SUPPLEMENTARY INFORMATION

Efficacy and safety of daridorexant in older and younger adults with insomnia disorder: a secondary analysis of a randomised placebo-controlled trial

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Figure S1. Conceptual framework of the IDSIQ

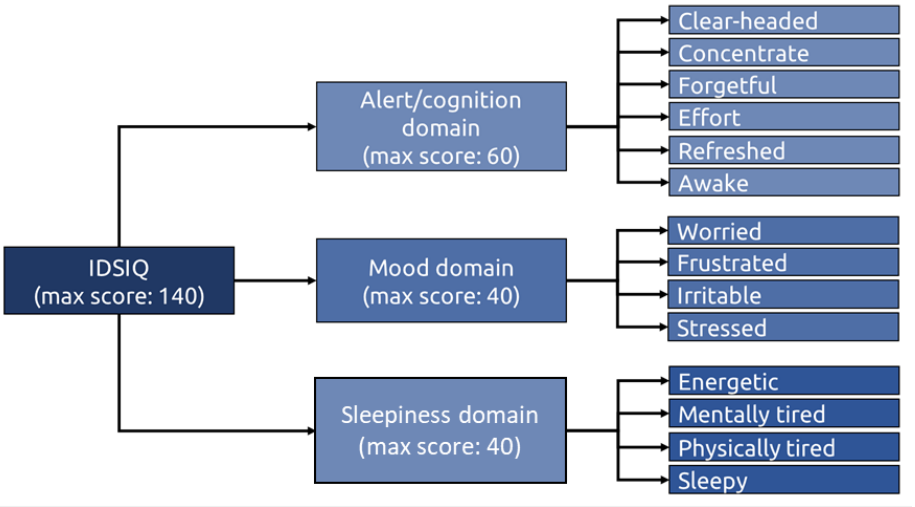
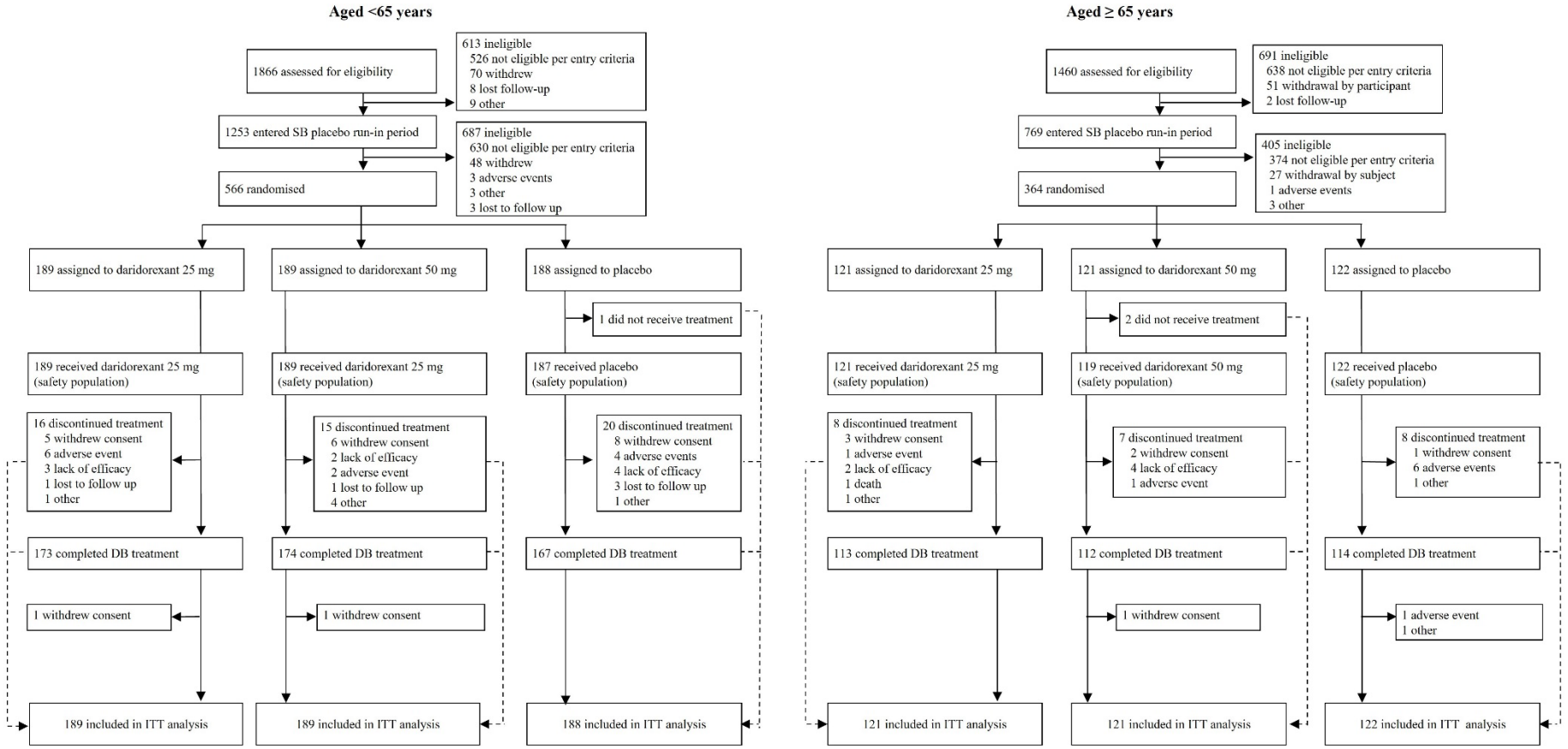


