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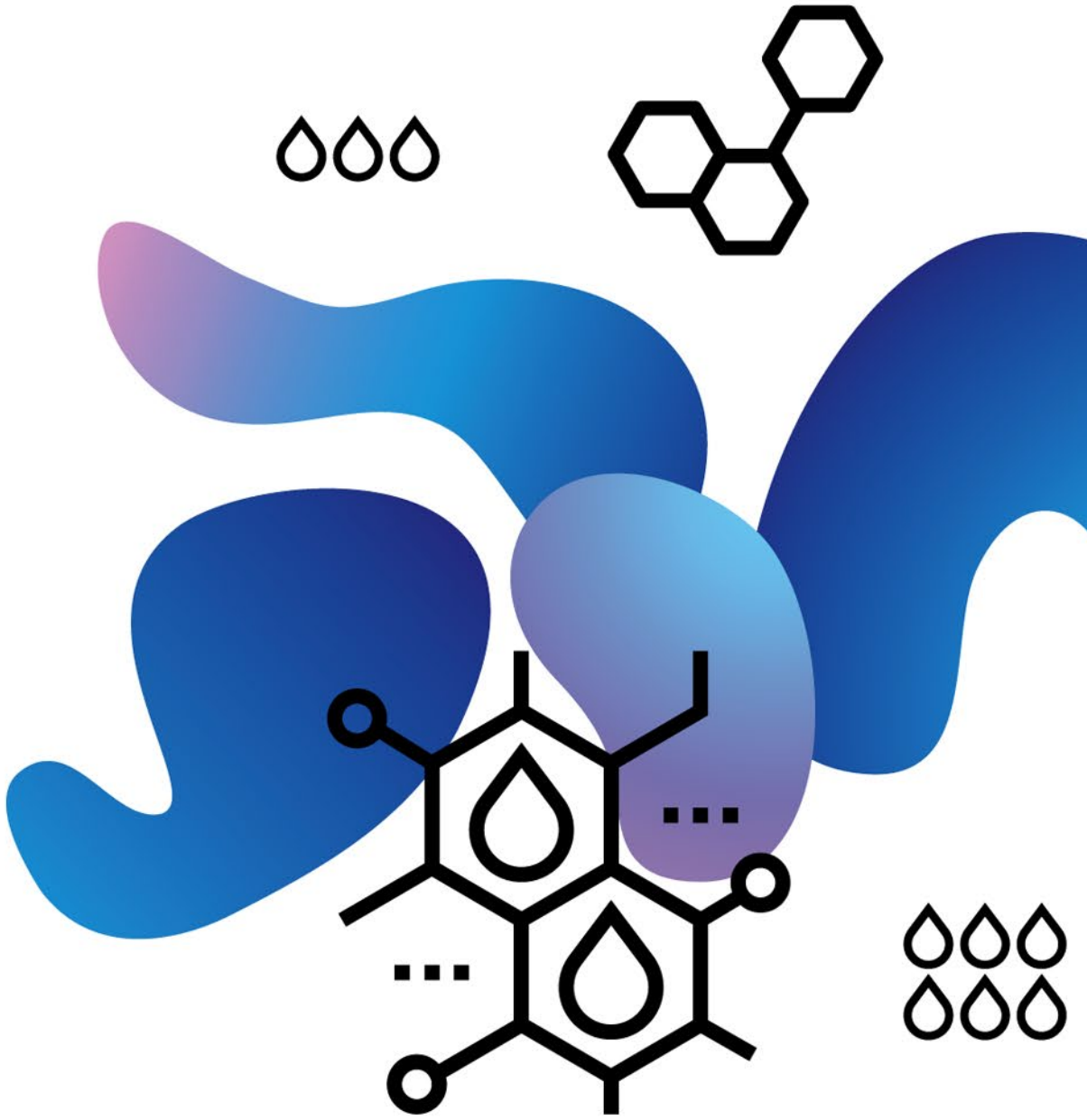
Daridorexant – Successful first pivotal study



Investor Webcast – April 2020

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“While we designed daridorexant to have the optimal profile for a sleep medicine, I am none-the-less stunned by the results.”

Jean-Paul Clozel
Chief Executive Officer

“The results have made working for over 20 years on the project completely worthwhile and prove that we were right to persevere.”

