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# The impact of comorbidities on selexipag treatment effect in patients with pulmonary arterial hypertension: insights from the GRIPHON study

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| **Aims** | The number of pulmonary arterial hypertension (PAH) patients with comorbidities is increasing and there are limited data on response to PAH-targeted therapies in this population. These *post hoc* analyses explored the effect of selexipag in PAH patients with cardiovascular comorbidities in the GRIPHON study. |
| **Methods and results** | Randomized patients (*n* = 1156) were classified using three methods: (i) by subgroups defined according to previously published comorbidity count and restrictive haemodynamic criteria: Subgroup A (<3 comorbidities and haemodynamic criteria met; *n* = 962) and Subgroup B (≥3 comorbidities and/or haemodynamic criteria not met; *n* = 144); comorbidities included body mass index ≥30 kg/m², essential hypertension, diabetes, history of coronary artery disease; (ii) by number of comorbidities, with addition of atrial fibrillation (0, 1, 2, 3, 4, or 5); (iii) by presence of individual comorbidities. Selexipag to placebo hazard ratios (HR) and 95% confidence intervals (CI) for morbidity/mortality (primary composite endpoint) were estimated using Cox regression adjusting selexipag effect for baseline covariates. Approximately half of the patients in GRIPHON (*n* = 584; 50.5%) had comorbidities. Selexipag reduced the risk of a morbidity/mortality event compared with placebo in both Subgroup A (HR 0.66, 95% CI 0.53, 0.82) and Subgroup B (HR 0.50, 95% CI 0.26, 0.96), with no evidence of an inconsistent treatment effect between subgroups (interaction *p* = 0.432). Consistent results were observed in analyses by number and by specific type of comorbidity. |
| **Conclusion** | Selexipag reduces the risk of a morbidity/mortality event vs. placebo irrespective of patient comorbidity status, suggesting that comorbidity status does not influence the treatment effect of selexipag. |

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## Graphical Abstract



**Impact of comorbidities on the efficacy of selexipag in GRIPHON: a *post hoc* analysis**
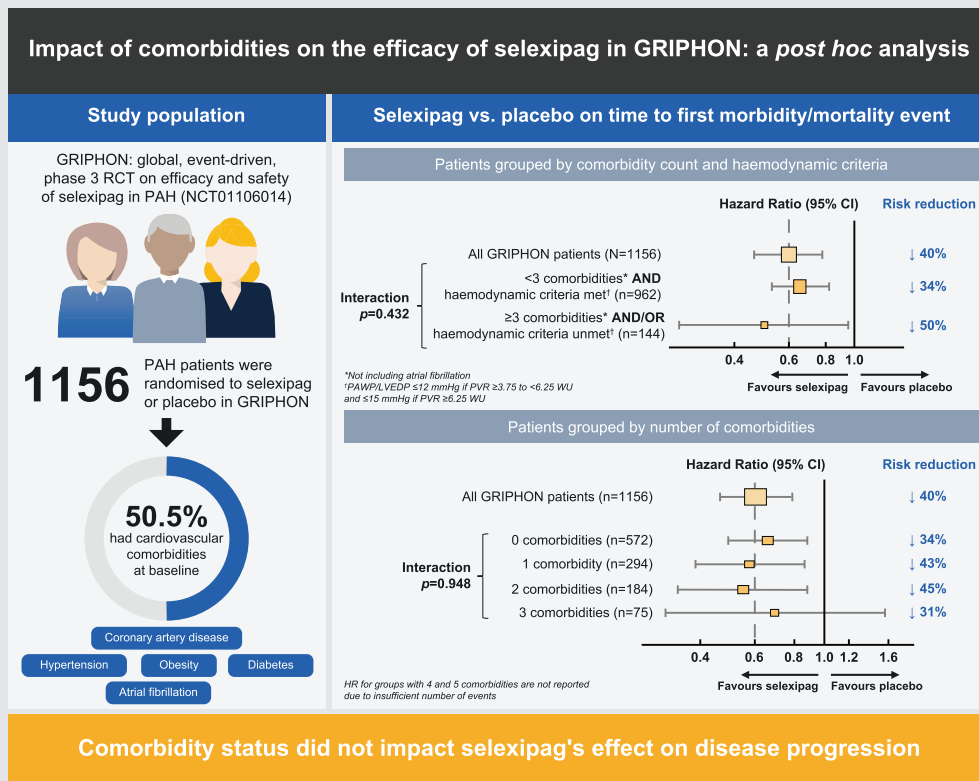
Selexipag reduced the risk of morbidity/mortality events in patients with pulmonary arterial hypertension (PAH) independently of the patients' comorbidity status. CI, confidence interval; LVEDP, left ventricular end-diastolic pressure; PAWP, pulmonary arterial wedge pressure; RCT, randomized controlled trial.