Figure reproduced with permission from Mignot E, et al. Lancet Neurol. 2022;21(2):125-39. IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire

Figure S2 Study flow and disposition of patients by age group



DB, double-blind; ITT, intention-to-treat; SB, single-blind

Supplementary Table 1 Baseline demographics and insomnia characteristics by treatment group

Characteristics	<65 years N=566			≥65 years N=364		
	Daridorexant 50 mg (n=189)	Daridorexant 25 mg (n=189)	Placebo (n=188)	Daridorexant 50 mg (n=121)	Daridorexant 25 mg (n=121)	Placebo (n=122)
Sex, n (%)						
Female	127 (67)	127 (67)	131 (70)	72 (60)	88 (73)	79 (65)
Male	62 (33)	62 (33)	57 (30)	49 (40)	33 (27)	43 (35)
Age at screening, years, mean (SD)	46.1 (12.0)	46.6 (12.6)	45.5 (12.0)	70.2 (4.4)	70.0 (4.6)	69.9 (4.1)
Aged ≥75 years, n (%)	-	-	-	19 (16)	18 (15)	17 (14)
Race, n (%)						
Caucasian	167 (88)	167 (88)	161 (86)	107 (88)	120 (99)	117 (96)
Black/African	18 (10)	19 (10)	23 (12)	12 (10)	0	5 (4)
Asian	3 (2)	3 (2)	2 (1)	1 (1)	0	0
Other	1 (1)	0	2 (1)	1 (1)	1 (1)	0
US region, n (%)	59 (31)	66 (35)	69 (37)	38 (31)	33 (27)	35 (29)
BMI, kg/m^2, mean (SD)	26.0 (4.5)	26.5 (4.5)	26.5 (4.4)	26.7 (3.9)	26.9 (4.1)	26.3 (3.6)
Patients with ≥1 concomitant condition, n (%)	112 (59)	129 (68)	110 (59)	98 (81)	100 (83)	97 (80)
Most common condition (>10% of at least one group)						
Hypertension	17 (9)	25 (13)	19 (10)	46 (38)	50 (41)	50 (41)
Hypercholesterolemia	7 (4)	9 (5)	7 (4)	18 (15)	19 (16)	14 (11)
Osteoarthritis	5 (3)	14 (7)	11 (6)	9 (7)	19 (16)	15 (12)
Patients with ≥1 concomitant medication[a], n (%)	103 (54)	117 (62)	105 (56)	87 (73)	88 (73)	83 (68)
No. medications/patient[a], mean (SD)	0.8 (1.4)	1.1 (1.7)	1.1 (1.6)	2.1 (2.2)	2.1 (2.0)	2.2 (2.4)
Most common medications (>10% of at least one group)[a], n (%)						
Statins	2 (1)	11 (6)	7 (4)	22 (18)	26 (21)	27 (22)
Beta blockers	2 (1)	16 (8)	6 (3)	16 (13)	18 (15)	18 (15)
ACE inhibitors	5 (3)	7 (4)	8 (4)	15 (13)	14 (12)	22 (18)
Antiplatelet agents, exc. heparin	1 (1)	4 (2)	4 (2)	15 (13)	17 (14)	16 (13)
ARBs	6 (3)	8 (4)	6 (3)	17 (14)	17 (14)	12 (10)
NSAIDs	32 (17)	27 (14)	30 (16)	10 (8)	16 (13)	15 (12)
PPIs	7 (4)	15 (8)	9 (5)	14 (12)	16 (13)	9 (7)
Thyroid hormones	13 (7)	17 (9)	12 (6)	11 (9)	13 (11)	15 (12)
Previous insomnia therapies [a,b], n (%)						
Non-benzodiazepine GABA-RA (Z-drugs)	2 (1)	0	0	2 (2)	2 (2)	2 (2)
Benzodiazepine GABA-RA	1 (1)	2 (1)	0	1 (1)	2 (2)	0
Other hypnotics and sedatives	1 (1)	0	1 (1)	0	2 (2)	2 (2)
