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# Evaluating oral selexipag in pulmonary arterial hypertension: Insights on survival, safety, and dosing patterns from the complete observation period of GRIPHON and its open-label extension

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**KEYWORDS:**
Selexipag;
Pulmonary arterial hypertension;
Open-label extension;
Long-term safety;
Long-term survival

**BACKGROUND:** Selexipag, an oral prostacyclin receptor agonist, significantly reduced morbidity/mortality risk versus placebo for patients with pulmonary arterial hypertension (PAH) in GRIPHON. Five-year survival estimates in real-world clinical practice for PAH patients are 57%. With its open-label extension (OLE), GRIPHON presents the longest follow-up in a PAH trial to date.

**METHODS:** Two main analysis sets were evaluated as follows: selexipag-treated patients i.e., those receiving selexipag in GRIPHON (NCT01106014) or OLE (NCT01112306) and selexipag-long term patients, i.e., those randomized to selexipag in GRIPHON, irrespective of entry into its OLE. Safety was analyzed in both. On-treatment survival was analyzed (Kaplan-Meier [KM] estimates; 95% confidence intervals [CI]) in the overall selexipag long-term patients and by subgroups (individualized maintenance dose, PAH-specific combination therapy and time from diagnosis, and 4-strata risk category), to end of treatment + 30 days.

**RESULTS:** Overall, 953 selexipag-treated patients were identified; 574 were selexipag long-term patients. For the latter, median follow-up time from selexipag initiation was 54 months and median

*Abbreviations:* 6MWD, 6-minute walk distance; AE, Adverse event; AESI, Adverse event of special interest; b.i.d., Twice-daily; CI, Confidence interval; DB, Double-blind; EOS, End of study; EOT, End of treatment; ERA, Endothelin receptor antagonist; ESC/ERS, European Society of Cardiology/European Respiratory Society; HIV, Human immunodeficiency virus; IMD, Individualized maintenance dose; IP, Prostacyclin receptor; KM, Kaplan-Meier; NT-proBNP, N-terminal pro-brain natriuretic peptide; OLE, Open-label extension; PAH, Pulmonary arterial hypertension; PDE5i, Phosphodiesterase 5 inhibitor; RCT, Randomized controlled trial; SAE, Serious adverse event; SD, Standard deviation; Q1, Q3, Interquartile range; WHO FC, World Health Organization functional class

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exposure duration was 35.8 months (total selexipag exposure: 2105.5 patient-years). KM (95% CI) survival estimates at 5 years were 74% (69-78) overall (n = 176) and 79% (67-87) when selexipag was initiated with an endothelin receptor antagonist and phosphodiesterase 5 inhibitor (n = 26). The most frequently reported adverse events (AEs) were related to known prostacyclin-related effects or underlying disease; AEs leading to selexipag discontinuation were reported in 223 (39%) patients.

**CONCLUSIONS:** These comprehensive, long-term safety and survival data for selexipag provide the longest follow-up period to date for a PAH therapy. Selexipag's safety profile, up to 10 years in almost 1000 patients, was consistent with previous observations.

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Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance, leading to right heart failure and reduced survival.[1,2] The current treatment landscape is becoming increasingly complex, with PAH-specific therapies now targeting 4 physiologically distinct pathways.[3] Recent randomized controlled trials (RCTs) and their open-label extension (OLE) studies have generated evidence for the safety and efficacy of PAH-specific therapies.[4-12] There is a need to understand the optimal use of these current treatments and maximize benefits for patients.

GRIPHON examined the efficacy and safety of the oral IP prostacyclin receptor agonist selexipag in the largest and longest placebo-controlled study in PAH to date.[11] In this pivotal trial, selexipag was demonstrated to delay PAH progression by 40% and this benefit was consistent regardless of PAH etiology, baseline risk profile (when assessed using the 3-strata method), individualized maintenance dose or background PAH therapy.[11,13,14] Evidence generated from the GRIPHON study and its OLE up to 7 years[12-16] is reflected in the PAH treatment guidelines relating to risk categories and timing of selexipag initiation in relation to diagnosis.[3,17,18] The 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) treatment guidelines recommend risk assessment at the first follow-up visit (3 months after treatment initiation), to guide therapeutic selection based on the patients' risk of 1-year mortality, categorized according to the 4-strata method.[17,18]

The current analyses complement earlier work from GRIPHON and its OLE[11,12] by providing observed safety and survival data for up to 10 years in the overall population. We also report observed long-term survival in subgroups that are relevant to treatment decision-making, including individualized selexipag maintenance dose groups, PAH-specific combination therapy regimen, time from diagnosis to selexipag initiation, and 4-strata risk category. Finally, we report the treatment effect of selexipag versus placebo for the GRIPHON primary endpoint, utilizing the current approach of 4-strata risk categorization.

## Methods

### Study design

GRIPHON (NCT01106014) was a phase 3, event-driven, randomized, double-blind, global, multicenter study, which assessed the safety and efficacy of selexipag in patients with PAH.[11] In GRIPHON, patients were randomly assigned 1:1 to selexipag or placebo, and were titrated to an individualized dose of 200 to 1600 μg twice daily (b.i.d.) based on tolerability over a 12-week period. Patients received double-blind (DB) treatment (selexipag or placebo) until they experienced a morbidity/mortality event (primary endpoint), discontinued prematurely or until end of study (EOS; reached when 331 primary endpoint events had occurred). Further details are provided in the **Supplement.** The study design has previously been described and illustrated in detail[11,12].

GRIPHON OLE (NCT01112306), the multicenter, open-label extension of GRIPHON, assessed long-term safety and tolerability of selexipag in patients with PAH.[12] Patients already enrolled in GRIPHON could enter GRIPHON OLE either after experiencing a morbidity event during the GRIPHON DB or at the end of the DB study, if they were still receiving study treatment. Further details on entering the OLE are provided in the Supplement. Patients in GRIPHON OLE received selexipag until either the patient/investigator decided to discontinue or selexipag became commercially available for PAH in the patient's country. At the end of selexipag treatment, an EOS visit was performed, followed by a post-treatment safety follow-up period of 30 days.