## Introduction

Historically, patients with pulmonary arterial hypertension (PAH) were mostly young females without significant cardiovascular comorbidities.[1,2] The contemporary PAH population is older,[1–3] partly due to increased availability of PAH-targeted therapies. This change brings accompanying challenges. For example, older PAH patients have an increased prevalence of cardiovascular comorbidities such as diabetes, hypertension, coronary artery disease, and obesity, which represent risk factors for left heart disease (LHD).[3–5] The presence of comorbidities in PAH patients can complicate disease management, contribute to disease progression and is associated with poor outcomes.[6–8]

There is currently no consensus on how to define PAH patients with comorbidities, but efforts have been made to better understand their phenotype and response to PAH-targeted therapies. During the AMBITION study,[9] the eligibility criteria were revised to exclude patients with ≥3 comorbidities/risk factors for LHD and/or patients who did not meet restrictive haemodynamic criteria, in order to reduce the likelihood of enrolling patients who may have left ventricular dysfunction contributing to their pulmonary hypertension. Subsequent analysis in this comorbid population, which was excluded from the main AMBITION analysis, suggested that initial double combination therapy may reduce the risk of clinical worsening as compared to initial monotherapy.[10] In a recent analysis of data from the COMPERA registry,[11] three distinct clusters of PAH patients were identified – one mostly female with no cardiovascular comorbidities, one predominantly female non-smokers with cardiovascular comorbidities, and one predominantly male with a significant smoking history and cardiovascular comorbidities. Patients with comorbidities were older, had more severe disease characteristics and were more likely to be receiving monotherapy than patients without comorbidities. Further data

are still needed to expand the growing body of evidence on the treatment effect of PAH-targeted therapies in PAH patients with cardiovascular comorbidities.[10,11]

To gain further insight, we used data from the large phase 3 GRIPHON study, which analyzed the efficacy and safety of the oral, selective prostacyclin receptor (IP receptor) agonist selexipag, approved for the long-term treatment of PAH in adult patients in World Health Organization (WHO) functional class (FC) II−III.[12] In GRIPHON, selexipag reduced the risk of the primary composite outcome of morbidity/mortality by 40% ($p < 0.001$) compared with placebo.[13] In this report, we evaluated the GRIPHON data, *post-hoc*, to determine the impact of comorbidities on the efficacy and safety of selexipag.

# Methods

## Study population

GRIPHON (NCT01106014) was a global, multicentre, double-blind, randomized, placebo-controlled, event-driven phase 3 study, assessing efficacy and safety of selexipag in PAH patients.[13] Patients aged 18−75 years with a diagnosis of idiopathic PAH, heritable PAH, or PAH associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, human immunodeficiency virus infection, drug use or toxin exposure were eligible.[13] All patients enrolled in GRIPHON were required to meet strict haemodynamic criteria for the diagnosis of PAH prior to entry into the study. Definition of PAH was according to guideline recommendations and clinical practice, with a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg, pulmonary vascular resistance (PVR) of ≥5 Wood units and pulmonary arterial wedge pressure (PAWP), or left ventricular end-diastolic pressure (LVEDP) if PAWP was missing, of ≤15 mmHg.[13] The diagnosis of PAH had to be confirmed by right heart catheterization (RHC) at any time prior to screening,[14] and patients were required to have a 6-min walk distance (6MWD) of 50−450 m at screening.[13] Concomitant medications including an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor or both were permitted, provided the dose had been stable for ≥3 months before randomization.[13]

## Study design and outcomes

GRIPHON was conducted in accordance with the amended Declaration of Helsinki and the protocol was reviewed by local institutional review boards with written informed consent obtained from all patients. Patients were randomized 1:1 to receive selexipag or placebo twice daily (b.i.d.). Selexipag was titrated from 200 μg b.i.d. to the highest tolerated dose (maximum dose allowed was 1600 μg b.i.d.) in weekly increments of 200 μg b.i.d. Double-blind treatment continued until a patient experienced a primary endpoint event, or until premature discontinuation of double-blind treatment or until end of study, which was declared after the pre-specified 331 primary endpoint events had occurred. GRIPHON used a composite primary endpoint of time from randomization to first morbidity/mortality event up to end of double-blind treatment +7 days. Morbidity events were disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral prostanoid therapy or long-term oxygen therapy, need for lung transplantation or balloon atrial septostomy, or death from any cause. All events were adjudicated by a blinded independent clinical event committee. Disease progression was defined as ≥15%

decrease in 6MWD from baseline, plus either worsening of WHO FC (patients in WHO FC II/III at baseline) or need for additional PAH treatment (patients in WHO FC III/IV at baseline). Adverse events (AEs) and serious AEs were collected up to 7 days and up to 30 days after the end of the study, respectively.
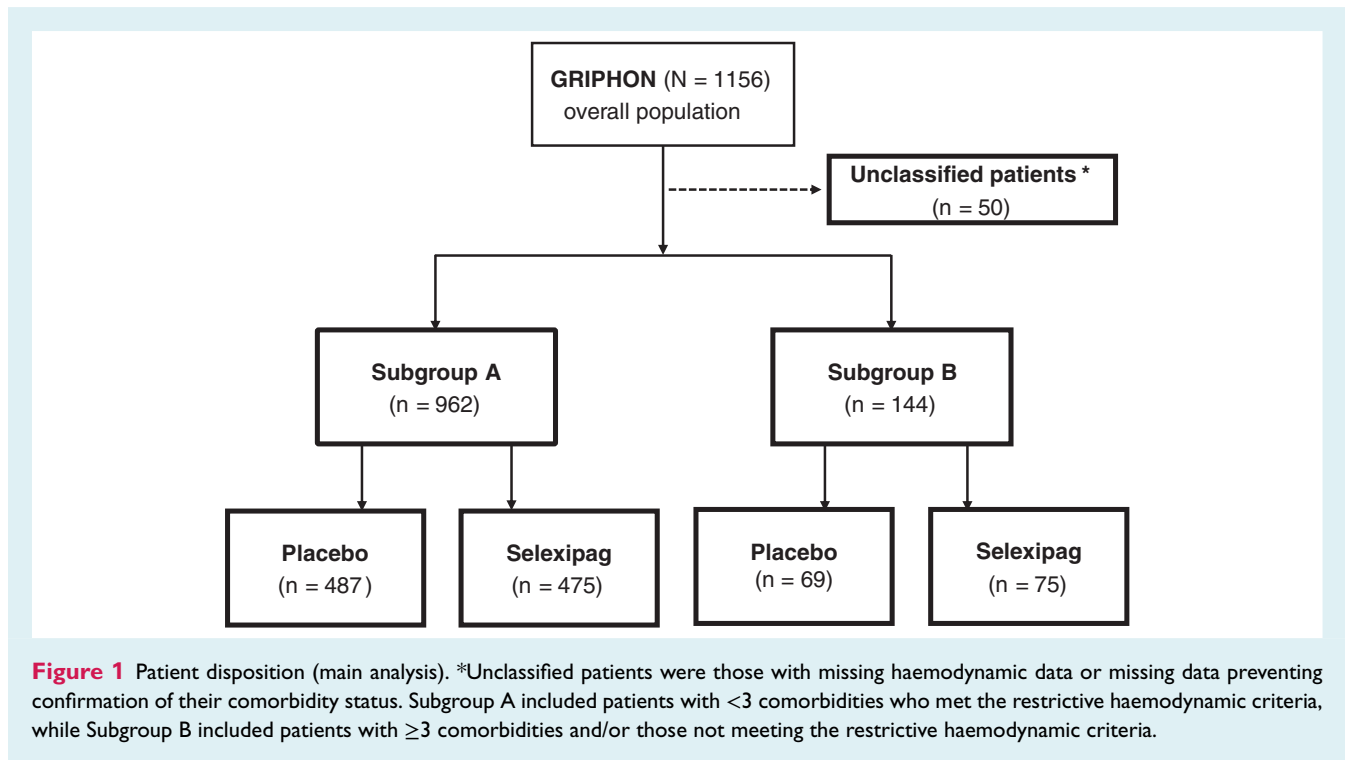
## Categorization by comorbidity

