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

Aged <65 years

1866 assessed for eligibility
1253 entered SB placebo run-in period
566 randomised

189 assigned to daridorexant 25 mg
189 assigned to daridorexant 50 mg
188 assigned to placebo

189 received daridorexant 25 mg
189 received daridorexant 50 mg
187 received placebo

16 discontinued treatment
6 withdrew consent
2 adverse events
3 lack of efficacy
1 lost to follow up
1 other
173 completed DB treatment
1 withdrew consent
189 included in ITT analysis

Aged ≥ 65 years

1400 assessed for eligibility
769 entered SB placebo run-in period
364 randomised

121 assigned to daridorexant 25 mg
121 assigned to daridorexant 50 mg
122 assigned to placebo

121 received daridorexant 25 mg
121 received daridorexant 50 mg
119 received placebo

8 discontinued treatment
3 withdrew consent
1 adverse event
2 lack of efficacy
1 death
1 other
113 completed DB treatment
1 withdrew consent
121 included in ITT analysis

DB, double-blind; ITT, intention-to-treat; SB, single-blind
## Supplementary Table 1 Baseline demographics and insomnia characteristics by treatment group

| Characteristics                 | <65 years | ≥65 years |
|--------------------------------|-----------|-----------|
|                                | N=566     | N=364     |
|                                | Daridorexant (n=189) | Placebo (n=188) | Daridorexant (n=121) | Placebo (n=121) |
|                                | 50 mg     | 25 mg     |               |               |
| Sex, n (%)                     |           |           |               |               |
| Female                         | 127 (67)  | 127 (67)  | 131 (70)      | 72 (60)       |
| Male                           | 62 (33)   | 62 (33)   | 57 (30)       | 49 (40)       |
| Age at screening, years (SD)   | 46.1 (12.0) | 46.6 (12.6) | 45.5 (12.0)  | 70.2 (4.4)    |
| Aged ≥75 years, n (%)          |           |           |               |               |
| Caucasian                      | 167 (88)  | 167 (88)  | 161 (86)      | 107 (88)      |
| Black/African                  | 18 (10)   | 19 (10)   | 23 (12)       | 12 (10)       |
| Asian                          | 3 (2)     | 3 (2)     | 2 (1)         | 1 (1)         |
| Other                          | 1 (1)     | 0 (0)     | 2 (1)         | 1 (1)         |
| US region, n (%)               | 59 (31)   | 66 (35)   | 69 (37)       | 38 (31)       |
| BMI, kg/m², mean (SD)          | 26.0 (4.5)| 26.5 (4.5)| 26.5 (4.4)    | 26.7 (3.9)    |
| Patients with ≥1 concomitant condition, n (%) | 112 (59) | 129 (68) | 110 (59) | 98 (81) |
| Most common condition (>10% of at least one group) |           |           |               |               |
| Hypertension                   | 17 (9)    | 25 (13)   | 19 (10)       | 46 (38)       |
| Hypercholesteremia             | 7 (4)     | 9 (5)     | 7 (4)         | 18 (15)       |
| Osteoarthritis                 | 5 (3)     | 14 (7)    | 11 (6)        | 9 (7)         |
| Patients with ≥1 concomitant medication, n (%) | 103 (54) | 117 (62) | 105 (56) | 87 (73) |
| No. medications/patient, mean (SD) | 0.8 (1.4) | 1.1 (1.7) | 1.1 (1.6) | 2.1 (2.2) |
| Most common medications (>10% of at least one group), n (%) |           |           |               |               |
| Statins                        | 2 (1)     | 11 (6)    | 7 (4)         | 22 (18)       |
| Beta blockers                  | 2 (1)     | 16 (8)    | 6 (3)         | 16 (13)       |
| ACE inhibitors                 | 5 (3)     | 7 (4)     | 8 (4)         | 15 (13)       |
| Antiplatelet agents, exc. heparin | 1 (1) | 4 (2) | 4 (2) | 15 (13) |
| ARBs                           | 6 (3)     | 8 (4)     | 6 (3)         | 17 (14)       |
| NSAIDs                         | 32 (17)   | 27 (14)   | 30 (16)       | 10 (8)        |
| PPIs                           | 7 (4)     | 15 (8)    | 9 (5)         | 14 (12)       |
| Thyroid hormones               | 13 (7)    | 17 (9)    | 12 (6)        | 11 (9)        |
| Previous insomnia therapies, n (%) |           |           |               |               |
| Non-benzodiazepine GABA-RA     | 2 (1)     | 0 (0)     | 2 (2)         | 2 (2)         |
| Benzodiazepine GABA-RA         | 1 (1)     | 2 (1)     | 0 (0)         | 1 (1)         |
| Other hypnotics and sedatives  | 1 (1)     | 0 (0)     | 1 (1)         | 0 (0)         |
| Other antidepressants          | 2 (1)     | 0 (0)     | 2 (1)         | 2 (2)         |
| 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)|
| stTST, 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, 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) |
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       | WASO, min |        |        | LPS, min |        |
|------------------------|-----------|--------|--------|----------|--------|
|                        | Baseline, mean (SD) | Month 1 | Month 3 | Baseline, mean (SD) | Month 1 | Month 3 |
|                        |            | LSM change from baseline | 95% CI | SEM | LSM change from baseline | 95% CI | SEM | LSM change from baseline | 95% CI | SEM |
| 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    | -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 |
| WASO, min              | Month 3    | -30.1 | -17.8 | -16.5 | -30.5 | -11.9 | -22.4, -3.6 |
|                        | 95% CI     | -30.1, -17.8 | -16.5, -5.4 | -30.5, -11.9 | -22.4, -3.6 | -21.2, -13.0 | - |
|                        | SEM        | -24.0 | -11.5 | -11.5 | -21.2 | -13.0 | - |
| 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    | -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 |
| LPS, min               | Month 3    | -16.4 | -3.5 | -15.1 | -20.2, -7.2 | -14.5, -1.4 | - |
|                        | 95% CI     | -16.4, -3.5 | -15.1, -2.1 | -20.2, -7.2 | -14.5, -1.4 | -3.3 | - |
|                        | SEM        | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 |
| 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    | 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 |
| sTST, min              | Month 3    | 6.5 | 26.6 | 0.9 | 21.0 | 18.7, 42.0 | 3.7, 27.1 | - |
|                        | 95% CI     | 6.5, 26.6 | 0.9, 21.0 | 18.7, 42.0 | 3.7, 27.1 | - | - |
|                        | SEM        | 5.1 | 5.1 | 5.1 | 5.9 | 5.9 | 6.0 |

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.