## Ethics

GRIPHON and GRIPHON OLE were conducted in accordance with the Declaration of Helsinki and International Society for Heart and Lung Transplantation ethics statement. Protocols were approved by the institutional review board/independent ethics committee at each site (Table S1). An independent Data Monitoring Committee consisting of experts in the fields of cardiovascular, respiratory medicine, pulmonary hypertension, and biostatistics evaluated safety data in the OLE from GRIPHON study initiation in 2009 up to July 01, 2016 (date of disbandment of the committee).[11] Written informed consent was obtained from all patients at entry into GRIPHON and GRIPHON OLE.

### Patient population

Inclusion/exclusion criteria for GRIPHON have been previously described.[11] Briefly, patients enrolled in the OLE

were 18 to 75 years old at the start of GRIPHON DB with a PAH diagnosis confirmed by right heart catheterization, including 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. Six-minute walk distance (6MWD) had to be 50 to 450 m at screening and background therapy with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase 5 inhibitor (PDE5i) was permitted at a stable dose at the start of GRIPHON.[4] In GRIPHON OLE, concomitant PAH therapies permitted during the study included ERAs, PDE5is, or riociguat. Temporary concomitant use of inhaled, intravenous, or subcutaneous prostacyclin and/or its analogs was permitted, if deemed medically indicated by the investigator, to stabilize a patient with worsening of PAH or to switch a patient to intravenous or subcutaneous treatment.

### Assessments/endpoints

Patients were followed for treatment-emergent adverse events (AEs) from selexipag initiation up to end of treatment (EOT) + 3 days and for serious AEs (SAEs), including deaths, from selexipag initiation up to EOT + 30 days. Collection of data after this time was not mandated.

### Statistical analyses

All analyses were descriptive in nature and performed using data from both GRIPHON DB and GRIPHON OLE up to the final patient observation on 29 September 2021. Changes based on updates to China's Human Genetic Resources regulations during the course of the study are described in the Supplement. Two main and 1 supportive analysis set were defined as follows:

- Selexipag-treated patients: all patients who received selexipag treatment at any time in GRIPHON DB and/or GRIPHON OLE; used for analyses of safety. This included placebo-randomized patients who entered the OLE.
- Selexipag long-term patients: a subset of selexipag-treated patients who received selexipag in GRIPHON DB, irrespective of entry into GRIPHON OLE; used for analyses of long-term survival and safety.
- Patients randomized to either selexipag or placebo in GRIPHON DB; used for supportive analyses of treatment effect by risk category (4-strata method) by end of GRIPHON DB

The Kaplan-Meier (KM) method was used to estimate survival on-treatment with selexipag, from selexipag initiation in GRIPHON DB to death in GRIPHON DB or OLE, up to EOT + 30 days. In GRIPHON DB, deaths were reported until the end of study (EOS), whereas in the OLE, it was not mandated to report deaths past EOT + 30 days. For that reason, KM estimates are reported as on-treatment, except when specified as EOS. Patients who discontinued treatment in the study (for any reason) but remained alive were censored at that timepoint (further details on EOS vs EOT analyses are in the Supplement). Median follow-up time was estimated using the reverse KM estimate of survival data. Analyses were performed for the overall selexipag long-term patients and for the following subgroups:

- Individualized maintenance dose group reached in GRIPHON DB by Week 12 (Low [200 or 400 μg b.i.d.], Medium [600, 800 or 1000 μg b.i.d.], High [1200, 1400 or 1600 μg b.i.d.]).
- PAH-specific combination therapy regimen at GRIPHON DB baseline: Selexipag initiated as part of either triple or double combination therapy, further grouped by time from diagnosis to selexipag initiation (≤6 months or > 6 months).
- Risk category at GRIPHON DB baseline according to the 2022 ESC/ERS recommended 4-strata method (described further in the Supplement).

Supportive analyses were performed using the primary (composite) endpoint of GRIPHON DB on patients categorized according to 4-strata risk category (described further in the Supplement).

## Results

### Patient characteristics

Overall, there were 953 selexipag-treated patients; 574 selexipag-randomized patients and 379 patients originally randomized to placebo who entered the OLE. Of the 574 patients randomized to selexipag in GRIPHON DB (selexipag long-term patients), 330 continued to receive selexipag in the OLE and 244 patients did not enter the OLE (Figure S1). At the end of GRIPHON OLE (from initiation of DB in June 2010 to last observation in September 2021), for the selexipag long-term patients (N = 574): 162 (28.2%) completed study treatment and 412 (71.8%) discontinued study treatment (reasons are listed in Table S2; Figure S1). For the patients who received selexipag at any time during GRIPHON DB or GRIPHON OLE (selexipag-treated; N = 953), 294 (30.8%) completed study treatment and 659 (69.2%) discontinued study treatment (Table S2; Figure S1).

Demographics and baseline characteristics for the overall selexipag long-term patients (Table 1) have been described previously.[11] Patient characteristics according to subgroup are in Tables S3-S6.

### Exposure

For the selexipag long-term patients, the median (range) exposure duration of selexipag was 35.8 (0-126) months, corresponding to a total selexipag exposure of 2105.5 patient-years (Table 2). A total of 176 (30.7%) patients received selexipag for or ≥5 years, and 10 (1.7%) for ≥10 years. Exposure for all selexipag-treated patients is shown in Table S7.

**Table 1** Demographics and Clinical Characteristics at Time of Selexipag Initiation in Selexipag Long-Term Patients

| Characteristics | Selexipag long-term patients[a] (N = 574) |
|---|---|
| Female, n (%) | 457 (79.6) |
| Age, years, mean ± SD | 48.2 ± 15.2 |
| Time from diagnosis of PAH[b], years, median (Q1, Q3) | 0.9 (0.3, 2.9) |
| PAH classification, n (%) | |
| Idiopathic PAH | 312 (54.4) |
| Heritable PAH | 13 (2.3) |
| Associated with | |
| Connective tissue disease | 167 (29.1) |
| Congenital heart disease | 60 (10.5) |
| HIV infection | 5 (0.9) |
| Drug- or toxin-induced | 17 (3.0) |
| 6MWD, m, mean ± SD | 358.5 ± 76.3 |
| WHO FC, n (%) | |
| I | 4 (0.7) |
| II | 273 (47.6) |
| III | 294 (51.2) |
| IV | 3 (0.5) |
| Background PAH-specific therapy, n (%) | |
| ERA and PDE5i combination therapy | 179 (31.2) |
| PDE5i monotherapy | 189 (32.9) |
| ERA monotherapy | 94 (16.4) |
| None | 112 (19.5) |

