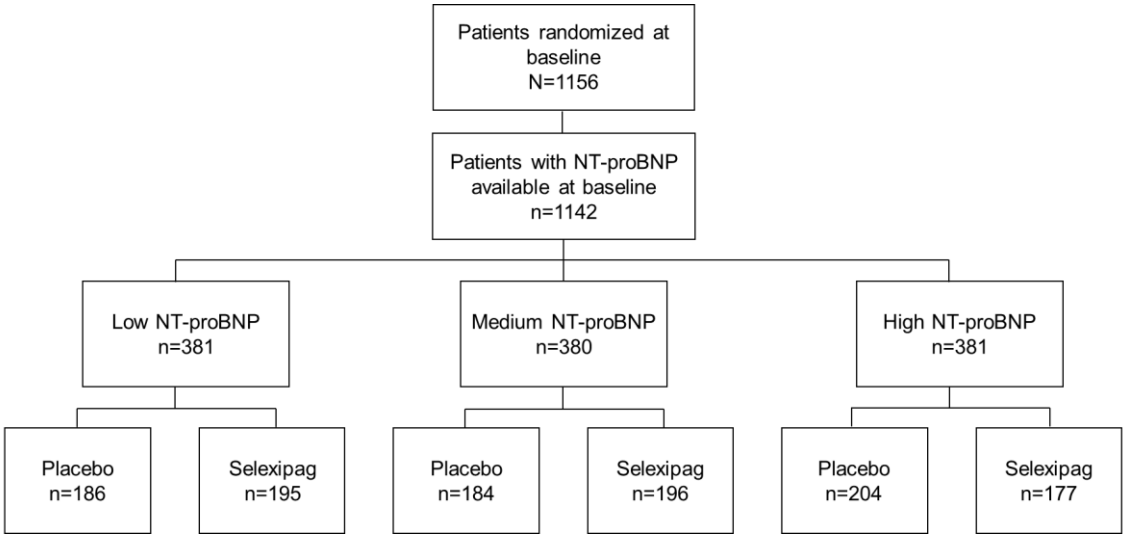
SUPPLEMENTAL MATERIAL

This supplement has been provided by the authors to give readers additional information about their work.

Supplement to: Chin KM, Rubin LJ, Channick R, et al. Association of NT-proBNP and long-term outcome in patients with pulmonary arterial hypertension: Insights from the phase III GRIPHON study

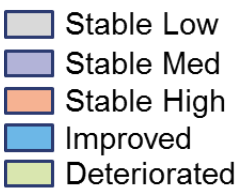
SUPPLEMENTAL FIGURES

Supplemental Figure 1. Patient disposition. Patients grouped according to N-terminal pro brain natriuretic peptide (NT-proBNP) level at baseline. Low, medium and high NT-proBNP cut-offs determined according to baseline NT-proBNP tertiles (Low: <271 ng/L; Medium: 271-1165 ng/L; High: >1165 ng/L).

