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BRIEF REPORT

# Long-Term Survival, Safety and Tolerability with Selexipag in Patients with Pulmonary Arterial Hypertension: Results from GRIPHON and its Open-Label Extension

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## ABSTRACT

***Introduction***: In the event-driven GRIPHON randomised-controlled trial, the oral prostacyclin receptor agonist selexipag significantly reduced the risk of disease progression (composite primary endpoint of morbidity/mortality), compared with placebo, in patients with pulmonary arterial hypertension (PAH). The ongoing open-label extension study (GRIPHON OL) collects further data on long-term safety, tolerability, and survival of PAH patients treated with selexipag.

***Methods***: Patients randomised to selexipag or placebo in GRIPHON could enter GRIPHON OL either after experiencing a morbidity event during double-blind treatment or at the end of the study. Patients were followed for adverse events (AE) and survival from selexipag initiation up to 3 days and 30 days after end of

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treatment, respectively. Data are presented up to a cut-off date of 1 September 2019.
***Results***: Overall, 953 patients in GRIPHON and GRIPHON OL were treated with selexipag. At the time of selexipag initiation, 81.2% of patients were receiving background PAH therapy. Median (min, max) exposure to selexipag was 31.7 months (0, 106), corresponding to a total of 3054.4 patient-years. The most frequently reported AEs were related to known prostacyclin-related effects or underlying disease. There were 305 (32.0%) patients who experienced an AE leading to treatment discontinuation. Survival during GRIPHON and GRIPHON OL was assessed for the 574 patients randomised to selexipag in GRIPHON. Kaplan–Meier survival estimates (95%CI) at 1, 3, 5 and 7 years were 92.0% (89.4, 94.0), 79.3% (75.4, 82.6), 71.2% (66.5, 75.3) and 63.0% (57.4, 68.1), respectively.
***Conclusions***: These results provide the longest follow-up period published to date for a PAH therapy. The safety profile of selexipag over this extended treatment period was consistent with that observed in GRIPHON. A large proportion of the population was receiving background therapy at selexipag initiation, providing further insight into the long-term safety of selexipag as part of a combination therapy regimen.
***Trial Registration***: ClinicalTrials.gov Identifiers: NCT01106014 and NCT01112306

**Keywords:** Selexipag; Pulmonary arterial hypertension; PAH; GRIPHON; Open-label extension; Safety; Tolerability; Survival; Combination therapy; Long-term outcomes

**Key Summary Points**

**Why carry out this study?**

The GRIPHON open-label extension study provides data on long-term safety, tolerability and survival for patients with pulmonary arterial hypertension (PAH) treated with the oral prostacyclin receptor agonist, selexipag.

**What did the study ask?**

This ongoing open-label extension study collected long-term data on adverse events (AEs) and vital status of PAH patients treated with selexipag.

**What were the study outcomes/conclusions?**

Over the 7-year follow-up period, the median (min, max) exposure to selexipag in the study population ($n = 953$) was 31.7 months (0, 106), corresponding to a total of 3054.4 patient-years. The most frequently reported AEs were related to known prostacyclin-related effects and/or underlying disease. Kaplan–Meier survival estimates at 1, 3, 5 and 7 years in the population of patients randomised to selexipag in GRIPHON ($n = 574$) were 92.0%, 79.3%, 71.2% and 63.0%, respectively.

**What has been learned from the study?**

These results provide the longest follow-up period published to date for PAH therapies. The long-term safety and tolerability profile of selexipag observed in this study was in line with previously published data over shorter time periods. As the majority of the population was receiving combination PAH therapy with an endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor, these analyses also provide further insights into the long-term safety of selexipag as part of a combination therapy regimen.

## INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive disease and, while outcomes remain poor, the availability of targeted therapies has led to improved prognosis [1, 2]. In this context, it is important to understand the long-term safety and tolerability of PAH therapies, as well as their impact on survival. Selexipag is an oral

selective prostacyclin receptor (IP receptor) agonist approved for the treatment of PAH [World Health Organization (WHO) Group I] to delay disease progression and to reduce the risk of hospitalisation for PAH [3]. In the event-driven randomised-controlled trial (RCT) GRIPHON, selexipag significantly delayed the progression of PAH [4]. The risk of a primary endpoint event of morbidity/mortality was reduced by 40% with selexipag versus placebo [hazard ratio 0.60; 99% confidence interval (CI) 0.46–0.78; $p < 0.001$] [4]. GRIPHON is, to date, the largest and longest RCT in PAH, with 1156 patients enrolled and a median follow-up time of 98.1 weeks. Its ongoing open-label extension study collects further data on long-term safety, tolerability and survival in patients treated with selexipag. The following report describes an analysis of long-term outcomes for patients treated with selexipag in GRIPHON and/or its open-label extension study.