6MWD, 6-minute walk distance; DB, double-blind; ERA, endothelin receptor antagonist; HIV, human immunodeficiency virus; OLE, open label extension; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; Q1, Q3, interquartile range; SD, standard deviation; WHO FC, World Health Organization functional class. Characteristics are based on the last value available prior to (or on) first dosing date and may differ from those presented in the primary manuscript[11] (based on randomization date)

[a]All patients who received selexipag in GRIPHON DB, regardless of whether they entered the OLE or not

[b]PAH diagnosis confirmed by right heart catheterization

## Survival outcomes

Median follow-up time, irrespective of treatment duration, from selexipag initiation was 54 months. Overall (n = 574), KM (95% confidence interval [CI]) estimates of survival at 1, 3, 5, 8 and 10 years were: 93% (90-95), 82% (78-86), 74% (69-78) and 63% (57-69) and 60% (53-66), respectively (Figure 1a). Overall survival until EOS is shown in Figure S2.

Survival was generally consistent across the low, medium, and high individualized maintenance dose groups (Figure 1b). For patients receiving selexipag as part of triple combination therapy (n = 179), KM (95% CI) estimates at 1, 5 and 8 years were 95% (89-97), 79% (67-87), and 73% (56-84) (Figure 2a); survival when grouped by time from diagnosis ≤6 versus > 6 months is shown in Figure 2b. For patients receiving selexipag as part of double combination therapy (n = 283), KM (95% CI) estimates at 1, 5 and 8 years were 93% (88-95), 69% (62-75), and 55% (46-63) (Figure 3a); survival when grouped by time from diagnosis ≤6 versus > 6 months is shown in Figure 3b. For analyses by 4-strata risk category, better survival was observed for the low and intermediate-low risk groups versus the higher risk groups (Figure 4). Supportive analyses were performed on time to morbidity/mortality (GRIPHON DB primary endpoint) according to 4-strata risk category, on patients randomized to either selexipag or placebo in GRIPHON DB. Treatment effect of selexipag was consistent across all risk categories (see Supplemental Results).

## Safety

Safety data for selexipag long-term patients (N = 574) are shown in Table 2. During the observation period, 99.7% of patients experienced at least 1 treatment-emergent AE and 64.1% experienced at least 1 SAE. The most frequently reported AEs were headache (67.9%), diarrhea (46.2%), nausea (36.4%) and PAH worsening (35.4%); 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 54.7, 21.1, 14.4, and 11.5, respectively (Table 2). There were 223 (38.9%) patients who experienced an AE leading to treatment discontinuation. The most common (≥3%) AEs leading to discontinuation were PAH worsening (16.7%), headache (3.7%), and right ventricular failure (3.3%); 47 (8.2%) discontinued due to a prostacyclin-associated AE. Adverse events of special interest are shown in Table S8. By EOT + 30 days, 126 (22.0%) patients died. The most common (> 1%) reasons for death were PAH worsening (6.4%), right ventricular failure (4.0%), sudden death (2.1%) and cardiac arrest (1.4%). Safety and survival data for selexipag-treated patients (N = 953) are shown in Table S7.

## Discussion

The prostacyclin pathway is one of the foundational pathways targeted for treatment of PAH, with the synthetic prostacyclin, epoprostenol, being the first drug approved as a PAH-specific therapy.[19] Selexipag is an orally administered, selective IP prostacyclin receptor agonist which targets this key pathway.[11] These analyses of GRIPHON and its OLE provide up to 10 years of long-term safety and survival data for selexipag use in PAH patients. This is the largest and longest dataset available for a PAH-specific therapy to date. Our main analyses used survival data up to EOT + 30 days, representing on-treatment data for patients who remained in the study. This is important when considering long-term follow-up data, as some patients may have discontinued selexipag and initiated parenteral prostacyclin or undergone lung transplantation, according to ESC/ERS treatment guidelines.[17,18] In the overall selexipag long-term patients, analyses of survival up to EOT + 30 days and up to EOS were similar.

**Table 2** Safety and Exposure

| | Selexipag long-term patients[a] (N = 574) | |
|---|---|---|
| Selexipag exposure (months), median (range) | 35.8 (0-126) | |
| Total selexipag exposure, patient-years | 2105.5 | |
| Adverse events, n (%) | | |
| Patients with ≥ 1 adverse event | 572 (99.7) | |
| Patients with ≥ 1 serious adverse event | 368 (64.1) | |
| Patients with ≥ 1 adverse event leading to selexipag discontinuation[b] | 223 (38.9) | |
| Patients with ≥ 1 prostacyclin-associated adverse event leading to selexipag discontinuation[c] | 47 (8.2) | |
| Most frequent adverse events[d] | n (%) | Incidence rate per year per 100 treated patients |
| Headache | 390 (67.9) | 54.7 |
| Diarrhea | 265 (46.2) | 21.1 |
| Nausea | 209 (36.4) | 14.4 |
| Pulmonary arterial hypertension worsening | 203 (35.4) | 11.5 |
| Pain in jaw | 156 (27.2) | 10.2 |
| Dyspnea | 131 (22.8) | 7.2 |
| Peripheral edema | 118 (20.6) | 6.4 |
| Vomiting | 115 (20.0) | 6.6 |
| Pain in extremity | 110 (19.2) | 6.1 |
| Dizziness | 106 (18.5) | 5.8 |
| Nasopharyngitis | 100 (17.4) | 5.6 |
| Myalgia | 96 (16.7) | 5.5 |
| Upper respiratory tract infection | 94 (16.4) | 5.3 |
| Cough | 90 (15.7) | 4.9 |
| Right ventricular failure | 84 (14.6) | 4.2 |
| Flushing | 79 (13.8) | 4.4 |
| Anemia | 77 (13.4) | 4.1 |
| Arthralgia | 75 (13.1) | 4.1 |
| Bronchitis | 64 (11.1) | 3.4 |
| Pneumonia | 63 (11.0) | 3.2 |
| Fatigue | 58 (10.1) | 3.0 |

DB: double blind; EOT: end of treatment; OLE: open-label extension; Treatment-emergent adverse events are presented from selexipag initiation until EOT + 3 days; serious adverse events were collected until EOT + 30 days; adverse events are as reported by the Investigator

[a]All patients who received selexipag in GRIPHON DB, regardless of whether they entered the OLE or not

[b]All adverse events leading to discontinuation of selexipag are reported here and not only those considered the primary reason for discontinuation

[c]Prostacyclin-associated reactions occurring at or after initiation of selexipag up to EOT + 3 days

[d]Occurring in ≥10% of patients.

