 in both studies with the use of daridorexant 25 mg; however, because these results are exploratory, no conclusions regarding efficacy can be made

- Long-term Exploratory Endpoints From IDSIQ: IDSIQ domain and Total score improvement with the use of daridorexant 25 mg was maintained in the extension study up to 1 year

Did Daridorexant 10 mg Improve Sleep and Daytime Impairment?

- Daridorexant 10 mg was the low-dose treatment in study 2, and is not an FDA-approved dose

- Use of daridorexant 10 mg did not significantly improve any sleep or daytime impairment endpoints, suggesting this is a subtherapeutic dose

Summary:

Did Daridorexant Significantly Improve Sleep and Daytime Impairment at Months 1 and 3?

		Daridorexant Dose			
		Study 1		Study 2	
		50 mg	25 mg	25 mg	10 mg
Objective Primary Endpoints	LPS	✓	✓	✗	✗
	WASO	✓	✓	✓	✗
Subjective Secondary Endpoints	sTST	✓	✓	✓	✗
	IDSIQ Sleepiness Domain	✓[a]	✗	✗	✗

[a]Clinically meaningful at month 3.

For additional context on these studies, please refer to the Interactive Infographic titled: "Daridorexant for the Treatment of Insomnia Disorder: Exploring the Results From a Pair of Pivotal Phase 3 Trials and Their Long-term Extension Study"

Was Treatment With Daridorexant Associated With Any Adverse Events?

- Daridorexant 50 mg had a safety profile similar to those of lower (25 mg, 10 mg) daridorexant doses and to that of placebo

- Rates of dizziness, fatigue, and somnolence (adverse events often associated with insomnia or drugs for insomnia treatment) were low, especially in the 50-mg daridorexant group

- Nasopharyngitis and headache were the most common adverse events in all groups

- The frequency of serious adverse events was low and comparable across all groups
- For all studies, adverse events leading to treatment discontinuation were no greater in any daridorexant group than in the placebo group
- Safety results were similar for the extension study, and there was no evidence of dependence or tolerance

What Are the Implications of This Research?

The authors stated that:

- The results of several trials have shown the efficacy of DORAs on sleep outcomes in adults with insomnia
- The trials presented here showed that daridorexant improved sleep outcomes for up to 1 year of treatment and had a favorable long-term safety profile
- Daridorexant 50 mg and 25 mg significantly improved nighttime symptoms of insomnia, including time to fall asleep and sleep maintenance
  - At month 3, daridorexant 50 mg improved these 2 parameters by about 30 minutes each, reflecting a total increase in sleep time of about 1 hour, which is clinically meaningful[5]
  - Subjects had a mean sleep time of 6.5 hours
  - These efficacy results were maintained by 1 year of treatment
- In addition to greater improvement in sleep parameters, in study 1 and the long-term extension, the higher 50-mg dose significantly reduced daytime sleepiness compared with placebo, as measured by the IDSIQ tool (Sleepiness domain), to a clinically meaningful degree

Where Can I Find More Information on These Studies?

- A video by one of the investigators and coauthors of the articles explaining these studies can be found at:
  - https://poweredbyscience.idorsia.com/us/s/video-1
- The full scientific articles of these studies can be accessed here:
  - https://link.springer.com/article/10.1007/s40263-022-00980-8
  - https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(21)00436-1/fulltext
  - https://doi.org/10.1016/S1474-4422(21)00436-1
- For more information on the clinical studies in general visit:
  - Study 1: https://clinicaltrials.gov/ct2/show/NCT03545191
  - Study 2: https://clinicaltrials.gov/ct2/show/NCT03575104
  - Long-term extension: https://clinicaltrials.gov/ct2/show/NCT03679884
- Information on the indication for daridorexant and full safety information can be found here:
  - https://www.idorsia.us/documents/us/label/Quviviq_PI.pdf

Disclosures

Full author disclosure information can be found in the original articles.

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