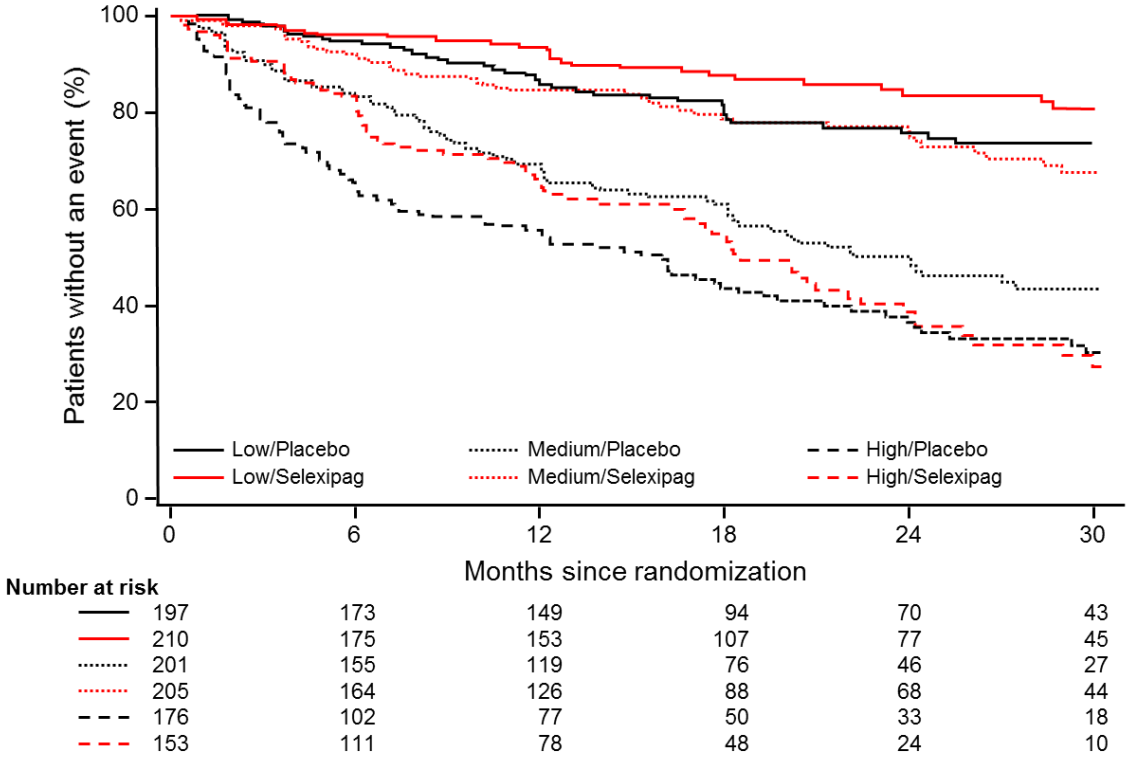


Supplemental Figure 2: Shift table for change in N-terminal pro brain natriuretic peptide (NT-proBNP) category from baseline to week 26 Values shown as n (%). Low, medium and high NT-proBNP cut-offs determined according to ESC/ERS guidelines thresholds (Low: <300 ng/L; Medium: 300-1400 ng/L; High: >1400 ng/L). Analyses performed only in patients who were still in the double-blind treatment at week 26 and who had an NT-proBNP value at baseline and week 26; 289 patients randomized at baseline were excluded from these analyses for the following reasons (categories are not mutually exclusive): primary endpoint event prior to week 26 (n=147), premature discontinuation of double-blind treatment prior to week 26 (n=121), missing NT-proBNP value at baseline (n=14) or at week 26 (n=239). Overall, an improvement in NT-proBNP category was reported in 76 (17.2%) patients in the selexipag arm compared with 43 (10.1%) patients in the placebo arm, and deterioration was reported in 39 (8.8%) patients in the selexipag arm compared with 57 (13.4%) patients in the placebo arm. BL indicates baseline.

		Week 26 Low	Week 26 Medium	Week 26 High
Selexipag (n=443)	BL Low	157 (35.4)	15 (3.4)	2 (0.5)
	BL Medium	43 (9.7)	97 (21.9)	22 (5.0)
	BL High	5 (1.1)	28 (6.3)	74 (16.7)
Placebo (n=424)	BL Low	141 (33.3)	28 (6.6)	0
	BL Medium	25 (5.9)	101 (23.8)	29 (6.8)
	BL High	0	18 (4.2)	82 (19.3)



Supplemental Figure 3. Time from randomization to first morbidity or mortality event in subgroups defined by N-terminal pro brain natriuretic peptide (NT-proBNP) level at baseline. Low, medium and high NT-proBNP cut-offs determined according to ESC/ERS guidelines thresholds (Low: <300 ng/L; Medium: 300-1400 ng/L; High: >1400 ng/L).



Number at risk

Low/Placebo	197	173	149	94	70	43
Low/Selexipag	210	175	153	107	77	45
Medium/Placebo	201	155	119	76	46	27
Medium/Selexipag	205	164	126	88	68	44
High/Placebo	176	102	77	50	33	18
High/Selexipag	153	111	78	48	24	10

SUPPLEMENTAL TABLES

Supplemental Table 1. Treatment effect of selexipag on time from randomization to first morbidity or mortality event in subgroups defined by N-terminal pro brain natriuretic peptide (NT-proBNP) level at baseline.

	NT-proBNP category at baseline (tertiles)*		
	Low	**Medium**	**High**
Unadjusted hazard ratio (95% CI)	0.57 (0.34-0.94)	0.48 (0.33-0.70)	0.73 (0.55-0.96)
Adjusted‡ hazard ratio (95% CI)	0.55 (0.33-0.92)	0.47 (0.33-0.69)	0.77 (0.58-1.02)
	NT-proBNP category at baseline (guidelines)†		
	Low	**Medium**	**High**
Unadjusted hazard ratio (95% CI)	0.59 (0.36-0.95)	0.43 (0.30-0.61)	0.83 (0.62-1.12)
Adjusted‡ hazard ratio (95% CI)	0.57 (0.35-0.92)	0.42 (0.30-0.60)	0.89 (0.66-1.21)

*Low, medium and high NT-proBNP cut-offs determined according to baseline NT-proBNP tertiles (Low: <271 ng/L; Medium: 271-1165 ng/L; High: >1165 ng/L).