While the long-term nature of these data makes them unique and valuable, this leads to challenges in contextualizing with other studies. US disease registry data with standard of care treatment suggest 5-year survival rates for patients with PAH of 57%[20] and are supported by more recent findings elsewhere.[21-23] In our analysis, the 5-year survival was 74%. In the real-world SPHERE and EXPOSURE observational studies for patients initiating selexipag, survival estimates were similar to those seen in GRIPHON OLE (Figure 5).[24,25]. Survival estimates in other selexipag RCT and real-world studies (summarized in Figure 5) are generally aligned, which is encouraging especially when considering differences between RCT and real-world study designs. For example, as an RCT population, patients in GRIPHON were generally younger, with less advanced disease than patients seen in the real-world EXPOSURE or SPHERE studies.[24,25] Despite these differences, we believe our findings can inform broader clinical practice, supporting the value of long-term selexipag use to optimize outcomes for patients.

A notable finding from GRIPHON DB was the consistent treatment effect of selexipag across different dose groups.[11] This was similarly reflected in real-world US claims data, in which a consistent effect on long-term hospitalization outcomes was observed across selexipag dose ranges.[26] Findings from GRIPHON OLE align with this, showing comparable long-term survival outcomes, regardless of a patient's individualized maintenance dose. This underscores the importance of titrating selexipag to the patient's maximal tolerated dose. For the majority, this is not the maximum approved dose (i.e., 1600 µg b.i.d.).[11,24,25] In GRIPHON and its OLE, selexipag titration was done per protocol[11] but in the real-world, there is the possibility to titrate more flexibly.[24,25] In clinical practice, selexipag is used across all dose ranges,[24,25] suggesting that patients are being titrated to their individualized maintenance dose. The ability to titrate selexipag according to tolerability allows for personalized treatment that maximizes efficacy while minimizing side effects and supports its use in long-term, continuous therapy.

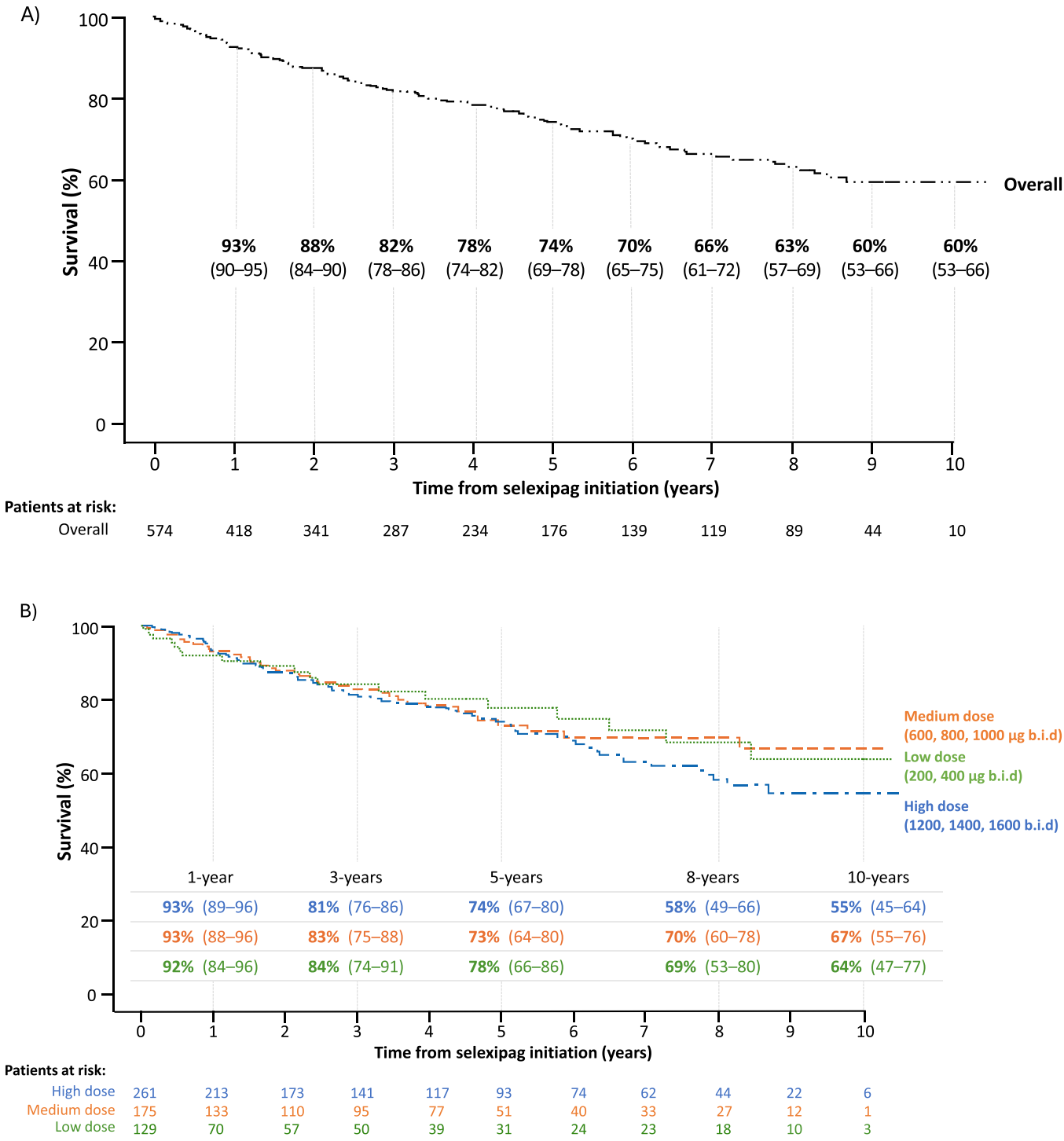


**Figure 1** KM estimates of survival for the selexipag long-term patients a) overall and b) by individualized maintenance dose group. KM (95% CI) estimates for time from selexipag initiation to death up to end of treatment + 30 days are shown. Patients in GRIPHON OLE received selexipag until either the patient/investigator decided to discontinue or selexipag became commercially available for PAH in the patient's country. Figure b) does not include 9 patients from the selexipag long-term patients: 8 patients who reached an IMD of selexipag < 200 µg b.i.d. and 1 patient whose IMD of 900 µg b.i.d. did not meet the criteria for "medium" dose (600, 800, or 1000 µg b.i.d.). The survival estimates should be interpreted with caution when < 10% of patients are still at risk in accordance with Pocock's stopping rule.[29]
b.i.d.: twice daily; CI, confidence interval; IMD, individualized maintenance dose; KM, Kaplan-Meier; OLE, open-label extension