## METHODS

The data sharing policy of the Sponsor is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to study data can be submitted through the Yale Open Data Access Project site at https://yoda.yale.edu.

### Study Design

GRIPHON (NCT01106014) was a global, multicentre, double-blind, randomised, placebo-controlled event-driven phase 3 study, which assessed the safety and efficacy of selexipag in patients with PAH [4]. Briefly, selexipag/placebo were titrated over 12 weeks to an individualised dose of 200–1600 μg twice daily (b.i.d), based on tolerability. Patients received double-blind treatment until they experienced a morbidity/mortality (primary endpoint) event, discontinued prematurely, or until the end of the study (reached when 331 primary endpoint events had occurred). Primary endpoint events included disease progression or worsening of PAH that resulted in hospitalisation, initiation of parenteral prostanoid therapy or long-term oxygen therapy, need for lung transplantation or balloon atrial septostomy, or death from any cause. Disease progression was defined as a decrease from baseline of at least 15% in the 6-min walk distance (6MWD) accompanied by a worsening in WHO functional class (FC) (for the patients with WHO FC II or III at baseline) or the need for additional treatment of PAH (for the patients with WHO FC III or IV at baseline). All events were adjudicated by a blinded independent critical-event committee [4].

GRIPHON OL (NCT01112306) is an open-label, multicentre study to assess the long-term safety and tolerability of selexipag in patients with PAH (Supplementary Fig. 1). Patients enrolled in GRIPHON could enter the GRIPHON OL study either after experiencing a morbidity event during double-blind treatment or at the end of the study if they were still receiving study treatment.

The dose at which selexipag was started in GRIPHON OL depended on the reason to enter the OL and/or the treatment allocation in GRIPHON. For patients who entered GRIPHON OL following a primary endpoint event in GRIPHON, the study treatment allocation and dose in GRIPHON remained blinded to preserve the integrity of the double-blind study, hence in these patients selexipag was started at the lowest dose (200 μg b.i.d), with up-titration to an individualised dose as described above. In contrast, for patients who entered GRIPHON OL at the end of the GRIPHON double-blind study, the study treatment allocation and dose in GRIPHON were known. Hence, patients randomised to selexipag in GRIPHON entered GRIPHON OL at the same dose received at the end of the study, and patients randomised to placebo started selexipag at the lowest dose (200 μg b.i.d), with up-titration of selexipag to an individualised dose, as described above [4]. In GRIPHON OL, patients received selexipag until either selexipag became commercially available for PAH in the patient's country or the patient/investigator decided to discontinue selexipag. At the end of selexipag treatment, an end-of-study visit was performed, followed by a post-treatment safety follow-up period of 30 days.

### Ethics

GRIPHON and GRIPHON OL were conducted in accordance with the Declaration of Helsinki. The protocols were approved by the institutional review board/independent ethics committee at each site (Supplementary Table 1). GRIPHON OL was monitored until 30 June 2016 by the same independent data and safety monitoring committee as in GRIPHON [4]. Written informed consent was obtained from all patients at entry into GRIPHON and GRIPHON OL.

### Patient Population

Full inclusion/exclusion criteria for GRIPHON have been described [4]. Briefly, enrolled patients were adults with a diagnosis of one of the following types of PAH, confirmed by right heart catheterisation: idiopathic PAH, heritable PAH, or PAH associated with either connective tissue disease, repaired congenital systemic-to-pulmonary shunts, human immunodeficiency virus infection, drug use or toxin exposure. Further inclusion criteria included a 6MWD of 50–450 m at screening. Background therapy with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 inhibitor (PDE5i) was permitted at a stable dose at the start of GRIPHON [4]. In GRIPHON OL, concomitant PAH therapies permitted during the study included ERAs, PDE5is and/or riociguat; prostacyclin and/or its analogues were permitted, if deemed medically indicated by the investigator, to stabilise a patient with worsening of PAH or to switch a patient to intravenous or subcutaneous treatment.