For the main analysis, patients were categorized *post-hoc* into subgroups according to previously published criteria that combined comorbidity count (<3 and ≥3) and restrictive haemodynamic cut-offs (met or not met).[9,10] Comorbidities were defined as[10]: body mass index (BMI) ≥30 kg/m$^2$, a history of essential hypertension, any type of diabetes mellitus and historical evidence of significant coronary artery disease [this included history of myocardial infarction or percutaneous coronary intervention, angiographic evidence of coronary artery disease (>50% stenosis in ≥1 vessel), positive stress test, previous coronary artery bypass graft, or stable angina] (online supplementary *Table S1*). The haemodynamic cut-offs[9] used in this analysis were more restrictive than the cut-offs (PVR ≥5 Wood units and PAWP/LVEDP ≤15 mmHg) used in GRIPHON for confirmation of PAH diagnosis, as they required a PAWP/LVEDP of ≤12 mmHg when PVR was ≥3.75 to <6.25 Wood units. If PVR was ≥6.25 Wood units, the PAWP/LVEDP had to be ≤15 mmHg. Patients in Subgroup A were those who had <3 comorbidities and met the restrictive haemodynamic criteria. Patients in Subgroup B were those who had ≥3 comorbidities and/or did not meet the restrictive haemodynamic criteria. For the main analysis, patients were excluded if haemodynamic data were missing or if medical history data did not allow confirmation of comorbidity status. Further analyses were performed in a subpopulation of patients with a RHC performed within 1 year of randomization.

Two supporting analyses were performed. For the first, patients were categorized *post-hoc* into six non-overlapping subsets according to comorbidity count (0, 1, 2, 3, 4 and 5 comorbidities). For the second, patients were categorized *post-hoc* into overlapping subsets according to the presence or absence of each specific comorbidity (BMI ≥30 kg/m$^2$, history of essential hypertension, diabetes, historical evidence of coronary artery disease, or atrial fibrillation).

## Statistical analyses

*Post-hoc* analyses were performed on patients grouped as defined above. For the GRIPHON primary endpoint (composite morbidity/mortality events up to end of treatment +7 days), Kaplan−Meier curves were plotted by treatment arm for Subgroup A and Subgroup B. Within each subgroup, selexipag effect was estimated as hazard ratio (HR) with 95% confidence interval (CI) using Cox models, which included terms for Subgroup A or Subgroup B status, treatment and their interaction. Models used were unadjusted and adjusted for baseline covariates: etiology, WHO FC, BMI, 6MWD and time from PAH diagnosis. Patients who were missing data for any of these baseline covariates were excluded from the adjusted analyses. The supporting analysis by comorbidity count included models with a categorical factor for count of comorbidities (0, 1, 2, 3, 4, or 5) and the supporting analysis by specific comorbidity used a series of five models each with a term for the specific comorbidity present or absent. In both supporting analyses, the effects of selexipag were estimated from baseline unadjusted and adjusted models, using the same covariates as for the main analysis. Additional analyses were performed on Subgroups A and B for the GRIPHON secondary

**Figure 1** Patient disposition (main analysis). *Unclassified patients were those with missing haemodynamic data or missing data preventing confirmation of their comorbidity status. Subgroup A included patients with <3 comorbidities who met the restrictive haemodynamic criteria, while Subgroup B included patients with ≥3 comorbidities and/or those not meeting the restrictive haemodynamic criteria.

endpoints[13] (online supplementary *Methods S1*). Consistency of the effect of selexipag across subgroups in each analysis was assessed with interaction tests. All statistical analyses were conducted using SAS version 9.4.

