**Electronic Supplementary Material**

# Targeting the prostacyclin pathway with selexipag in pulmonary arterial hypertension patients receiving double combination therapy: Insights from the randomized controlled GRIPHON study

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**Online Table S1 Individualized maintenance dose in patients receiving double combination therapy[a] at baseline**

| | | Overall[b] | | WHO FC II symptoms at baseline | | WHO FC III symptoms at baseline | |
|---|---|---|---|---|---|---|---|
| **Dose groups** | **Twice-daily dose µg** | **Selexipag (*N* = 179) *n* (%)** | **Placebo (*N* = 197) *n* (%)** | **Selexipag (*N* = 55) *n* (%)** | **Placebo (*N* = 60) *n* (%)** | **Selexipag (*N* = 122) *n* (%)** | **Placebo (*N* = 133) *n* (%)** |
| Low-dose group (200–400 µg) | 200 | 21 (11.7) | 7 (3.6) | 6 (10.9) | 2 (3.3) | 15 (12.3) | 5 (3.8) |
| | 400 | 15 (8.4) | 5 (2.5) | 3 (5.5) | 2 (3.3) | 12 (9.8) | 3 (2.3) |
| Medium-dose group (600–1000 µg) | 600 | 20 (11.2) | 4 (2.0) | 9 (16.4) | 2 (3.3) | 10 (8.2) | 2 (1.5) |
| | 800 | 29 (16.2) | 6 (3.0) | 10 (18.2) | 1 (1.7) | 19 (15.6) | 5 (3.8) |
| | 1000 | 16 (8.9) | 7 (3.6) | 3 (5.5) | 3 (5.0) | 13 (10.7) | 4 (3.0) |
| High-dose group (1200–1600 µg) | 1200 | 14 (7.8) | 5 (2.5) | 5 (9.1) | 1 (1.7) | 9 (7.4) | 4 (3.0) |
| | 1400 | 10 (5.6) | 18 (9.1) | 4 (7.3) | 2 (3.3) | 6 (4.9) | 14 (10.5) |
| | 1600 | 50 (27.9) | 143 (72.6) | 15 (27.3) | 45 (75.0) | 34 (27.9) | 96 (72.2) |

Four patients in the selexipag group (all with WHO FC III symptoms at baseline) and two patients in the placebo group (both with WHO FC II symptoms at baseline) had an individualized maintenance dose of 0 µg and are not reported here.

[a] Receiving an endothelin receptor antagonist and phosphodiesterase-5 inhibitor.

[b] Includes 6 patients with WHO FC IV symptoms at baseline.

WHO FC: WHO functional class.

**Online Table S2 Cumulative incidence of all-cause death up to the end of study in patients receiving double combination therapy[a] at baseline**

| | **Cumulative number of patients with an event of all-cause death up to the end of the study, *n***<br>**Kaplan-Meier survival estimates, % (95% CI)** | | | | | |
|---|---|---|---|---|---|---|
| | **Overall[b]** | | **WHO FC II symptoms at baseline[c]** | | **WHO FC III symptoms at baseline** | |
| **Time-point** | **Selexipag**<br>**(*N* = 179)** | **Placebo**<br>**(*N* = 197)** | **Selexipag**<br>**(*N* = 55)** | **Placebo**<br>**(*N* = 60)** | **Selexipag**<br>**(*N* = 122)** | **Placebo**<br>**(*N* = 133)** |
| Month 12 | 13<br>92.5 (87.4 to 95.6) | 12<br>93.8 (89.3 to 96.4) | 1 | 2 | 11<br>90.8 (84.0 to 94.8) | 9<br>93.1 (87.2 to 96.4) |
| Month 24 | 22<br>84.8 (77.5 to 89.9) | 24<br>85.7 (79.3 to 90.2) | 2 | 4 | 19<br>81.4 (72.1 to 87.9) | 19<br>83.4 (75.0 to 89.2) |
| Month 36 | 27<br>77.7 (68.1 to 84.7) | 34<br>74.5 (65.2 to 81.6) | 4 | 5 | 22<br>75.1 (63.4 to 83.6) | 28<br>68.9 (57.1 to 78.1) |
| Month 48 | 30<br>64.4 (47.1 to 77.4) | 34<br>74.5 (65.2 to 81.6) | 4 | 5 | 25<br>59.7 (40.2 to 74.7) | 28<br>68.9 (57.1 to 78.1) |

Patients who experienced a non-fatal primary endpoint event were eligible to receive open-label selexipag or standard of care, including i.v. prostacyclin analogs, during the study. This cross-over may influence the analysis of all-cause death up to end of study. For patients in the overall population in these analyses, 62% of placebo-treated patients went on to receive open-label selexipag.