With respect to selexipag treatment effect, selexipag reduced the risk of morbidity and mortality in a consistent manner across all risk categories when using the 4-strata method. This finding is aligned with earlier analyses in GRIPHON based on 3-strata categories and REVEAL 2.0 and REVEAL Lite 2 risk scores.[13,27] Robust patient numbers for most of the subgroups in this analysis make these data relevant for current treatment decision-making. At selexipag initiation in GRIPHON, most patients were in the intermediate-low (47%; N = 266) or intermediate-high (31%; N = 177) risk categories and recent real-world findings are aligned with this, with the majority of patients

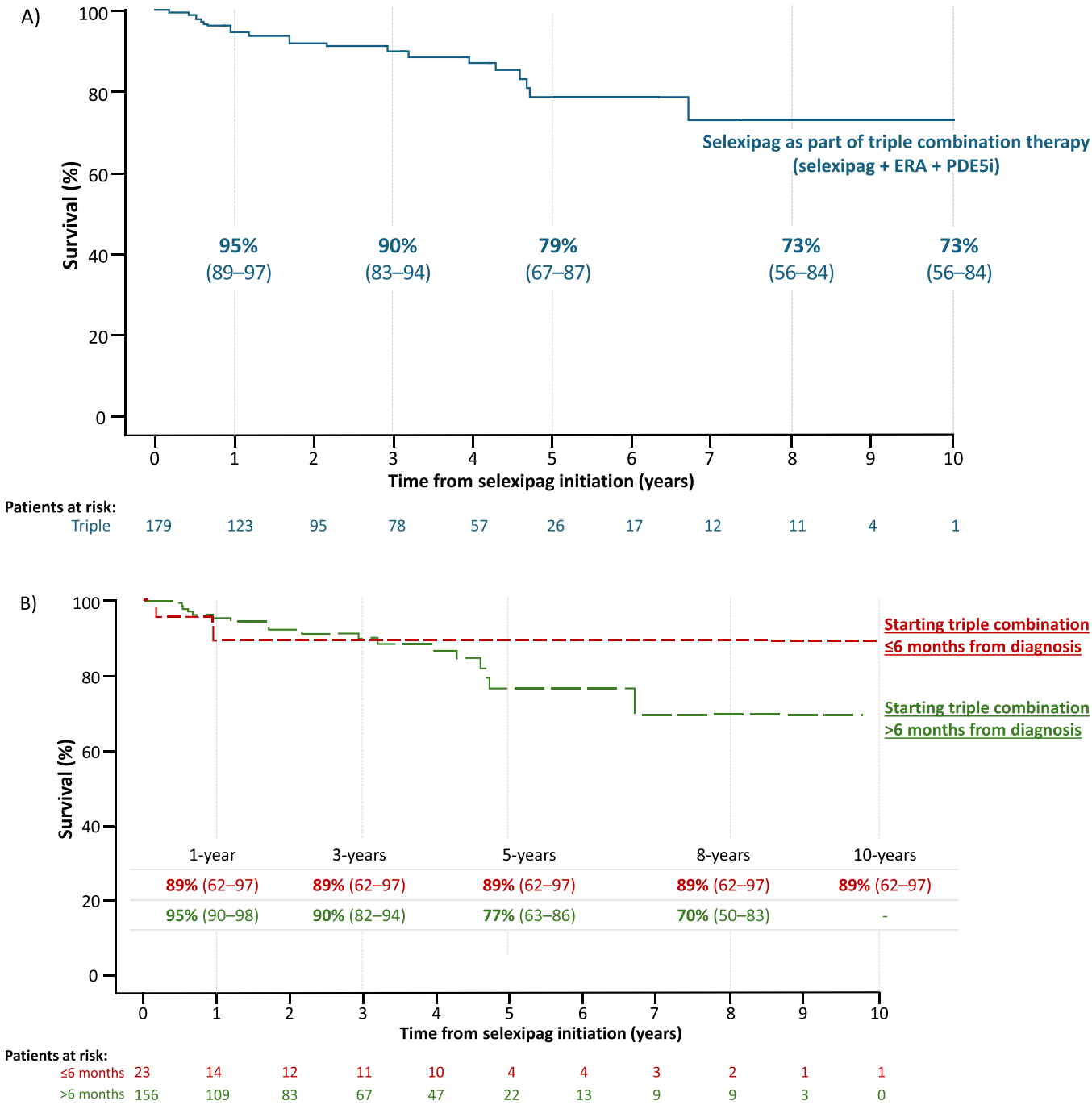


**Figure 2** KM estimates of survival for the selexipag long-term patients by selexipag as part of triple PAH-specific combination therapy regimen a) overall and b) by time from diagnosis. KM (95% CI) estimates for time from selexipag initiation to death up to end of treatment + 30 days are shown. Does not include 112 patients from the overall selexipag long-term patients who did not have a PAH-specific background therapy at baseline or 283 patients initiating selexipag as part of double combination therapy. The survival estimates should be interpreted with caution when subgroups are n < 50 patients, or when < 10% of patients are still at risk in accordance with Pocock's stopping rule.[32] CI, confidence interval; ERA, endothelin receptor antagonist; KM, Kaplan-Meier; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor

from EXPOSURE also initiating selexipag at intermediate-low (31% [N = 168]) or intermediate-high risk (34% [N = 182]) category.[24] Observations from GRIPHON OLE are reassuring in light of this, demonstrating good survival outcomes for patients at low, intermediate-low and intermediate-high risk. In EXPOSURE, survival at 3 years was 98%, 92% and 76% for patients at low, intermediate-low, and intermediate-high risk, respectively.[24] This is comparable with our observations in GRIPHON OLE (92%, 88% and 67%, respectively), with the context that patients in EXPOSURE were more likely to be receiving selexipag as part of triple combination therapy: 78% of patients in EXPOSURE versus 31% here. The large proportion of patients in the intermediate-low and intermediate-high categories at selexipag initiation indicates the potential to benefit from treatment with selexipag and that there is an opportunity to initiate selexipag in less severe disease states, maximizing potential benefit.