Martine Clozel
Chief Scientific Officer

The optimization process

> 25,000
compounds synthesized in the orexin program

1,361
High affinity in receptor binding and functional assays

Potent DUAL OX1 and OX2 receptor blockade *in vitro*

236
In vitro cytochrome P450 profile

No major drug-drug interaction

83
Physicochemical properties and confirmation *in vivo*

High brain penetration

12
In vivo efficacy tested in rats and dogs

Optimal *in vivo* efficacy

Daridorexant
Human Pharmacokinetic and Pharmacodynamics prediction

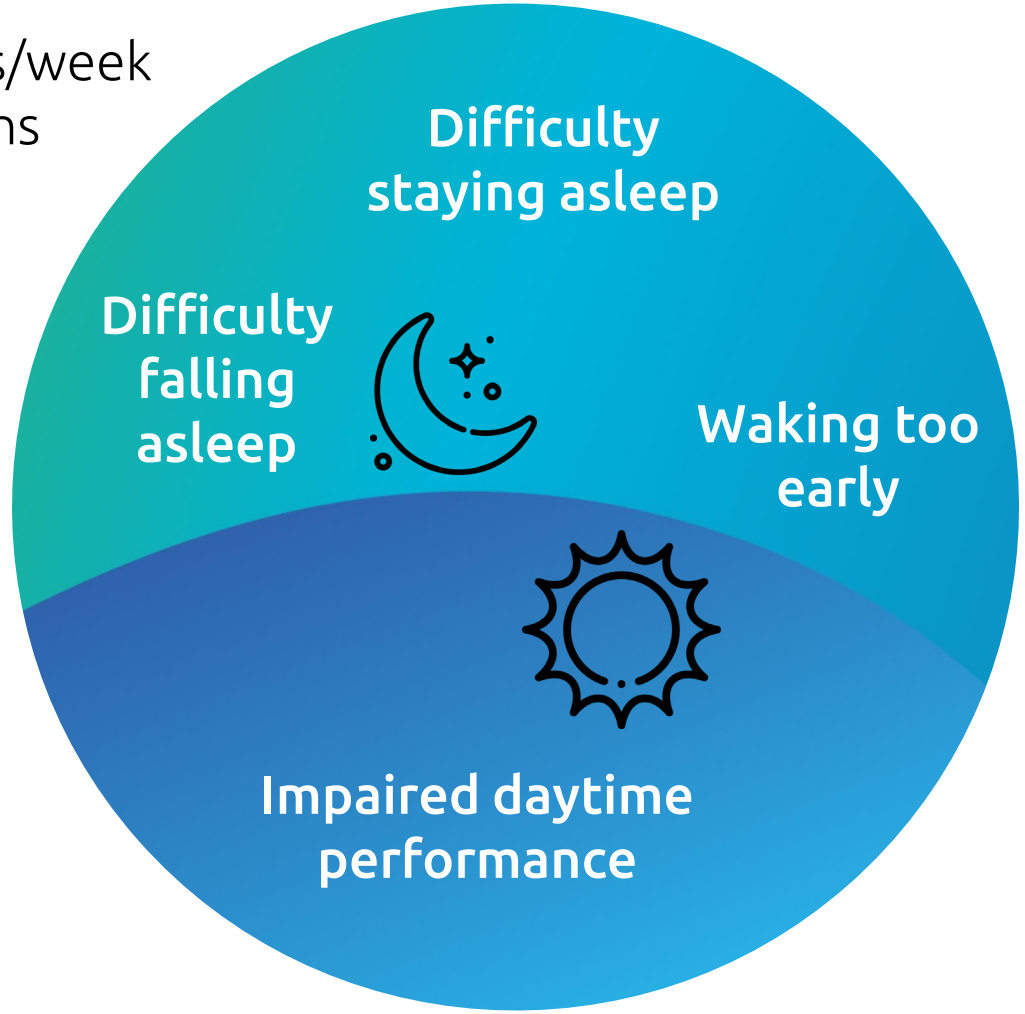
Optimized duration of action (fast onset, no next-day hangover)

“The results from this pivotal study are truly remarkable… this is the first study to demonstrate an insomnia product can improve how the patient feels during the day.”