Other antidepressants[c]	2 (1)	0	2 (1)	2 (2)	2 (2)	0
WASO, min, mean (SD)	87.1 (33.8)	92.1 (39.6)	95.7 (40.3)	108.6 (40.1)	106.9 (35.7)	112.9 (39.5)
LPS, min, mean (SD)	66.3 (40.8)	68.8 (38.5)	67.3 (37.3)	59.4 (30.9)	64.9 (38.6)	65.4 (43.4)
TST, min, mean (SD)	333.4 (51.4)	326.4 (57.1)	324.3 (53.9)	320.2 (47.3)	316.3 (51.6)	309.9 (54.3)
sTST, min, mean (SD)	315.3 (53.7)	310.7 (59.6)	316.8 (52.0)	309.8 (63.3)	308.5 (61.1)	314.4 (55.0)
ISI score[d], mean (SD)	19.6 (4.0)	19.4 (4.5)	19.6 (4.1)	18.8 (3.9)	18.2 (4.0)	18.6 (3.8)
IDSIQ scores[e] mean (SD)						
IDSIQ sleepiness domain (0-40)	22.8 (7.1)	23.0 (6.9)	22.9 (6.8)	21.9 (7.4)	20.7 (6.6)	21.3 (7.1)
IDSIQ mood domain (0-40)	20.3 (8.3)	20.3 (8.8)	19.7 (8.9)	18.9 (8.9)	17.6 (8.2)	18.1 (8.4)
IDSIQ alert/cognition domain (0-60)	33.0 (10.1)	33.1 (10.0)	33.3 (10.1)	31.2 (11.2)	29.5 (9.8)	30.5 (10.2)
IDSIQ total score (0-140)	76.1 (24.2)	76.4 (24.7)	75.9 (24.5)	72.0 (26.4)	67.9 (23.5)	69.9 (24.5)
VAS scores[f], mean (SD)						
VAS quality (0-100)	34.5 (16.8)	34.0 (18.4)	33.5 (17.0)	38.9 (17.2)	38.0 (16.6)	38.9 (18.5)
VAS depth (0-100)	35.0 (17.1)	34.0 (17.9)	33.8 (17.3)	39.3 (17.8)	37.6 (16.9)	39.4 (18.8)
VAS daytime alertness (0-100)	39.0 (20.1)	37.1 (19.8)	36.5 (19.6)	42.7 (19.5)	44.5 (20.3)	43.0 (20.3)
VAS ability to function (0-100)	38.6 (18.9)	38.2 (19.5)	37.6 (19.4)	42.8 (19.9)	44.5 (19.1)	42.7 (19.7)
VAS morning sleepiness[a] (0-100)	36.7 (18.9)	34.6 (18.5)	33.9 (17.4)	40.1 (18.4)	41.8 (18.5)	42.2 (20.2)

Full analysis set, unless specified otherwise.
[a]Safety analysis set (<65 years: N=565; ≥65 years: N=362); [b]Per protocol, stopped before screening and only reported within the 30 days preceding the screening period; [c] Classification includes trazodone hydrochloride, mirtazapine, and trazodone; [d] ISI score 0–7 = absence of insomnia; 8–14 = sub-threshold insomnia; 15–21 = moderate insomnia; and 22–28 = severe insomnia [59]; [e] Lower IDSIQ scores indicate better patient-perceived daytime functioning; [f] Higher VAS scores indicate better outcome.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; GABA-RA, gamma-aminobutyric acid receptor agonist IDSIQ, Insomnia Daytime Symptoms and Impacts Questionnaire; ISI, Insomnia Severity Index; LPS, latency to persistent sleep; min, minutes; NSAIDS, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SD, standard deviation; sTST, subjective total sleep time; TST, total sleep time; VAS, Visual Analog Scale; WASO, wake after sleep onset.