# Results

## Patient characteristics

Of the 1156 randomized patients in GRIPHON, 1106 patients could be categorized according to haemodynamic and comorbidity criteria and were included in the main analysis. Of these, 962 (87.0%) patients were in Subgroup A and 144 (13.0%) were in Subgroup B (*Figure 1*, online supplementary *Table S2*). In Subgroup A, 551 (57.3%) patients had no cardiovascular comorbidities and 411 (42.7%) patients had one or two comorbidities. In Subgroup B, 87 (60.4%) patients had three or four comorbidities (online supplementary *Table S2*). Out of the 1106 patients included in the main analysis, 63 (5.7%) patients did not meet the restrictive haemodynamic criteria. At baseline, patients in both subgroups were predominantly female and diagnosed with idiopathic or connective tissue disease-associated PAH (*Table 1*). Patients in Subgroup B were older, had a higher BMI and lower 6MWD, and were more likely to be in WHO FC III/IV than those in Subgroup A. Patients in Subgroup B tended to have lower PVR and mPAP and higher PAWP compared to those in Subgroup A. Similar proportions of patients in both Subgroups were receiving background PAH therapy.

When grouped by comorbidity count, about half of the patients in GRIPHON (*n* = 584; 50.5%) had comorbidities (online supplementary *Figure S1*). The most common comorbidities

were history of essential hypertension (*n* = 376; 32.5%) and BMI ≥30 kg/m² (*n* = 312; 27.0%), each occurring in approximately one third of patients (online supplementary *Figure S2*). Approximately 10% of patients had a history of coronary artery disease (*n* = 106; 9.2%), diabetes (*n* = 130; 11.2%), or atrial fibrillation (*n* = 89; 7.7%). Similar to the main analysis, when grouped by comorbidity count or presence of a specific comorbidity, patients with comorbidities were older, had a higher BMI and lower 6MWD, and were more likely to be in WHO FC III/IV than those without comorbidities (online supplementary *Tables S3 and S4*).

## Effect of selexipag on risk of morbidity/mortality events according to presence of cardiovascular comorbidities

For the main analysis, morbidity/mortality events were reported in 136 (28.6%) selexipag and 200 (41.1%) placebo patients in Subgroup A, and in 14 (18.7%) selexipag and 27 (39.1%) placebo patients in Subgroup B. Selexipag reduced the risk of a morbidity/mortality event compared with placebo in patients in both Subgroup A [HR adjusted for baseline covariates (95% CI) 0.66 (0.53, 0.82); HR unadjusted for baseline covariates (95% CI) 0.67 (0.54, 0.83)] and Subgroup B [HR adjusted for baseline covariates (95% CI) 0.50 (0.26, 0.96); HR unadjusted for baseline covariates (95% CI) 0.40 (0.21, 0.76)], with no evidence of an inconsistent treatment effect in Subgroups (interaction *p* = 0.432 for the baseline adjusted analyses) (*Figures 2 and 3A*). Consistent results were observed in a subpopulation of patients with a RHC performed within 1 year of randomization (online supplementary *Figure S3*).