Guy Braunstein
Head of Global Clinical Development

Insomnia: A disease of the night and the day

≥ 3 nights/week
≥ 3 months



Insomnia **patients' desire** from a pharmaceutical intervention:

1 - Increase in total sleep time

2 - Improvement in daily performance

Key assessments in daridorexant Phase 3 studies

Objective sleep assessment

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

Patient's oriented outcome daily recorded

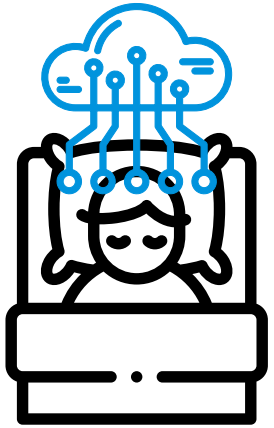
Subjective measures of night parameters by the **sleep diary questionnaire (SDQ)**

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

Objective sleep assessments

Repeated polysomnography recordings in a sleep lab in all patients

- Assess insomnia objectively
- Ensure well-characterized insomnia patients are randomized
- Establish solid baseline during placebo run-in
- Measure primary endpoint at Month 1 and Month 3
  - **Latency to persistent sleep**
  - **Wakening after sleep onset**
- Asses the potential for rebound
- Collect comprehensive information on total sleep time and sleep architecture



Sensors measure brain activity, eye movements, muscle tone, respiratory, and heart parameters.

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 feeling 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

Subjective assessment of daytime performance

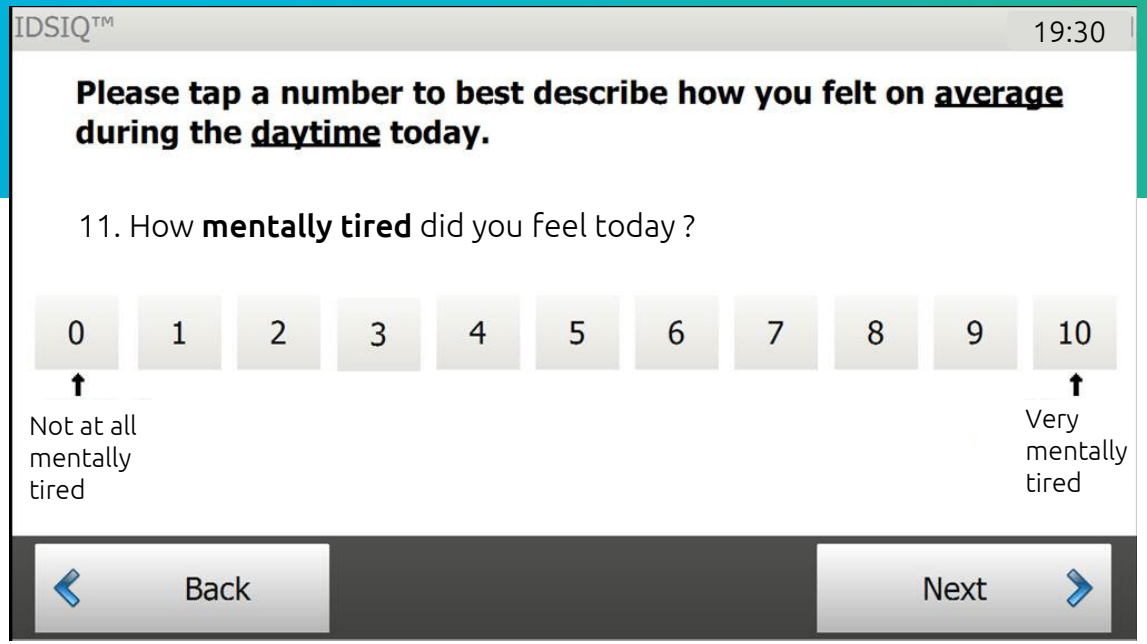
Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) validated according to FDA guidelines

Measures
1 Clear-Headed
2 Concentrate
3 Forgetful
4 Worried
5 Frustrated
6 Irritable
7 Stressed
8 Energetic
9 Effort
10 Refreshed
11 Mentally Tired
12 Physically Tired
13 Sleepy
14 Awake

"Alert/cognition" domain score

"Mood" domain score

"Sleepiness" domain score



Daytime performance measured by sleepiness domain score

Secondary endpoint

Daridorexant registration program

Robust program in adult and elderly insomnia patients

Following completion of Phase 2 studies, two similar pivotal studies of 3-month duration in moderate and severe insomnia