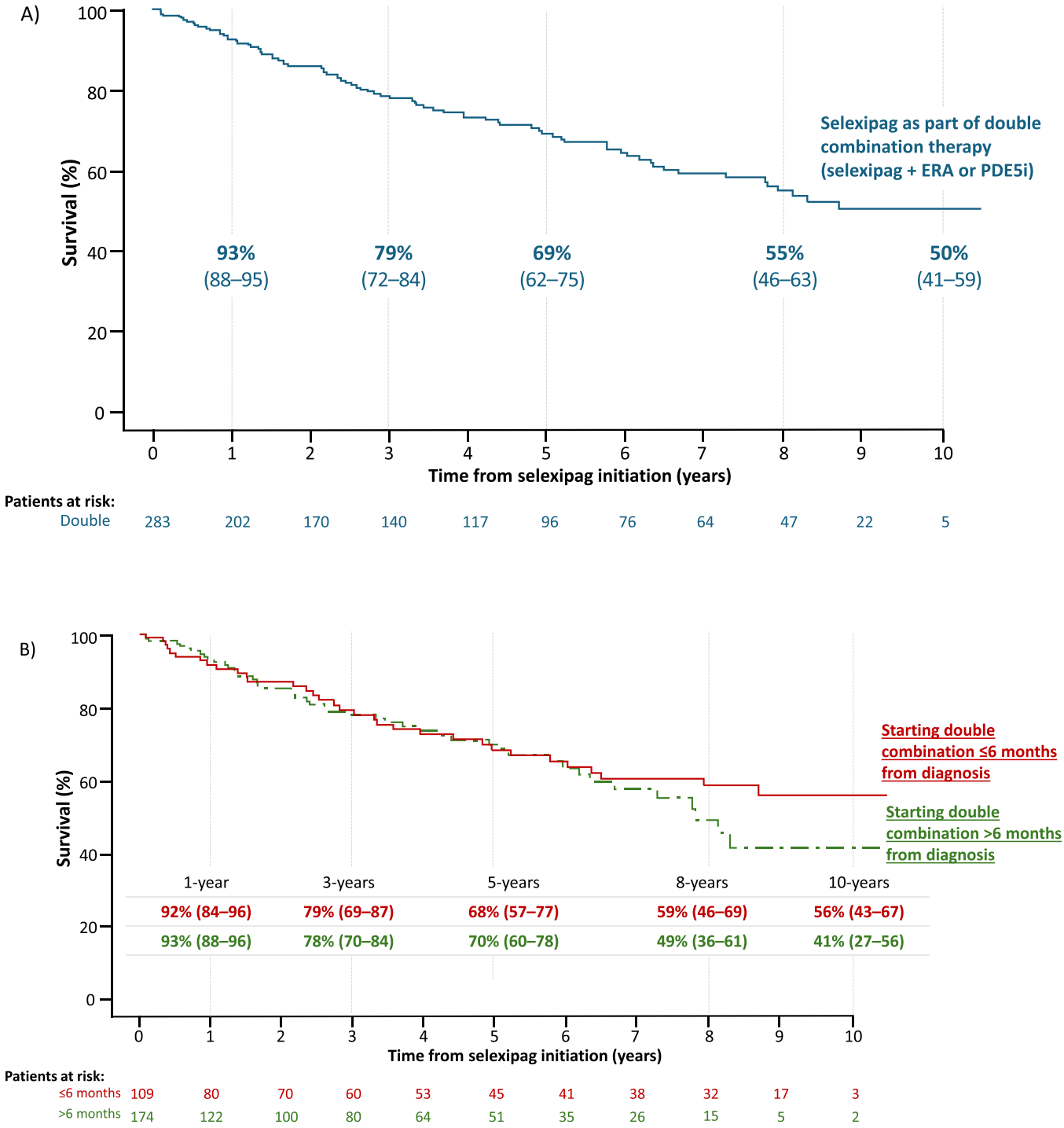


**Figure 3** KM estimates of survival for selexipag long-term patients by selexipag as part of double PAH-specific combination therapy regimen. a) overall and b) by time from diagnosis. KM (95% CI) estimates for time from selexipag initiation to death up to end of treatment + 30 days are shown. Does not include 112 patients from the overall selexipag long-term patients who did not have a PAH-specific background therapy at baseline or 179 patients initiating selexipag as part of triple combination therapy. The survival estimates should be interpreted with caution when < 10% of patients are still at risk in accordance with Pocock's stopping rule.[32] CI, confidence interval; ERA, endothelin receptor antagonist; KM, Kaplan-Meier; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor

As PAH is a chronic disease, treatment decisions should look beyond the 1-year mortality risk. Treatment strategies need to be considered at diagnosis and first follow-up that allow for the best possible survival in the future, not only in the next year or after disease progression. The majority of patients in GRIPHON received selexipag as part of double or triple combination therapy, and the treatment effect of selexipag (as reported in the primary manuscript) was consistent across different background therapies.[11] In the current study, 5-year KM (95% CI) survival estimates in patients treated with selexipag as triple oral combination therapy were 79% (67-87; n = 26) and in patients receiving selexipag as part of double oral combination therapy were 69% (62-75; n = 96). Due to the progressive nature of PAH,