### Assessments

Patients were followed for adverse events (AEs) from selexipag initiation up to 3 days after end of treatment and for serious AEs and vital status from selexipag initiation up to 30 days after end of treatment. Collection of vital status after this time was not mandated; however, if death was reported to the study sponsor, it was included in the survival analysis.

### Statistical Analyses

All analyses were performed using data from both GRIPHON and GRIPHON OL up to a cut-off date of 1 September 2019 and were descriptive in nature. For the analyses of safety and tolerability, all patients treated with at least one dose of selexipag in GRIPHON or GRIPHON OL were included, defined as the safety/tolerability set. For the post hoc analyses of long-term survival, all patients randomised to selexipag in GRIPHON were included, defined as the survival analysis set. The Kaplan–Meier (KM) method was used to estimate time from selexipag initiation to death. This analysis included deaths that occurred more than 30 days after end of treatment, if reported to the study sponsor. Analyses were performed on all patients, as well as on subsets of patients grouped according to REVEAL 2.0 risk category (based on REVEAL 2.0 risk score; low: $\leq 6$, intermediate: 7–8, high: $\geq 9$; Supplementary Methods) [5] or WHO FC at baseline (WHO FC II or WHO FC III).

## RESULTS

### Patient Characteristics

Overall, 953 patients in the GRIPHON and GRIPHON OL studies were treated with selexipag and were included in the safety/tolerability set (Fig. 1). Of these, 330 patients received selexipag in both GRIPHON and GRIPHON OL, 244 received selexipag in GRIPHON only (i.e. randomised to selexipag in GRIPHON and did not enter GRIPHON OL), and 379 received selexipag in GRIPHON OL only (i.e. randomised to placebo and entered GRIPHON OL). As of 1 September 2019, 216 (22.7%) patients continued to receive treatment in GRIPHON OL (Table 1).

At selexipag initiation, patients in the safety/tolerability set ($n = 953$) had a mean (SD) age of 48.0 (15.3) years; the majority of patients