†Low, medium and high NT-proBNP cut-offs determined according to ESC/ERS guidelines thresholds tertiles (Low: <300 ng/L; Medium: 300-1400 ng/L; High: >1400 ng/L).

‡Adjusted for PAH therapy, WHO functional class, sex, age (categorized as <65 years vs ≥65 years), race, etiology, geographical location, baseline 6-minute walk distance and baseline creatinine level.

CI indicates confidence intervals.

Supplemental Table 2. Adverse events.

	NT-proBNP category at baseline					
	Low		Medium		High	
	Placebo N=186	Selexipag N=195	Placebo N=183	Selexipag N=197	Placebo N=204	Selexipag N=177
Adverse events	1280	1443	1292	1550	1344	1561
Patients with ≥1 adverse events	175 (94.1)	190 (97.4)	178 (97.3)	194 (98.5)	202 (99.0)	175 (98.9)
Patients with ≥1 serious adverse events	53 (28.5)	67 (34.4)	89 (48.6)	83 (42.1)	128 (62.7)	98 (55.4)
Patients with adverse events leading to discontinuation of study drug	12 (6.5)	22 (11.3)	11 (6.0)	31 (15.7)	18 (8.8)	29 (16.4)
Adverse event*						
Headache	72 (38.7)	140 (71.8)	59 (32.2)	128 (65.0)	58 (28.4)	102 (57.6)
Diarrhea	34 (18.3)	73 (37.4)	41 (22.4)	86 (43.7)	35 (17.2)	83 (46.9)
Nausea	40 (21.5)	67 (34.4)	35 (19.1)	58 (29.4)	32 (15.7)	67 (37.9)
Pain in jaw	8 (4.3)	51 (26.2)	17 (9.3)	50 (25.4)	11 (5.4)	46 (26.0)
Myalgia	12 (6.5)	31 (15.9)	11 (6.0)	36 (18.3)	10 (4.9)	24 (13.6)
Vomiting	13 (7.0)	30 (15.4)	22 (12.0)	31 (15.7)	14 (6.9)	43 (24.3)
Flushing	13 (7.0)	28 (14.4)	10 (5.5)	22 (11.2)	6 (2.9)	20 (11.3)
Upper respiratory tract infection	36 (19.4)	27 (13.8)	19 (10.4)	25 (12.7)	25 (12.3)	23 (13.0)
Dizziness	30 (16.1)	25 (12.8)	30 (16.4)	29 (14.7)	23 (11.3)	32 (18.1)
Arthralgia	17 (9.1)	25 (12.8)	15 (8.2)	25 (12.7)	12 (5.9)	12 (6.8)
Pain in extremity	15 (8.1)	25 (12.8)	18 (9.8)	35 (17.8)	13 (6.4)	33 (18.6)
Nasopharyngitis	24 (12.9)	23 (11.8)	21 (11.5)	25 (12.7)	18 (8.8)	24 (13.6)
Cough	21 (11.3)	22 (11.3)	22 (12.0)	14 (7.1)	24 (11.8)	20 (11.3)
Fatigue	21 (11.3)	22 (11.3)	19 (10.4)	14 (7.1)	19 (9.3)	10 (5.6)
Dyspnea	34 (18.3)	20 (10.3)	33 (18.0)	34 (17.3)	51 (25.0)	38 (21.5)
Abdominal pain	12 (6.5)	19 (9.7)	8 (4.4)	16 (8.1)	13 (6.4)	13 (7.3)
PAH	39 (21.0)	17 (8.7)	65 (35.5)	38 (19.3)	100 (49.0)	69 (39.0)
Peripheral edema	24 (12.9)	15 (7.7)	31 (16.9)	24 (12.2)	48 (23.5)	40 (22.6)
Syncope	11 (5.9)	9 (4.6)	21 (11.5)	12 (6.1)	19 (9.3)	16 (9.0)
Right ventricular failure	4 (2.2)	6 (3.1)	20 (10.9)	6 (3.0)	34 (16.7)	33 (18.6)

Safety population.
Values shown are n or n (%).
Low, medium and high NT-proBNP cut-offs determined according to baseline NT-proBNP tertiles (Low: <271 ng/L; Medium: 271-1165 ng/L; High: >1165 ng/L).
*All AEs reported for more than 10% of patients in any group. Ordered by incidence in the selexipag-treated patients with a low NT-proBNP at baseline.
AE indicates adverse event; NT-proBNP, N-terminal pro brain natriuretic peptide; PAH, pulmonary arterial hypertension.