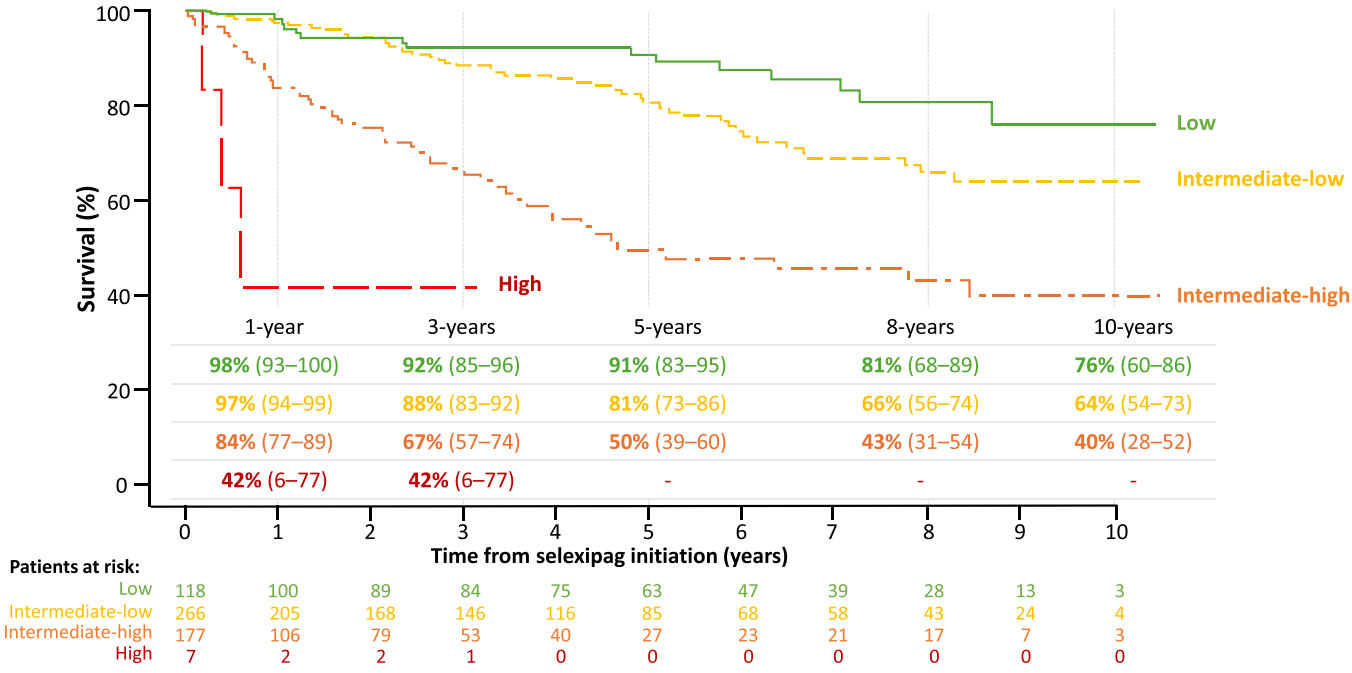


**Figure 4** KM estimates of survival for the selexipag long-term patients by 4-strata risk category. KM (95% CI) estimates for time from selexipag initiation to death up to end of treatment + 30 days are shown. Does not include 6 patients from the selexipag long-term patients who did not have data available for risk assessment. The survival estimates should be interpreted with caution when subgroups are with an n < 50 patients, or when < 10% of patients are still at risk in accordance with Pocock's stopping rule.[32] CI, confidence interval; KM, Kaplan-Meier

the earlier treatment can be initiated, the better for patient outcomes. Previous observations from pooled analyses show patients who received selexipag as part of triple combination therapy within 6 months of diagnosis had a 53% reduced risk of all-cause death (hazard ratio: 0.47; 95% CI: 0.19-1.16) versus patients receiving placebo added to double oral combination therapy.[8] The subgroup analyses in GRIPHON OLE further stratifying patients with selexipag as part of triple therapy by time from diagnosis are supportive of a positive impact of early initiation on survival, but due to low patient numbers and wide CI, results must be interpreted with caution. These long-term survival data (summarized in Figure S3) provide additional support for treatment recommendations that advocate for initial double therapy and escalation to triple combination therapy at first follow-up (3 months)[3,17,18].

Long-term safety is a critical factor in PAH treatment, given that patients require lifelong therapy. Selexipag's long-term safety profile has been well-established by RCT and extensive real-world data.[9,12,24] Safety observed in GRIPHON OLE in 953 patients up to 10 years is aligned with these previous observations, with no unexpected safety concerns. Adverse events of special interest typically monitored during selexipag use include increased risk of bleeding and hyperthyroidism.[11] Although selexipag has potential anti-platelet effects in vitro,[28,29] there was no increased risk of bleeding events observed in GRIPHON DB, and over the long-term OLE, there was no increase in rate compared to the DB period (bleeding events observed in 2.4% and 2.8% of patients, respectively).[11] Similarly, there was no indication of increased risk for hyperthyroidism between GRIPHON DB and the OLE.[11] Although discontinuation rates might seem high over the course of GRIPHON and its OLE (72% of selexipag long-term patients), only 8% of patients discontinued selexipag due to a prostacyclin-related AE. The discontinuation rates due to AEs observed here (29%) are in line with those for real-world selexipag use: in EXPOSURE approximately 16% of patients discontinued due to tolerability/an AE (median exposure of 10 months)[24] and 25% discontinued due to an AE in SPHERE (mean duration of treatment 19 months).[25]

## Limitations

Open-label studies are subject to inherent limitations, such as the lack of a placebo control arm, which can introduce bias and affect data interpretation. In this analysis, patient numbers were low at the later timepoints (i.e., beyond 7 years) and in certain subgroups, limiting the analyses to descriptive statistics which should be interpreted with caution. Subgroups were based on characteristics at selexipag initiation or reaching an individualized maintenance dose group and changes in factors such as risk category or treatment regimen over the long-term follow-up were not considered. Dose adjustments were permitted during the OLE, however, due to prespecified design, these stayed within the dose group of low, medium, or high. Variation in selexipag treatment duration was also not taken into account, although the analysis focused primarily on the on-treatment period, which allowed for a clearer assessment of drug-related effects by reducing confounding from post-treatment events. To minimize selection bias, survival analyses were restricted to the 574 patients originally randomized to selexipag in the DB. This is important given that patients assigned to placebo in the DB could later receive selexipag in the open-label, following a morbidity event or after completing the DB study, potentially skewing long-term outcomes. Despite these