Supplementary Table 2 Effect of daridorexant on objective and subjective sleep parameters by age group

Sleep parameters	<65 years N=566			≥65 years N=364		
	Daridorexant 50 mg n=189	**Daridorexant 25 mg n=189**	**Placebo n=188**	**Daridorexant 50 mg n=121**	**Daridorexant 25 mg n=121**	**Placebo n=122**
WASO, min						
Baseline, mean (SD)	87.1 (33.8)	92.1 (39.6)	95.7 (40.3)	108.6 (40.1)	106.9 (35.7)	112.9 (39.5)
Month 1						
LSM change from baseline	–37.5	–25.0	–13.5	–22.6	–14.4	–1.4
95% CI	–41.7, –33.2	–29.3, –20.7	–17.9, –9.2	–29.2, –16.0	–21.1, –7.7	–8.0, 5.2
SEM	2.2	2.2	2.2	3.4	3.4	3.3
LSM difference to placebo	–24.0	–11.5	–	–21.2	–13.0	–
95% CI	–30.1, –17.8	–17.6, –5.4	–	–30.5, –11.9	–22.4, –3.6	–
SEM	–24.0	–11.5	–	–21.2	–13.0	–
Month 3						
LSM change from baseline	–38.9	–29.8	–21.5	–21.4	–18.8	–1.8
95% CI	–43.6, –34.2	–34.4, –25.2	–26.3, –16.8	–28.4, –14.3	–25.9, –11.7	–8.7, 5.2
SEM	2.4	2.4	2.4	3.6	3.6	3.6
LSM difference to placebo	–17.4	-8.3	–	–19.6	–17.0	–
95% CI	–24.0, –10.7	–14.9, –1.6	–	–29.5, –9.7	–27.0, –7.0	–
SEM	3.4	3.4	–	5.1	5.1	–
LPS, min						
Baseline, mean (SD)	66.3 (40.8)	68.8 (38.5)	67.3 (37.3)	59.4 (30.9)	64.9 (38.6)	65.4 (43.4)
Month 1						
LSM change from baseline	–31.5	–30.2	–21.6	–31.1	–25.4	–17.4
95% CI	–36.1, –27.0	–34.8, –25.6	–26.2, –17.0	–35.8, –26.5	–30.1, –20.7	–22.0, –12.8
SEM	2.3	2.3	2.3	2.4	2.4	2.3
LSM difference to placebo	–10.0	–8.6	–	–13.7	–8.0	–
95% CI	–16.4, –3.5	–15.1, –2.1	–	–20.2, –7.2	–14.5, –1.4	–
SEM	3.3	3.3	–	3.3	3.3	–
Month 3						
LSM change from baseline	–35.7	–33.7	–26.0	–33.8	–26.7	–18.9
95% CI	–39.9, –31.5	–37.9, –29.5	–30.3, –21.7	–39.1, –28.6	–32.0, –21.4	–24.1, –13.7
SEM	2.1	2.1	2.1	2.7	2.7	2.6
LSM difference to placebo	-9.7	–7.7	–	–14.9	–7.8	–
95% CI	–15.7, –3.7	–13.7, –1.7	–	–22.3, –7.5	–15.2, –0.4	–
SEM	3.1	3.1	–	3.8	3.8	–
sTST, min						
Baseline, mean (SD)	315.3 (53.7)	310.7 (59.6)	316.8 (52.0)	309.8 (63.3)	308.5 (61.1)	314.4 (55.0)
Month 1						
LSM change from baseline	43.9	38.3	27.4	44.8	29.9	14.4
95% CI	36.9, 51.0	31.2, 45.4	20.3, 34.5	36.5, 53.0	21.5, 38.2	6.2, 22.7
SEM	3.6	3.6	3.6	4.2	4.2	4.2
LSM difference to placebo	16.5	10.9	–	30.3	15.4	–
95% CI	6.5, 26.6	0.9, 21.0	–	18.7, 42.0	3.7, 27.1	–
SEM	5.1	5.1	–	5.9	6.0	–
Month 3						
LSM change from baseline	57.1	49.1	44.8	59.9	47.9	29.3
95% CI	48.9, 65.3	40.9, 57.3	36.5, 53.1	49.6, 70.3	37.6, 58.3	19.1, 39.5
SEM	4.2	4.2	4.2	5.3	5.3	5.2
LSM difference to placebo	12.4	4.3	–	30.6	18.7	–
95% CI	0.7, 24.0	(–7.3, 16.0)	–	16.1, 45.2	4.1, 33.2	–
SEM	5.9	5.9	–	7.4	7.4	–

Baseline data are presented as mean (SD). LSM change from baseline and LSM difference to placebo are presented as LSM (95% CI).

CI, confidence interval; LPS, latency to persistent sleep; LSM, least squares mean; SD, standard deviation; SEM, standard error of the mean; sTST, self-reported total sleep time; WASO, wake after sleep onset.