[a] Receiving an endothelin receptor antagonist and phosphodiesterase-5 inhibitor.

[b] Includes 6 patients with WHO FC IV symptoms at baseline.

[c] Kaplan-Meier survival estimates and 95% CI not shown as there were too few events to perform meaningful statistical comparisons.

CI: confidence interval; WHO FC: WHO functional class.

**Online Table S3 Prostacyclin-associated adverse events in the titration and maintenance periods for patients receiving double combination therapy[a] and with WHO FC II and FC III symptoms at baseline**

| | **WHO FC II symptoms at baseline** | | | | **WHO FC III symptoms at baseline** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Titration period** | | **Maintenance period** | | **Titration period** | | **Maintenance period** | |
| | **Selexipag** | **Placebo** | **Selexipag** | **Placebo** | **Selexipag** | **Placebo** | **Selexipag** | **Placebo** |
| | ***N* = 55** | ***N* = 60** | ***N* = 51** | ***N* = 54** | ***N* = 122** | ***N* = 133** | ***N* = 104** | ***N* = 118** |
| Exposure to double-blind treatment, weeks, median (IQR) | 12.4 (12.4, 12.4) | 12.4 (12.4, 12.4) | 56.7 (38.9, 122.4) | 59.5 (41.6, 89.7) | 12.4 (12.4, 12.4) | 12.4 (12.4, 12.4) | 60.3 (28.9, 101.0) | 54.2 (35.4, 95.4) |
| Patients with ≥1 prostacyclin-associated AE, *n* (%) | 51 (92.7) | 27 (45.0) | 44 (86.3) | 28 (51.9) | 114 (93.4) | 81 (60.9) | 87 (83.7) | 75 (63.6) |
| AE,[b] *n* (%) | | | | | | | | |
| Headache | 42 (76.4) | 14 (23.3) | 24 (47.1) | 10 (18.5) | 88 (72.1) | 48 (36.1) | 62 (59.6) | 37 (31.4) |
| Diarrhea | 30 (54.5) | 4 (6.7) | 22 (43.1) | 7 (13.0) | 54 (44.3) | 23 (17.3) | 45 (43.3) | 30 (25.4) |
| Nausea | 24 (43.6) | 9 (15.0) | 16 (31.4) | 7 (13.0) | 44 (36.1) | 25 (18.8) | 32 (30.8) | 19 (16.1) |
| Pain in jaw | 19 (34.5) | 1 (1.7) | 18 (35.3) | 3 (5.6) | 50 (41.0) | 8 (6.0) | 36 (34.6) | 11 (9.3) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Vomiting | 11 (20.0) | 3 (5.0) | 4 (7.8) | 5 (9.3) | 23 (18.9) | 6 (4.5) | 12 (11.5) | 8 (6.8) |
| Myalgia | 8 (14.5) | 1 (1.7) | 3 (5.9) | 0 | 15 (12.3) | 7 (5.3) | 9 (8.7) | 4 (3.4) |
| Dizziness | 7 (12.7) | 7 (11.7) | 6 (11.8) | 8 (14.8) | 14 (11.5) | 9 (6.8) | 14 (13.5) | 16 (13.6) |
| Pain in extremity | 7 (12.7) | 2 (3.3) | 6 (11.8) | 4 (7.4) | 28 (23.0) | 9 (6.8) | 23 (22.1) | 10 (8.5) |
| Flushing | 6 (10.9) | 3 (5.0) | 7 (13.7) | 2 (3.7) | 24 (19.7) | 8 (6.0) | 22 (21.2) | 8 (6.8) |
| Arthralgia | 2 (3.6) | 1 (1.7) | 3 (5.9) | 3 (5.6) | 7 (5.7) | 12 (9.0) | 12 (11.5) | 9 (7.6) |
| Musculoskeletal pain | 2 (3.6) | 0 | 2 (3.9) | 1 (1.9) | 7 (5.7) | 1 (0.8) | 5 (4.8) | 4 (3.4) |
| Temporomandibular joint syndrome | 0 | 1 (1.7) | 0 | 1 (1.9) | -- | 1 (0.8) | -- | -- |

[a] Receiving an endothelin receptor antagonist and phosphodiesterase-5 inhibitor.

[b] Adverse events listed are all those that occurred in any of the patients in any study group during the double-blind period and up to 7 days after placebo or selexipag was discontinued. A patient with multiple occurrences of an adverse event during one treatment period is counted only once in the adverse event category for that treatment and period.

AE: Adverse event; WHO FC: WHO functional class.