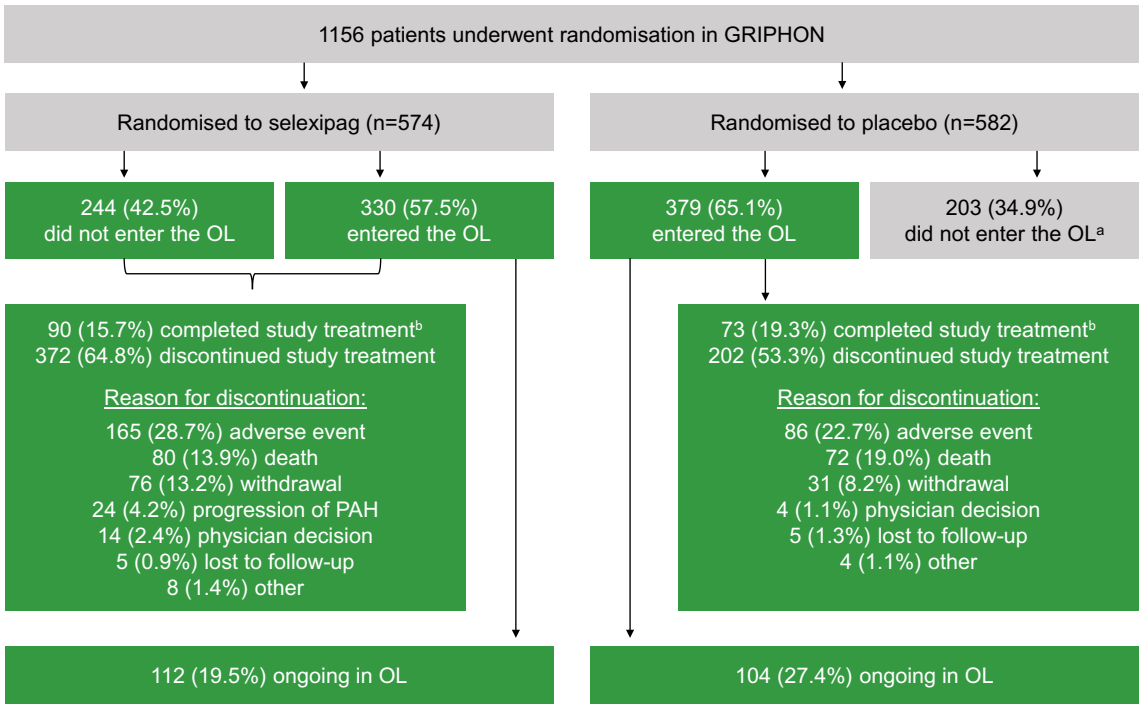


**Fig. 1** Patient disposition. Data cut-off 1 September 2019. *PAH* pulmonary arterial hypertension, *OL* open-label. [a]Four patients did not receive placebo as assigned. [b]Completed study treatment in GRIPHON or GRIPHON OL: Patients who performed the end of study assessment. Green shading indicates patients who received selexipag

were female (80.8%) and in WHO FC II (43.5%) or III (50.3%). 81.2% of patients were treated with an ERA and/or PDE5i: 33.3% with both an ERA and a PDE5i, 14.7% with an ERA and 33.3% with a PDE5i (Table 2).

## Safety and Tolerability

In the safety/tolerability set, the median (min, max) exposure to selexipag was 31.7 (0.0, 106.0) months, corresponding to a total exposure of 3054.4 patient-years. At the time of data cut-off, 99 (10.4%) patients had been receiving selexipag for at least 7 years and 286 (30.0%) patients had been receiving selexipag for at least 5 years. During the observation period, 99.6% of patients experienced at least one treatment-emergent AE and 60.1% experienced at least one serious AE. The most frequently reported AEs were headache (67.9%), diarrhoea (44.6%), nausea (32.8%) and PAH worsening (32.6%) (Table 3); these were either known prostacyclin-related effects and/or associated with progression of underlying disease. After adjusting for exposure, the incidences per year per 100-treated patients for these AEs were 66.3, 23.0, 14.3 and 11.9, respectively (Table 3).

Of the 953 patients in the safety/tolerability set, there were 305 (32.0%) patients who experienced an AE leading to treatment discontinuation, with an incidence rate of 10 AEs leading to discontinuation per year per 100 patients. The most common AEs leading to discontinuation were PAH worsening (12.9%), right ventricular failure (2.9%), headache (3.4%), diarrhoea (2.0%), nausea (1.4%), dyspnoea (1.5%) and pain in extremity (1.0%). There were 65 (6.8%) patients who discontinued due to a prostacyclin-associated AE. Overall, during the study, 212 (22.2%) patients had died by end of treatment + 30 days. The most common (> 1%) reasons for death were PAH worsening (6.4%), right ventricular failure (4.4%), sudden death (1.7%) and cardiac arrest (1.2%).

**Table 1** Treatment disposition at the cut-off date (1 Sep 2019)

| | Selexipag treated patients, ($n$ = 953) |
|---|---|
| Ongoing in study, $n$ (%) | 216 (22.7) |
| Completed study treatment, $n$ (%) | 163 (17.1) |
| Discontinued study treatment, $n$ (%) | 574 (60.2) |
| Reason for discontinuation[a], $n$ (%) | |
| Adverse event | 251 (26.3) |
| Death | 152 (15.9) |
| Withdrawal by patient | 107 (11.2) |
| Progression of PAH | 24 (2.5) |
| Physician decision | 18 (1.9) |
| Lost to follow-up | 10 (1.0) |
| Other | 12 (1.3) |

Data presented for the safety/tolerability set
*PAH* pulmonary arterial hypertension
[a]A patient may have discontinued selexipag for multiple reasons, but only the primary reason for discontinuation is reported here