Efficacy

- Objective and subject sleep parameters (onset and maintenance) by PSG and SDQ
- Daytime performance assessed by IDSIQ
- Replicated in two confirmatory studies

Safety

- Adverse events, vital signs, biochemistry and hematology
- Next morning residual “hang-over” effect
- Withdrawal/physical dependence, and rebound insomnia

Comprehensive clinical pharmacology program including:

- Driving performance, interaction (medicines, alcohol), Safety in specific population (COPD, obstructive sleep apnea, liver and renal impairment), drug abuse potential

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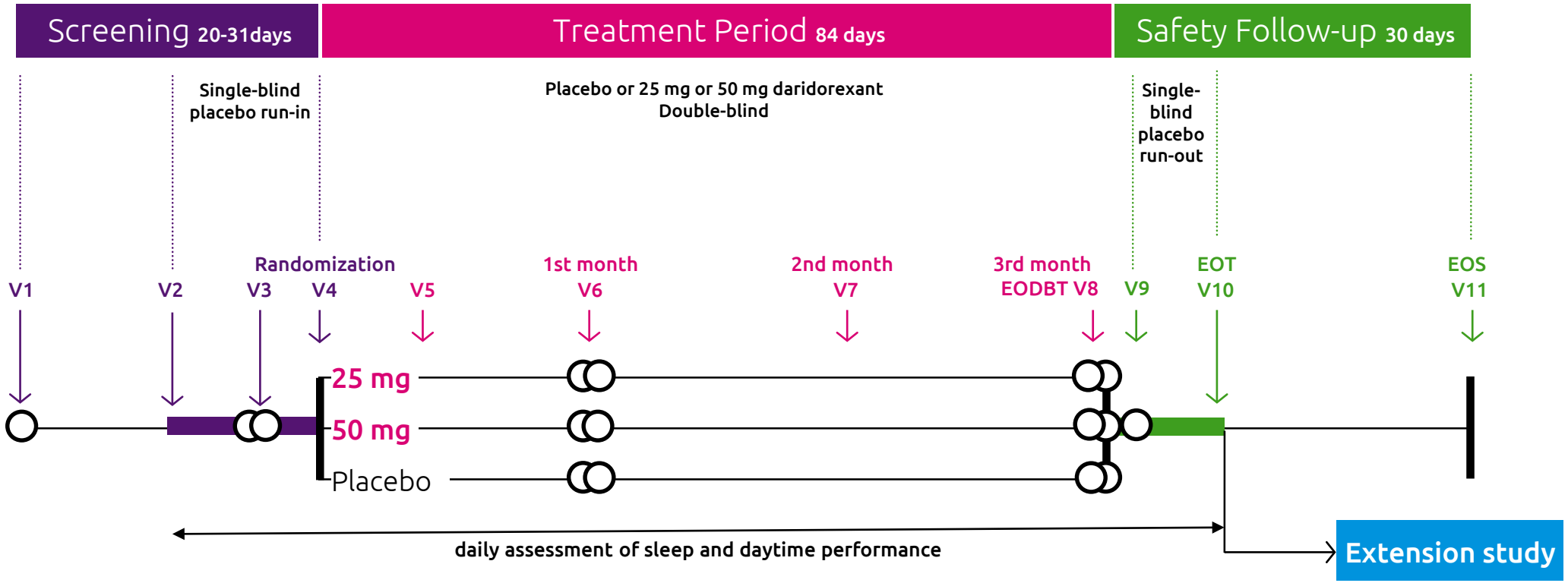
Study design



V = site visit

= 1 polysomnography night

= 2 consecutive polysomnography nights

EODBT = End of double-blind treatment
EOT = End-of-Treatment
EOS = End-of-Study

Study objectives

Primary objective

- To evaluate the efficacy of 25 mg and 50 mg daridorexant on objective sleep parameters in patients with insomnia.

Secondary objective

- To evaluate the efficacy of 25 mg and 50 mg daridorexant on subjective sleep parameters and daytime performance in patients with insomnia.

Safety objective

- To assess the safety and tolerability of daridorexant in patients with insomnia during treatment and upon treatment discontinuation.