**Table 1** Baseline characteristics (main analysis)

| Characteristic | Subgroup A (n = 962) | | Subgroup B (n = 144) | |
|---|---|---|---|---|
| | Placebo (n = 487) | Selexipag (n = 475) | Placebo (n = 69) | Selexipag (n = 75) |
| Female sex, n (%) | 395 (81.1) | 386 (81.3) | 49 (71.0) | 55 (73.3) |
| Age, years, median (range) | 48.0 (18.0−75.0) | 47.0 (18.0−78.0) | 61.0 (26.0−80.0) | 60.0 (28.0−77.0) |
| Age, years, n (%) | | | | |
| <65 | 409 (84.0) | 404 (85.1) | 39 (56.5) | 48 (64.0) |
| 65−74 | 75 (15.4) | 66 (13.9) | 28 (40.6) | 24 (32.0) |
| ≥75 | 3 (0.6) | 5 (1.1) | 2 (2.9) | 3 (4.0) |
| BMI, kg/m$^2$, mean ± SD[a] | 25.9 ± 5.5 | 26.0 ± 5.8 | 31.9 ± 7.2 | 32.9 ± 7.1 |
| Geographical region, n (%) | | | | |
| Asia | 103 (21.1) | 110 (23.2) | 8 (11.6) | 3 (4.0) |
| Eastern Europe | 124 (25.5) | 116 (24.4) | 12 (17.4) | 16 (21.3) |
| Latin America | 52 (10.7) | 49 (10.3) | 4 (5.8) | 5 (6.7) |
| North America | 80 (16.4) | 76 (16.0) | 15 (21.7) | 17 (22.7) |
| Western Europe/Australia | 128 (26.3) | 124 (26.1) | 30 (43.5) | 34 (45.3) |
| Time since PAH diagnosis, years, mean ± SD | 2.5 ± 3.8 | 2.3 ± 3.5 | 2.3 ± 2.8 | 2.1 ± 2.6 |
| PAH etiology, n (%) | | | | |
| Idiopathic | 275 (56.5) | 241 (50.7) | 45 (65.2) | 50 (66.7) |
| Heritable | 12 (2.5) | 13 (2.7) | 1 (1.4) | 0 |
| Drug- or toxin-induced | 6 (1.2) | 14 (2.9) | 2 (2.9) | 3 (4.0) |
| Connective tissue disease | 148 (30.4) | 150 (31.6) | 18 (26.1) | 15 (20.0) |
| Congenital heart disease | 42 (8.6) | 52 (10.9) | 3 (4.3) | 7 (9.3) |
| HIV infection | 4 (0.8) | 5 (1.1) | 0 | 0 |
| 6MWD, m, mean ± SD | 354.6 ± 80.3 | 359.9 ± 74.3 | 308.4 ± 88.8 | 337.8 ± 89.0 |
| WHO FC, n (%) | | | | |
| I/II | 231 (47.4) | 239 (50.3) | 19 (27.5) | 24 (32.0) |
| III/IV | 256 (52.6) | 236 (49.7) | 50 (72.5) | 51 (68.0) |
| Haemodynamic variables | | | | |
| dPAP, n | 478 | 465 | 68 | 73 |
| mmHg, mean ± SD | 35.4 ± 12.9 | 35.3 ± 11.9 | 30.3 ± 11.8 | 28.9 ± 8.6 |
| mPAP, n | 487 | 475 | 69 | 75 |
| mmHg, mean ± SD | 54.1 ± 15.0 | 53.5 ± 13.9 | 48.1 ± 15.3 | 44.9 ± 11.3 |
| mPAWP, n | 462 | 456 | 63 | 74 |
| mmHg, mean ± SD | 9.0 ± 3.3 | 9.0 ± 3.4 | 11.3 ± 4.7 | 11.6 ± 4.2 |
| DPG[b], n | 453 | 446 | 62 | 72 |
| mmHg, mean ± SD | 26.5 ± 12.7 | 25.9 ± 11.2 | 18.4 ± 11.2 | 17.3 ± 8.6 |
| Cardiac index, n | 392 | 389 | 57 | 69 |
| L/min/m$^2$, mean ± SD | 2.5 ± 0.8 | 2.4 ± 0.7 | 2.5 ± 0.8 | 2.6 ± 0.8 |
| PVR, n | 487 | 475 | 67 | 75 |
| Wood units, mean ± SD | 12.3 ± 7.5 | 11.9 ± 6.1 | 8.8 ± 6.6 | 7.3 ± 3.6 |
| mRAP, n | 427 | 419 | 61 | 68 |
| mmHg, mean ± SD | 8.3 ± 5.3 | 8.8 ± 5.4 | 9.2 ± 5.3 | 9.3 ± 5.1 |
| SvO$_2$, n | 293 | 306 | 40 | 55 |
| %, mean ± SD | 65.7 ± 10.6 | 65.9 ± 10.4 | 64.4 ± 7.6 | 64.6 ± 10.5 |
| SBP, n | 487 | 475 | 69 | 75 |
| mmHg, mean ± SD | 113.3 ± 15.0 | 114.1 ± 16.1 | 121.5 ± 16.9 | 119.7 ± 16.1 |
| Background PAH therapy, n (%) | 380 (78.0) | 385 (81.1) | 61 (88.4) | 63 (84.0) |
| PDE-5i | 148 (30.4) | 156 (32.8) | 23 (33.3) | 22 (29.3) |
| ERA | 60 (12.3) | 77 (16.2) | 15 (21.7) | 16 (21.3) |
| ERA and PDE-5i | 172 (35.3) | 152 (32.0) | 23 (33.3) | 25 (33.3) |

6MWD, 6-min walk distance; BMI, body mass index; dPAP, diastolic pulmonary arterial pressure; DPG, diastolic pulmonary gradient; ERA, endothelin receptor antagonist; HIV, human immunodeficiency virus; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary arterial wedge pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type 5 inhibitor; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; SD, standard deviation; SvO$_2$, mixed venous oxygen saturation; WHO FC, World Health Organization functional class.

[a]n = 74 for selexipag-treated patients in Subgroup B.

[b]Calculated as: dPAP − mPAWP.
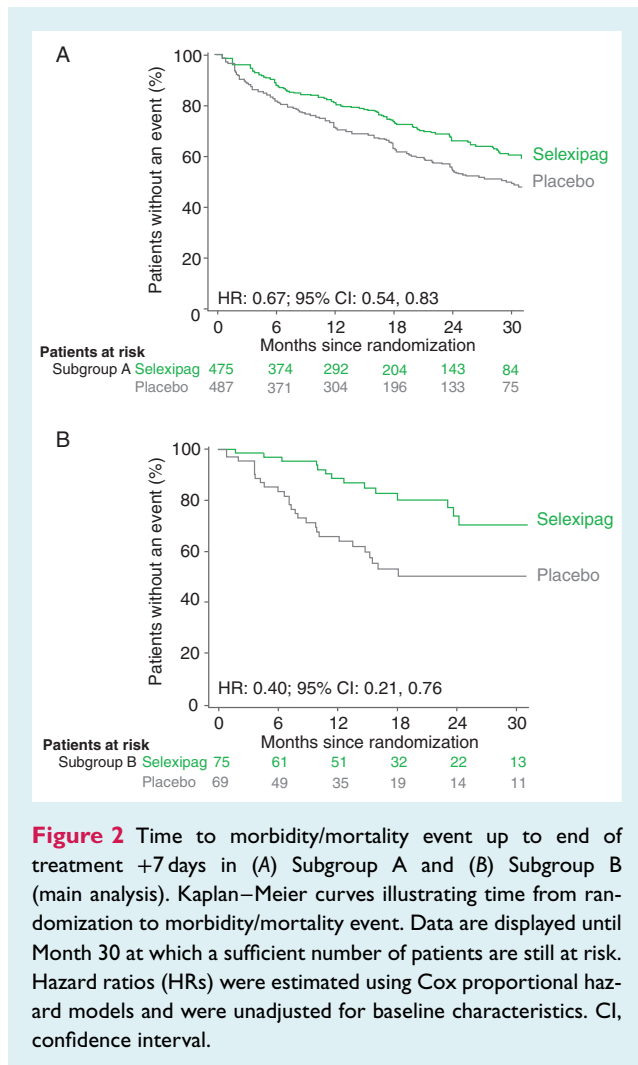
**Figure 2** Time to morbidity/mortality event up to end of treatment +7 days in (*A*) Subgroup A and (*B*) Subgroup B (main analysis). Kaplan–Meier curves illustrating time from randomization to morbidity/mortality event. Data are displayed until Month 30 at which a sufficient number of patients are still at risk. Hazard ratios (HRs) were estimated using Cox proportional hazard models and were unadjusted for baseline characteristics. CI, confidence interval.