**Table 2** Demographics and clinical characteristics at time of selexipag initiation

| Characteristic | Selexipag-treated patients, ($n$ = 953) |
|---|---|
| Female, $n$ (%) | 770 (80.8) |
| Age, years, mean ± SD | 48.0 ± 15.3 |
| Time from diagnosis of PAH[a], years, mean ± SD | 2.4 ± 3.7 |
| PAH classification, $n$ (%) | |
| Idiopathic PAH | 532 (55.8) |
| Heritable PAH | 22 (2.3) |
| Associated with connective tissue disease | 273 (28.6) |
| Associated with congenital heart disease | 96 (10.1) |
| Associated with HIV | 8 (0.8) |
| Drug or toxin induced | 22 (2.3) |
| 6MWD, $m$, mean ± SD | 346.4 ± 99.2 |
| WHO FC, $n$ (%) | |
| I | 12 (1.3) |
| II | 415 (43.5) |
| III | 479 (50.3) |
| IV | 47 (4.9) |
| Background PAH therapy, $n$ (%) | |
| ERA and PDE5i combination therapy | 317 (33.3) |
| ERA monotherapy | 140 (14.7) |
| PDE5i monotherapy | 317 (33.3) |
| None | 179 (18.8) |

Data presented for the safety/tolerability set
*6MWD* 6-min walk distance, *ERA* endothelin receptor antagonist, *HIV* human immunodeficiency virus, *m* metres, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase 5 inhibitor, *SD* standard deviation, *WHO FC* World Health Organization functional class
[a]Confirmed by right heart catheterisation

## Survival

Analyses of time to death were performed in all patients randomised to selexipag in GRIPHON [survival analysis set ($n$ = 574)]. Patients in the survival analysis set had a mean age (SD) of 48.2 (15.2) years; the majority of patients were female (79.6%) and in WHO FC II (47.7%) or III (51.0%). A total of 80.5% of patients were treated with a stable dose of an ERA and/or a PDE5i: 31.2% with both an ERA and a PDE5i, 16.4% with an ERA, and 32.9% with a PDE5i [4]. The median (min, max) exposure to selexipag in the survival analysis set was 35.8 (0.0, 106.0) months, corresponding to a total exposure of 1983 patient-years. During this time in GRIPHON and GRIPHON OL, 163 (28.4%) patients initiated a new class of PAH therapy. The most common PAH therapies newly initiated were an

**Table 3** Safety and exposure

| | **Selexipag treated patients, ($n$ = 953)** | |
|---|---|---|
| Selexipag exposure, months, median (range) | 31.7 (0.0–106.0) | |
| Adverse events, *n* (%) | | |
| Patients with ≥ 1 adverse event | 949 (99.6) | |
| Patients with ≥ 1 serious adverse event | 573 (60.1) | |
| Patients with ≥ 1 adverse event leading to selexipag discontinuation[a] | 305 (32.0) | |
| **Most frequent[b] adverse events** | ***n* (%)** | **Incidence rate per year per 100 treated patients** |
| Headache | 647 (67.9) | 66.3 |
| Diarrhoea | 425 (44.6) | 23.0 |
| Nausea | 313 (32.8) | 14.3 |
| PAH worsening | 311 (32.6) | 11.9 |
| Pain in jaw | 268 (28.1) | 12.0 |
| Pain in extremity | 175 (18.4) | 6.7 |
| Vomiting | 174 (18.3) | 6.8 |
| Dyspnoea | 172 (18.0) | 6.4 |
| Oedema peripheral | 159 (16.7) | 5.8 |
| Myalgia | 157 (16.5) | 6.1 |
| Dizziness | 156 (16.4) | 5.9 |
| Nasopharyngitis | 149 (15.6) | 5.6 |
| Right ventricular failure | 147 (15.4) | 5.1 |
| Upper respiratory tract infection | 136 (14.3) | 5.1 |
| Cough | 130 (13.6) | 4.8 |
| Arthralgia | 119 (12.5) | 4.4 |
| Flushing | 117 (12.3) | 4.4 |
| Anaemia | 108 (11.3) | 3.9 |
| Bronchitis | 100 (10.5) | 3.6 |

Data presented for the safety/tolerability set
*PAH* pulmonary arterial hypertension
[a]All adverse events leading to discontinuation of selexipag are reported here and not only those considered the primary reason for discontinuation as presented in Table 1
[b]Occurring in ≥ 10% of patients