Primary and secondary endpoints and analysis

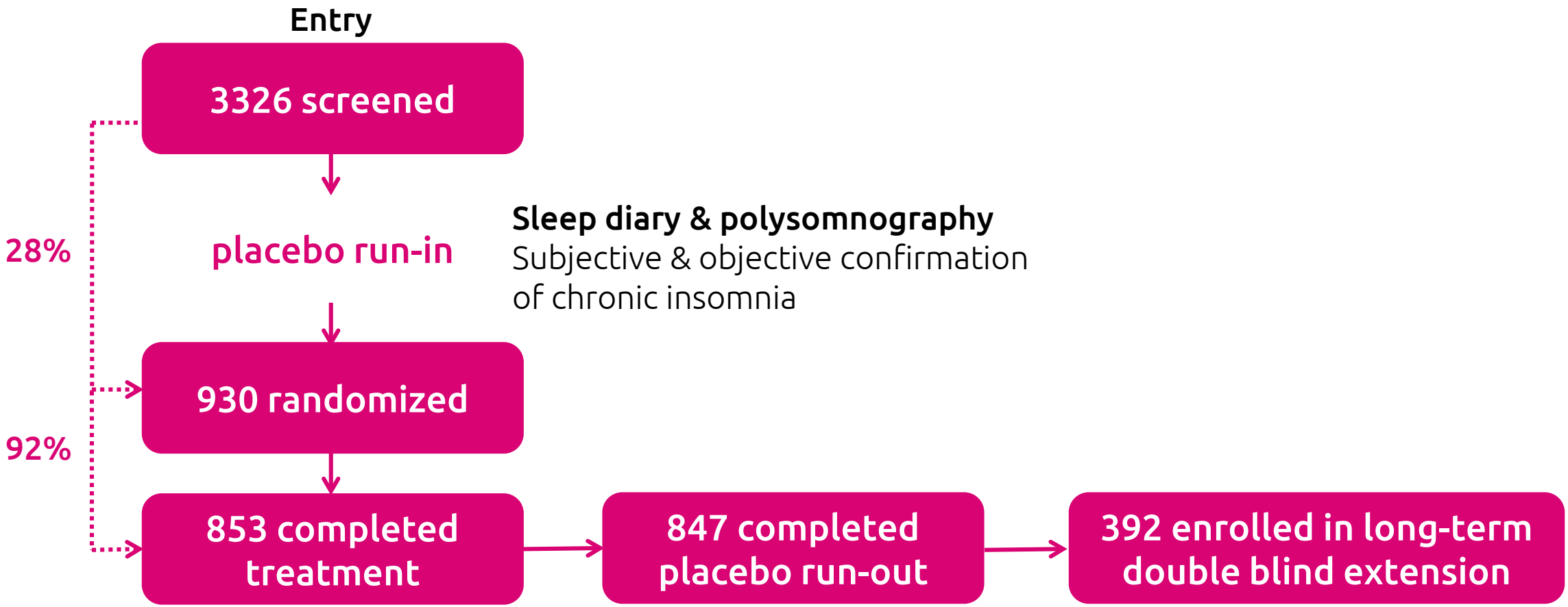
Study-wise type 1 error controlled at 0.05 (across 16 comparisons to placebo)

- **Primary endpoints (night)**
  - Wakening after sleep onset by PSG
  - Latency to persistent sleep by PSG

- **Secondary endpoints (night and day patients' feeling)**
  - Subjective total sleep time by SDQ
  - Sleepiness score during the day by IDSIQ

- **Two dose levels**
  - 50 mg vs. placebo
  - 25 mg vs. placebo
- **Two assessment time points**
  - Month 1
  - Month 3

Study patient disposition



Demographics and baseline characteristics

N = 930

Demographic characteristic	
Female, n (%)	624 (67.1)
Mean age, years (SD)	55.4 (15.3)
BMI	
< 25	39.5%
25 – ≤ 30	41.7%
>30	18.8%
Median time from diagnosis, years	7.1

The study was conducted at 75 hospitals and sleep centers in 10 countries (Germany, Australia, Canada, Denmark, Italy, Poland, Serbia, Spain, Switzerland and the United States).