For the first supporting analysis of comorbidity count, the treatment effect of selexipag vs. placebo on morbidity/mortality was consistent across comorbidity count groups (interaction $p = 0.948$). The baseline-adjusted treatment effect [HR (95% CI)] was 0.66 (0.49, 0.88) in patients with no comorbidities, 0.57 (0.38, 0.86) in patients with 1 comorbidity, 0.55 (0.34, 0.89) in patients with 2 comorbidities and 0.69 (0.31, 1.55) in patients with 3 comorbidities (*Figure 3B*). HR could not be reliably estimated in the 4 or 5 comorbidities subgroup due to the low number of patients and subsequent low number of morbidity/mortality events (4 comorbidities: 4 and 6 events in the selexipag and placebo arms, respectively; 5 comorbidities: 2 patients in the selexipag arm with 0 events).

When grouped by specific comorbidity, baseline-adjusted treatment effect of selexipag vs. placebo on morbidity/mortality was not impacted by the presence of any of the comorbidities specified in this analysis (interaction *p*-values were 0.761, 0.332, 0.175, 0.359 and 0.958 for BMI ≥30 kg/m², history of essential hypertension, diabetes, history of coronary artery disease, and atrial fibrillation, respectively) (*Figure 3C*).

## Effect of selexipag on secondary endpoints in GRIPHON according to presence of cardiovascular comorbidities

Analyses of the secondary endpoints in GRIPHON for Subgroups A and B were aligned with those for the primary endpoint. The effect of selexipag was consistent across subgroups for time to death or hospitalization due to PAH (interaction $p = 0.531$) and for the absence of worsening in WHO FC from baseline at Week 26 (interaction $p = 0.803$). The point estimates for the effect of selexipag vs. placebo on the change in 6MWD and N-terminal pro brain natriuretic peptide (NT-proBNP) from baseline to Week 26 favored selexipag in both Subgroups, albeit with large confidence intervals for Subgroup B (online supplementary *Figure S4*).

## Safety and tolerability

In the main analysis, the median (range) exposure to selexipag was 69.9 (0.3–199.7) and 72.6 (0.6–216.7) weeks for patients in Subgroups A and B, respectively. Median (range) exposure to placebo was 66.3 (0.9–188.0) and 53.8 (0.7–192.0) weeks for patients in Subgroups A and B, respectively. The proportion of patients with at least one AE was similar across Subgroups and treatments (*Table 2*). The most frequent AEs in Subgroups A and B are shown in online supplementary *Table S5*. The proportion of patients with at least one serious AE was similar across treatments in Subgroup A (47.0% placebo and 44.7% selexipag) and slightly more in placebo vs. selexipag-treated patients in Subgroup B (54.4% vs. 45.3%) (*Table 2*). The proportion of patients with an AE leading to treatment discontinuation was generally higher in Subgroup B vs. Subgroup A for placebo and selexipag-treated patients. A higher proportion of selexipag-treated patients had an AE leading to treatment discontinuation vs. placebo-treated patients in both Subgroups A and B (Subgroup A: 13.2% vs. 6.0%; Subgroup B: 21.3% vs. 13.2%) (*Table 2*).

In the supporting analyses, when grouped by comorbidity count, the proportion of patients with an AE leading to treatment discontinuation in both selexipag and placebo treatment arms generally increased in patients with a higher number of comorbidities (online supplementary *Table S6*). Similarly, when grouped by a specific comorbidity, the proportion of AEs leading to treatment discontinuation was higher in both treatment arms in patients with a specific comorbidity compared to those without a specific comorbidity (online supplementary *Table S7*).