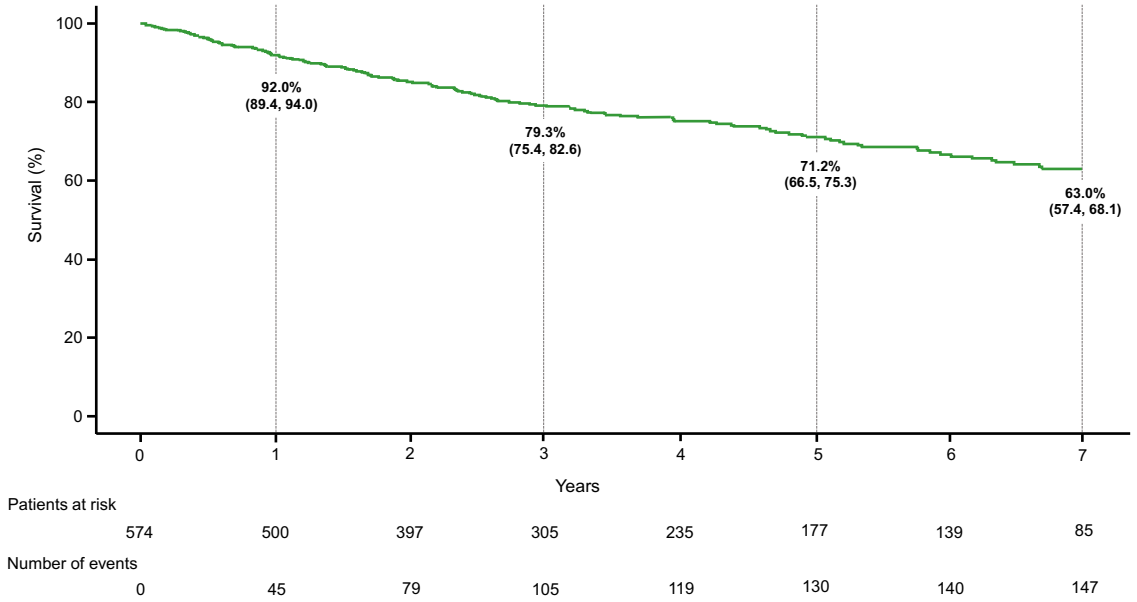


**Fig. 2** Survival in selexipag treated patients. Analyses performed in the survival analysis set. Kaplan–Meier curve for time from selexipag initiation to death up to data cut-off (1 September 2019). Kaplan–Meier estimates (95% CI) are shown at 1, 3, 5 and 7 years

ERA ($n = 40$; 7.0%), a PDE5i ($n = 42$; 7.3%) and prostacyclin or its analogue ($n = 55$; 9.6%). However, most (86.3%) of the selexipag exposure in the survival analysis set ($n = 574$) was accumulated without or prior to the addition of any new PAH therapies.

KM estimates (95%CI) for the survival analysis set at 1, 2, 3, 5 and 7 years were 92.0% (89.4, 94.0), 85.3% (82.0, 88.0), 79.3% (75.4, 82.6), 71.2% (66.5, 75.3) and 63.0% (57.4, 68.1) respectively (Fig. 2). Additional survival analyses were performed on patients grouped according to REVEAL 2.0 risk category (Supplementary Fig. 2) or WHO FC at baseline (Supplementary Fig. 3). Survival estimates [KM (95%CI)] in the REVEAL 2.0 low- ($n = 284$), intermediate- ($n = 145$) and high-risk ($n = 145$) categories, respectively, were: 97.1% (94.3, 98.5), 96.5% (91.7, 98.5), and 77.7% (69.9, 83.7) at 1 year, 89.1% (84.5, 92.4), 82.9% (75.0, 88.6), and 55.7% (46.3, 64.1) at 3 years, and 83.7% (77.9, 88.1), 78.5% (69.1, 85.3), and 35.2% (24.7, 45.9) at 5 years. Seven-year survival estimates [KM (95%CI)] were calculated for the low- and intermediate-risk categories only and were 76.7% (69.2, 82.5) and 59.8% (46.3, 70.9), respectively (Supplementary Fig. 2). Patients in WHO FC II ($n = 273$) had an estimated survival [KM (95%CI)] of 96.6% (93.5, 98.2), 91.2% (86.9, 94.1), 84.7% (79.4, 88.7), 80.2% (74.1, 85.0), and 70.0% (62.0, 76.6), at 1, 2, 3, 5, and 7 years respectively. For patients in WHO FC III ($n = 294$), estimated survival [KM (95%CI)] was 88.0% (83.7, 91.2), 79.8% (74.5, 84.1), 74.5% (68.6, 79.4), 61.8% (54.3, 68.4) and 56.0% (47.6, 63.6) at 1, 2, 3, 5 and 7 years respectively (Supplementary Fig. 3).