BMI, body mass index ; LPS, latency to persistent sleep;
SD, standard deviation; TST, Total Sleep Time;
WASO, wake after sleep onset

Well-characterized moderate and severe insomnia patients

	Self-reported insomnia at entry	Confirmed by polysomnography at baseline
Sleep induction	≥ 30 minutes to fall asleep	Mean LPS ≥ 20 min
Sleep maintenance	Wake time during sleep ≥ 30 minutes	Mean WASO ≥ 30 min
Total sleep time	Total sleep time ≤ 6.5 h	Mean TST < 420 minutes

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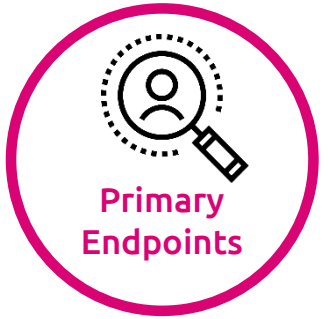
Objective sleep parameters

At both doses of 50 and 25 mg vs. placebo: highly consistent effect



The study demonstrated the efficacy of daridorexant in **inducing** and **maintaining sleep**

- Statistically **significant improvement** in LPS at **1 month**
- Statistically **significant improvement** in WASO at **1 month**

The effect observed at 1 month was **sustained** at 3 months

- Statistically **significant improvement** in LPS at **3 month**
- Statistically **significant improvement** in WASO at **3 month**

LPS, latency to persistent sleep; WASO, wake after sleep onset

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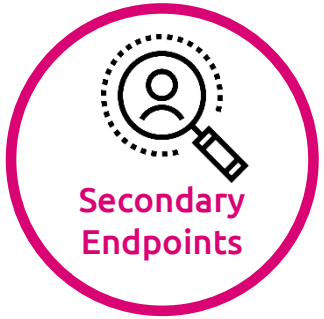
Subjective sleep parameter

SDQ



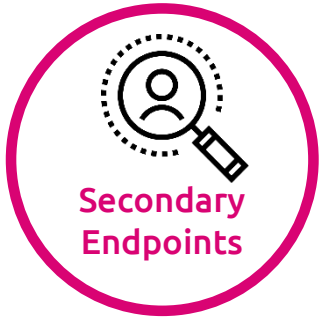
The study demonstrated the efficacy of daridorexant in increasing **patient's assessed total sleep time** at both doses of 50 and 25 mg vs. placebo

- Statistically **significant improvement** in sTST at **1 month**
- Statistically **significant improvement** in sTST at **3 month**

sTST, subjective Total Sleep Time

Daytime performance

IDSIQ



The study demonstrated the efficacy of daridorexant in improving **patient's daytime performance**

50 mg

- Statistically **significant improvement** in IDSIQ sleepiness domain at **1 month**
- Statistically **significant improvement** in IDSIQ sleepiness domain at **3 month**

25 mg

- Numerical **improvement** in IDSIQ sleepiness domain at **1 and 3 months**

IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

Overview of treatment emergent adverse events

	Daridorexant 25 mg n = 310 n (%)	Daridorexant 50 mg n = 308 n (%)	Placebo n = 309 n (%)
Subjects with at least one:			
AE during the double-blind study period	117 (37.7)	116 (37.7)	105 (34.0)
AEs leading to premature discontinuation of double-blind study treatment	7 (2.3)	3 (1.0)	10 (3.2)
Serious AE*	2 (0.6)	3 (1.0)	7 (2.3)
AE of special interest (after blinded, independent adjudication)	4 (1.3)	2 (0.6)	1 (0.3)
AE with fatal outcome**	1 (0.3)	0	0

* Placebo: syncope (2), depression (2), anal abscess (1), ankle fracture (1), herpes zoster (1), panic attack (1);
25 mg daridorexant: cardiac arrest (1), influenza-like illness (1)
50 mg daridorexant: syncope (1), adenocarcinoma (1), hemoglobin decrease (1), post-procedural hemorrhage (1) renal colic (1)

** A 78-year male patient died due to cardiac arrest in the ER after presenting with chest pain. The patient had a history of stroke, hypertension and systolic murmur and the investigator assessed the case as not related to the study drug

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Adverse events during the DB study period