## Discussion

Demographics of PAH patients are changing, with a greater proportion of older patients, and thereby an increasing number of patients with comorbidities.[2–5,15] As management of these patients is not specifically defined, analyses such as those presented here, which support an evidence-based approach, are important. In the GRIPHON trial, about half of the population had at least one cardiovascular comorbidity at baseline. These *post-hoc* analyses of
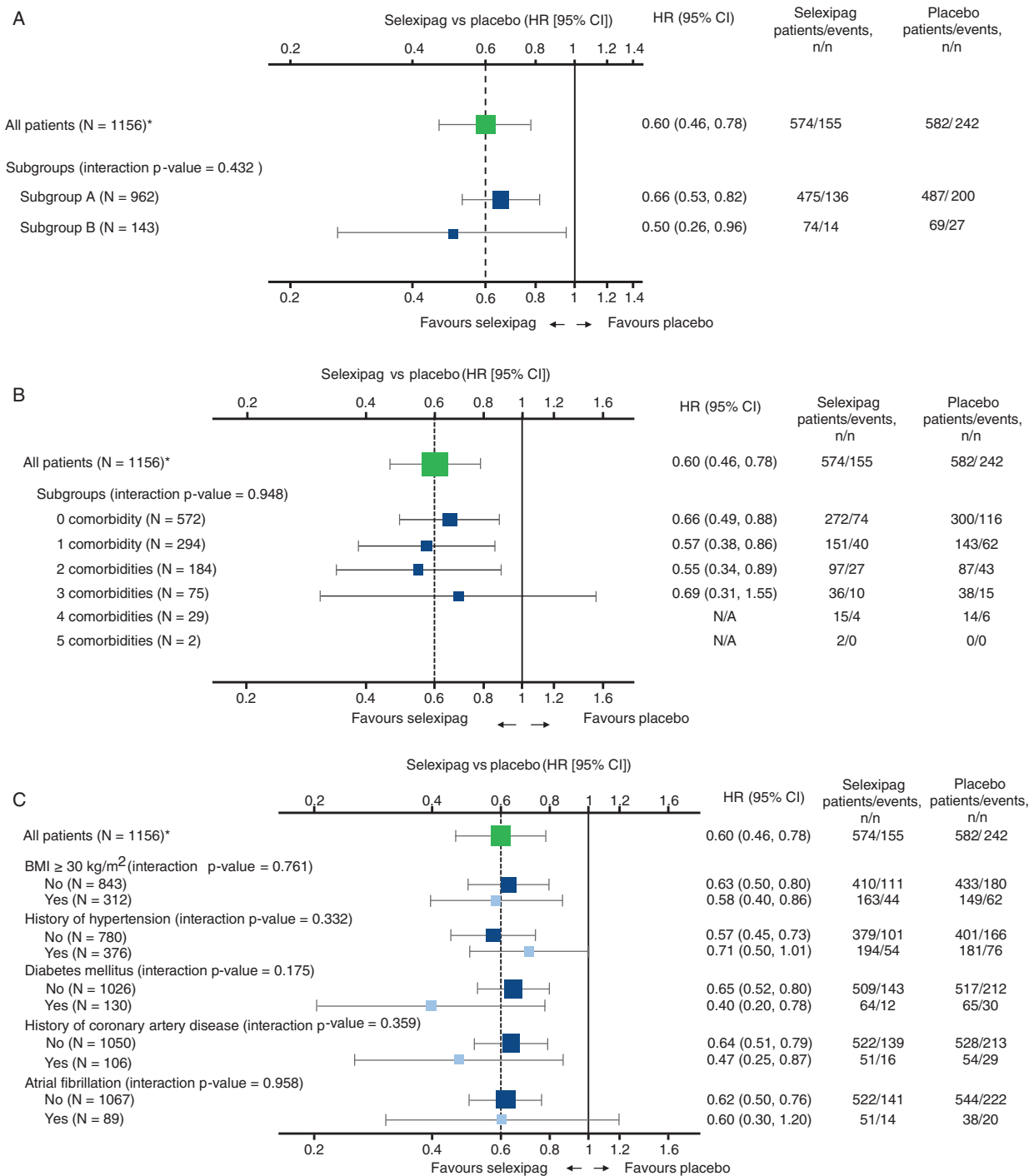
**Figure 3** Treatment effect of selexipag on time to morbidity/mortality event up to end of treatment +7 days according to (A) Subgroups, (B) comorbidity count and (C) specific comorbidity (baseline adjusted analyses). *Hazard ratio (HR) [99% confidence interval (CI)] as for the primary GRIPHON manuscript.[13] HRs estimated using Cox proportional hazard models. HRs were adjusted for the following baseline characteristics: etiology, World Health Organization functional class, body mass index (BMI), 6-min walk distance and time from pulmonary arterial hypertension diagnosis, apart from HRs for all patients ($n = 1156$) which were unadjusted for baseline characteristics. From the 144 patients assigned to Subgroup B, 143 patients were included in the baseline adjusted analysis; 1 selexipag patient categorized as Subgroup B because haemodynamic criteria were not met could not be included in this analysis due to lack of information on BMI at baseline.

**Table 2** Safety (main analysis)

| | Subgroup A | | Subgroup B | |
| --- | --- | --- | --- | --- |
| | Placebo (n = 483) | Selexipag (n = 476) | Placebo (n = 68) | Selexipag (n = 75) |
| Patients with ≥1 AE, n (%) | 468 (96.9) | 466 (97.9) | 67 (98.5) | 75 (100) |
| Patients with ≥1 serious AE, n (%) | 227 (47.0) | 213 (44.7) | 37 (54.4) | 34 (45.3) |
| Patients with ≥1 AE leading to discontinuation of study drug[a], n (%) | 29 (6.0) | 63 (13.2) | 9 (13.2) | 16 (21.3) |
| Patients with ≥1 PGI$_2$-like AE during titration phase, n (%) | 252 (52.2) | 417 (87.6) | 43 (63.2) | 64 (85.3) |
| Patients with ≥1 PGI$_2$-like AE during maintenance phase[b], n (%) | 206 (47.9) | 302 (71.7) | 26 (45.6) | 53 (80.3) |

AE, adverse event; PGI$_2$, prostacyclin.

[a]Includes study drug discontinuations due to an AE prior to end of study in patients without a primary endpoint morbidity/mortality event with onset date prior to or on the date of study drug discontinuation.

[b]n = 430 for placebo and 421 for selexipag for Subgroup A; n = 57 for placebo and 66 for selexipag for Subgroup B. In Subgroup A, three patients randomized to placebo did not receive the study agent and were excluded from the safety analysis, one patient randomized to placebo received a single dose of selexipag and was assigned to the selexipag group for the safety analysis.

GRIPHON show that selexipag reduced the risk of a morbidity/mortality event irrespective of patients' comorbidity status. The treatment effect of selexipag was consistent across all analyses performed, in patients grouped according to: previously published criteria for comorbidities and haemodynamic cut-offs,[10] comorbidity count, and presence of a specific comorbidity. Taken together, these data indicate that selexipag is efficacious and well tolerated in comorbid PAH patients in the setting of a randomized controlled trial (*Graphical Abstract*).