## DISCUSSION

These analyses of GRIPHON and its open-label extension study (GRIPHON OL) provide long-term survival, tolerability and safety data in patients with PAH treated with selexipag. The 7-year observation period in this selexipag study is the longest follow-up period published to date for PAH patients treated with any PAH medication. These data are of clinical importance in the setting of a rare disease, where long-term survival data in a well-characterised population are limited.

The combination of the long follow-up period and the large patient population makes this

the most extensive study of safety and tolerability for a PAH therapy published to date, as previous long-term OL studies in PAH typically report safety in the range of 2–3 years [6–9]. Tolerability for selexipag over the extended treatment period was in line with that observed in GRIPHON and in real-world clinical settings [4, 10]. The median exposure time to selexipag in this analysis was over 2.5 years (31.7 months), with 30% of patients having received selexipag for at least 5 years, providing evidence for long-term tolerability of selexipag in patients with PAH. Overall, 305 (32%) patients experienced at least one AE leading to treatment discontinuation, with 6.8% discontinuing due to a prostacyclin related AE. However, of the patients that discontinued due to an AE, the largest proportion (12.9%; $n = 123$) did so due to PAH worsening, reflecting the progressive nature of the disease over the extended observation period. Furthermore, taking into consideration the study's uniquely long exposure period, the incidence rate of AEs leading to discontinuation was 10 AEs per year per 100 patients.

Previous long-term OL studies in PAH typically report survival estimates in the range of 2–3 years [6–9]. Our post hoc analyses provide up to 7 years contemporary survival data, making this a unique long-term analysis of outcomes from trial data in PAH. As over 80% of patients in GRIPHON/GRIPHON OL were receiving selexipag as combination therapy, including a third on triple oral combination therapy, these results provide contemporary data on the long-term survival of patients treated with combination therapy. These data also suggest that patients in GRIPHON/GRIPHON OL were managed in a way that broadly reflects the treatment paradigm of combination therapy for patients with PAH, recommended by the European Society of Cardiology/European Respiratory Society guidelines and the World Symposium on Pulmonary Hypertension proceedings [11–13]. Patients in the low- or intermediate-REVEAL 2.0 risk categories at baseline had better long-term survival than those in the high-risk category. Similarly, patients in WHO FC II at baseline had better long-term survival compared to those in WHO FC III, in line with previous observations [1, 14]. These data further highlight the importance of proactively treating less severe patients with multiple therapies for delaying the progression of PAH. With 5-year estimated survival rates of approximately 80%, these results also suggest that patients treated with selexipag in WHO FC II or at low/intermediate-risk have good long-term survival.

One limitation to these analyses, inherent to OL extension studies, is the uncontrolled nature of the results. Furthermore, the number of patients included in the survival analyses was lower than the total number exposed to selexipag. These analyses were performed in patients originally randomised to selexipag in the GRIPHON trial to ensure robust and non-biased assessment of survival in selexipag treated patients. Patients originally randomised to placebo who received selexipag in GRIPHON OL were not included as they initiated selexipag at different timepoints and with varying disease characteristics, which would lead to significant challenges for interpretation of the results. In addition, although the duration of follow-up is extensive, there is a lack of follow-up data after discontinuation of selexipag, including for patients who switched from receiving selexipag in GRIPHON OL to commercial selexipag.

## CONCLUSIONS

This analysis provides novel insights into long-term outcomes of PAH patients treated with selexipag. Furthermore, as these analyses include a population of patients where the majority were receiving combination therapy, they further our understanding of the long-term benefit–risk implications of combination therapy including selexipag.

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***Compliance with Ethics Guidelines.*** GRIPHON and GRIPHON OL were conducted in accordance with the Declaration of Helsinki. The protocols were approved by the institutional review board/independent ethics committee at each site (Supplementary Table 1). GRIPHON OL was monitored until 30 June 2016 by the same independent data and safety monitoring committee as in GRIPHON [4]. Written informed consent was obtained from all patients at entry into GRIPHON and GRIPHON OL.

***Data Availability.*** The datasets generated during and/or analysed during the current study are available; requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site http://yoda.yale.edu.



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