Preferred Term	Daridorexant 25 mg N = 310 n (%)	Daridorexant 50 mg N = 308 n (%)	Placebo N = 309 n (%)
Subjects with at least one event	117 (37.7)	116 (37.7)	105 (34.0)
Most frequent adverse events (based on 50 mg daridorexant)			
Nasopharyngitis	21 (6.8)	20 (6.5)	20 (6.5)
Headache	16 (5.2)	19 (6.2)	12 (3.9)
Accidental overdose	4 (1.3)	8 (2.6)	5 (1.6)
Fatigue	7 (2.3)	7 (2.3)	2 (0.6)
Dizziness	6 (1.9)	7 (2.3)	2 (0.6)
Nausea	1 (0.3)	7 (2.3)	3 (1.0)
Most clinically relevant adverse events			
Somnolence	11 (3.5)	5 (1.6)	6 (1.9)
Rapid eye movements sleep abnormal	0	3 (1.0)	0
Vertigo	1 (0.3)	2 (0.6)	2 (0.6)
Fall	1 (0.3)	1 (0.3)	8 (2.6)
Depressed mood	1 (0.3)	1 (0.3)	0
Overdose	1 (0.3)	1 (0.3)	0
Sleep paralysis	1 (0.3)	1 (0.3)	0
Syncope	0	1 (0.3)	2 (0.6)

Study conclusion

Daridorexant 25mg and 50 mg

Consistency of efficacy across

- Objective and subjective endpoints
- Doses
- Timepoints

		Daridorexant 25 mg		Daridorexant 50 mg	
		1 month	3 months	1 month	3 months
Primary endpoints	**WASO**	√	√	√	√
	LPS	√	√	√	√
Secondary endpoints	**sTST**	√	√	√	√
	IDSIQ	NS*	NS*	√	√

* Numerical trend

Safety and tolerability profile at the tested doses

- Rate of AE similar between placebo and daridorexant at both treatment doses
- No next morning hang-over effect
- No sign of rebound insomnia
- No withdrawal symptoms

LPS, latency to persistent sleep; WASO, wake after sleep onset; sTST, subjective Total Sleep Time; IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