To ensure a diagnosis of PAH, all patients enrolled in GRIPHON had to meet the following haemodynamic criteria prior to entry in the study: mPAP ≥25 mmHg, PVR ≥5 Wood units and PAWP or LVEDP ≤15 mmHg. For the main analysis here, we used more restrictive cut-offs[9]: a PAWP/LVEDP ≤12 mmHg if PVR was ≥3.75 to <6.25 Wood units, or a PAWP/LVEDP ≤15 mmHg if PVR was ≥6.25 Wood units. Out of all patients included in these analyses, approximately 95% met these more restrictive haemodynamic criteria as expected for a PAH population (Group 1 pulmonary hypertension), despite the presence of cardiovascular comorbidities in some patients. The cardiovascular comorbidities examined here represent risk factors for LHD and are not indicative of the disease itself. Patients in Subgroup B tended to be older and presented with more severe disease characteristics than patients in Subgroup A. Similarly, in the AMBITION study, the patients with cardiovascular risk factors (defined using the same criteria as our Subgroup B) who were excluded from the primary analysis were older, with lower 6MWD, PVR, mPAP and higher PAWP than those patients included in the primary analysis (defined using the same criteria as for Subgroup A).[10] In GRIPHON, patients had fewer cardiovascular comorbidities than reported in an analysis of idiopathic PAH patients in the COMPERA registry (defined using the same criteria here),[11] likely due to the more stringent selection criteria for patients in clinical trials and possibly due to differences in geography. However, the number of patients in GRIPHON was sufficient to gain valuable insights into the efficacy and safety of selexipag in patients with comorbidities.

The *post-hoc* analysis of the AMBITION trial suggested that patients with cardiovascular risk factors may benefit from initial double combination therapy to reduce clinical worsening vs. initial monotherapy.[10] When we categorized patients in our analysis using the same criteria as in AMBITION,[10] we also observed a reduction in the risk of disease progression with selexipag vs. placebo, when used primarily as part of a combination treatment strategy. Further to this approach, we categorized patients according to the number and presence of specific comorbidities and observed a consistent treatment effect of selexipag on morbidity/mortality irrespective of how patients were classified as comorbid. Additional analyses also suggested there was no difference in the effect of selexipag between Subgroups A and B on time to hospitalization or death due to PAH, absence of WHO FC worsening at Week 26, and changes in 6MWD and NT-proBNP from baseline to Week 26. Our findings suggest that the presence of comorbidities does not impact the efficacy of selexipag on long-term outcome in PAH patients. With approximately 30% of patients on double background therapy at baseline, our analysis is the first to suggest that long-term outcomes can be improved in a population of comorbid patients that includes patients receiving triple oral combination therapy. Taken together, results from the *post-hoc* analysis of AMBITION[10] and those presented here from GRIPHON, suggest that treatment with a combination of PAH-targeted therapies may provide long-term outcome benefit in PAH patients with comorbidities.

Real-world evidence can be used to supplement analyses of response to treatment in patients with comorbidities. In an analysis from the COMPERA registry, patients with and without cardiovascular comorbidities (defined using the same criteria as in our main analysis) showed similar improvement in exercise capacity, functional class, and natriuretic peptides in response to treatment over a period of 12 months.[16] In a recent analysis of COMPERA,[11] a modest treatment response for 6MWD and NT-proBNP was observed in patients with comorbidities. However, long-term outcomes were not assessed and a low proportion of these patients were receiving combination therapy, with few receiving treatment

with a prostacyclin receptor agonist, limiting direct comparison of this observation with our findings.

Trials for PAH-targeted therapies typically use exclusion criteria that minimize enrolment of patients with comorbidities, leading to limited data in this population. This may be due to concerns of poorer response to treatment in patients with comorbidities compared to those without[17] or to reduce the risk of including patients that may not have 'true' Group 1 pulmonary hypertension.[10] The data presented here suggest that use of less restrictive eligibility and inclusion criteria for comorbidities or risk factors for LHD could be considered for future trials of PAH-targeted therapies, to enable evaluation of efficacy in comorbid PAH patients.

Comorbid patients are on average older than patients without comorbidities and are likely to require closer follow-up, as tolerability to PAH-targeted therapy is known to be a greater challenge in older vs. younger patients.[2,15] In the AMBITION study, more adverse events were observed in patients with cardiovascular risk factors than those without.[10] In our analyses, the proportion of patients with AEs leading to treatment discontinuations was similar in selexipag-treated patients in both Subgroups, indicating that the tolerability of selexipag did not differ between patients with and without comorbidities. Overall, the results observed here were consistent with the known tolerability profile of selexipag.

One strength of our analyses is that we categorized GRIPHON patients according to several different approaches and obtained consistent results. As our analyses are *post-hoc*, they are subject to limitations, for example, the small number of patients and events in the subgroups of patients with 4 and 5 comorbidities prevented meaningful analyses. The low number of patients in the three comorbidities subgroup may also have contributed to the wide CI observed for the treatment effect. Patients from GRIPHON may not be fully representative of real-world cohorts due to the upper age limit of 75 years. The average age of patients in Subgroup B (60 years) is younger than that observed for patients in registries with a similar comorbidity status.[11,18] In addition, we only examined the impact of specific cardiovascular comorbidities.

In conclusion, in these *post-hoc* analyses, selexipag reduced the risk of experiencing a morbidity/mortality event vs. placebo in PAH patients irrespective of comorbidity status. In addition, selexipag was generally well tolerated in comorbid patients.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

## Funding

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