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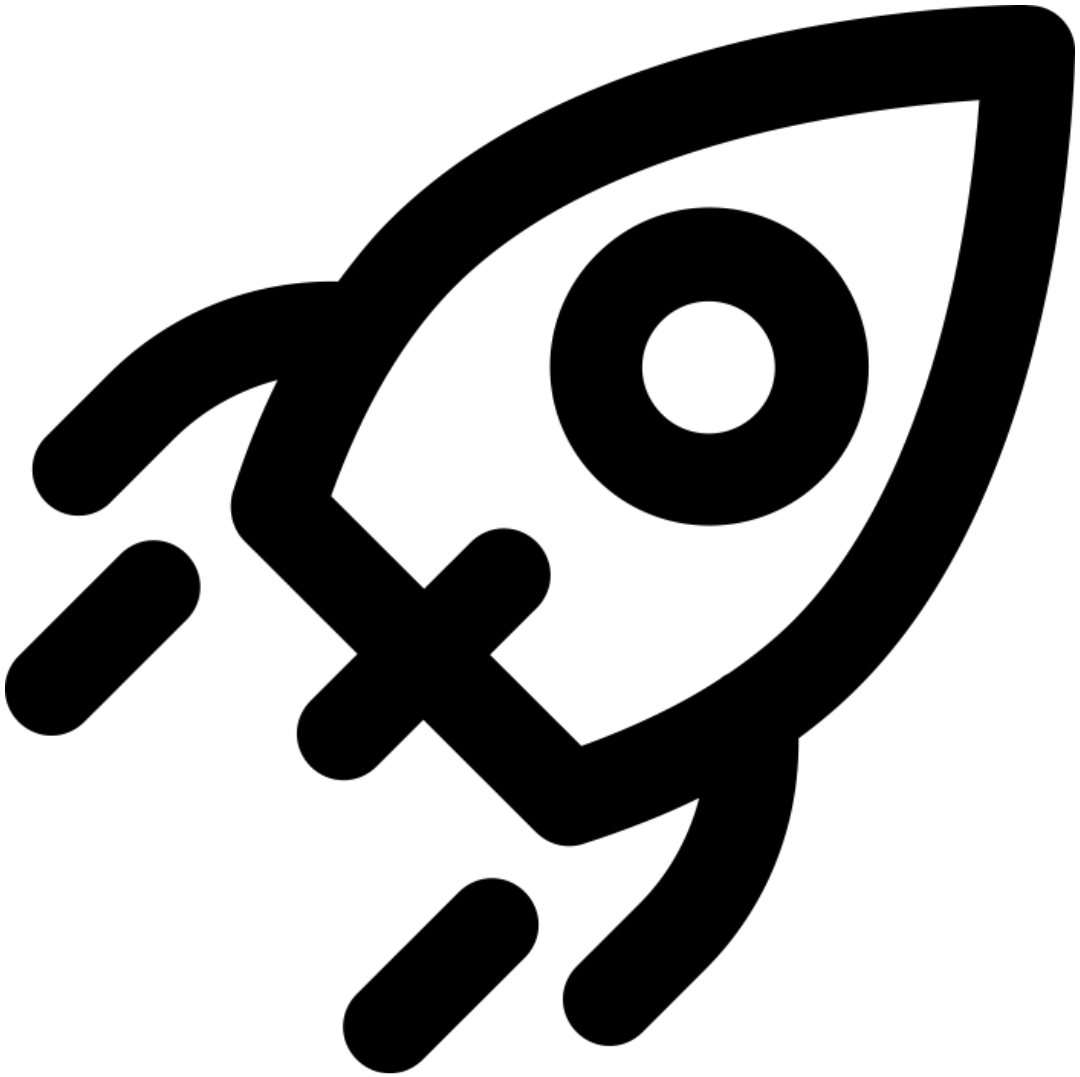
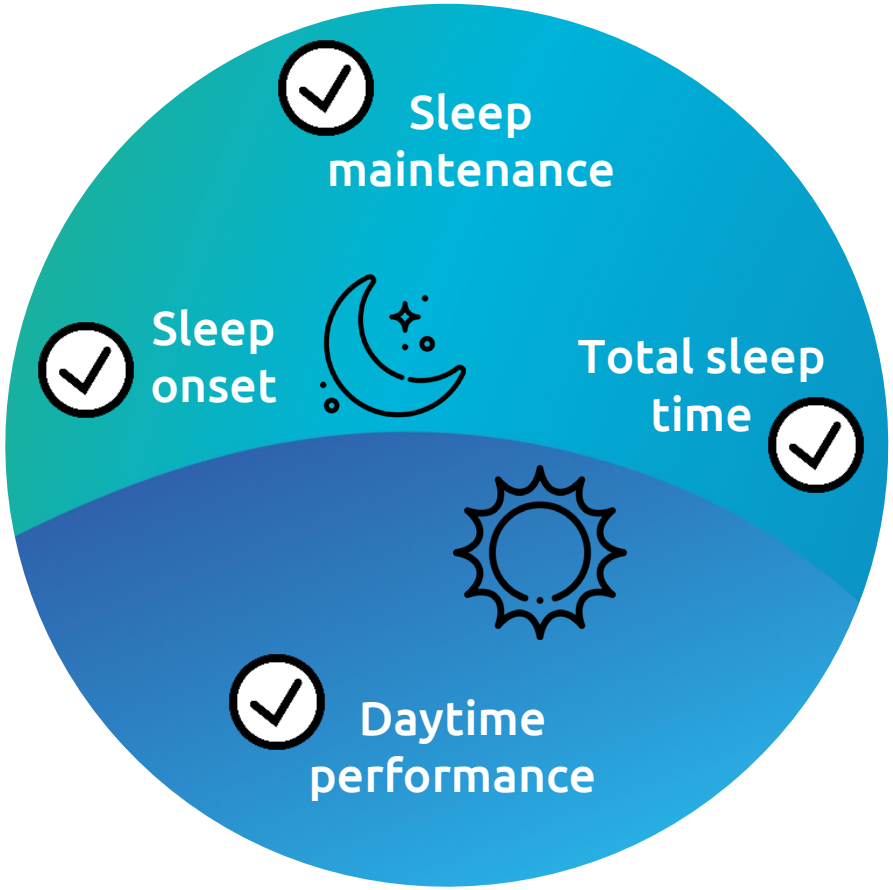
Idorsia is entering a new era



Study conclusion: Daridorexant 25mg and 50 mg

Treatment demonstrated statistically significant and clinically meaningful improvements at month 1 and at month 3

Efficacy during the night and the day



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