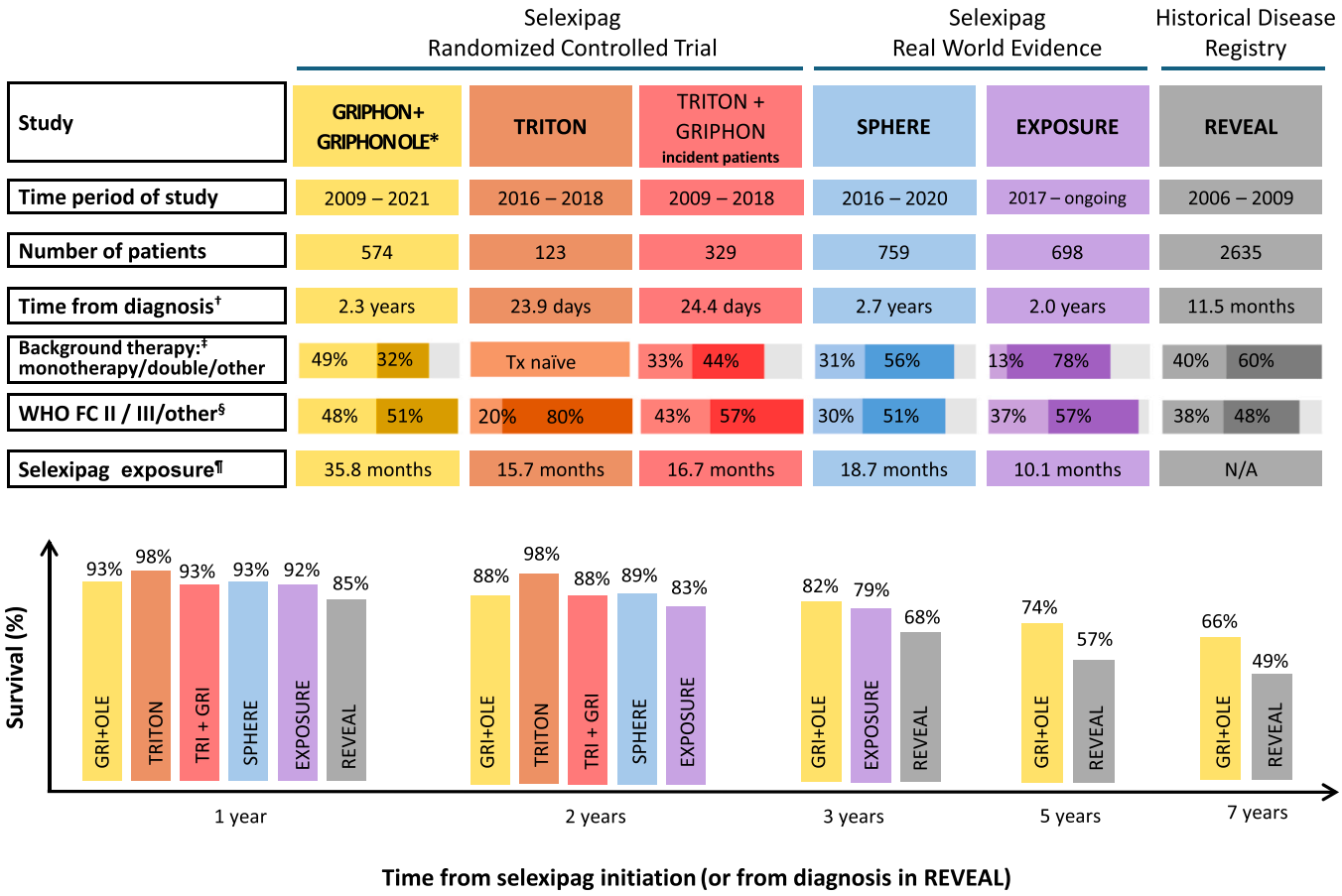


**Figure 5** Summary of survival across selexipag studies with REVEAL registry for context. Summary of study design, patient characteristics, and survival in previous selexipag studies (GRIPHON,[11] TRITON,[9] pooled TRITON + GRIPHON analyses,[8] SPHERE,[25] EXPOSURE[24]), with REVEAL[20] included for context. *Upon entering GRIPHON OLE, randomization status in the double-blind period (i.e., to selexipag or placebo) was no longer maintained. †Median time from diagnosis, apart from TRITON (mean). ‡Data from REVEAL are from Benza *et al* 2010 (n = 2716)[33] and show monotherapy versus combination therapy (≥2 PAH-specific therapies). §For TRITON and TRITON + GRIPHON, WHO FC I/II and WHO FC III/IV are presented; data from REVEAL are from Benza *et al* 2010 (n = 2716).[30] ¶Median selexipag exposure, apart from SPHERE (mean). GRI, GRIPHON; OLE, open-label extension; RCT, randomized controlled trial; TRI, TRITON; WHO FC, World Health Organization functional class

limitations, the extended treatment period of up to 10 years across GRIPHON and its open-label extension provides a valuable perspective on long-term outcomes with selexipag, including safety from nearly 1000 patients.

## Conclusions

These comprehensive, long-term safety and survival data for selexipag provide the longest follow-up period to date for a PAH therapy. The safety profile of selexipag, up to 10 years, in almost 1000 patients, was consistent with previous observations and survival in the overall population compared favorably with results reported in the literature. Our subgroup analyses provide insights into how to optimize the benefits of selexipag therapy, showing that survival was comparable across individualized dose groups and suggesting that approaches utilizing selexipag as part of escalation in a timely manner may be beneficial. Analyses based on 4-strata risk methods showed benefit across all risk strata, in particular in low and intermediate-low risk patients.

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## Author Contributions

All authors contributed to the writing of the manuscript. Vallerie V. McLaughlin, Luke Howard, Jean Elwing, Sean Gaine, Nazzareno Galiè, Ronald J. Oudiz, Paul Strachan, and Nick H. Kim contributed to collection of the data as investigators and to interpretation of the data. Mylène Stefani contributed to statistical analyses and interpretation of the data. Catarina C. Fernandes, Simone Stickel, and Yuichi Tamura contributed to the interpretation of the data.

## List of Investigators

Investigators for GRIPHON and GRIPHON OLE were as previously described.[11,12]

## Financial Disclosure Statement

**V.V.M.** has served as a Scientific Committee member for Johnson & Johnson; received research grants from Aerovate, Altavant, Gossamer Bio, Johnson & Johnson, Merck, and SoniVie; and received consultant fees from Aerami, Aerovate, Altavant, Bayer, Caremark, Corvista, Gossamer Bio, Johnson & Johnson, L.L.C, Merck and United Therapeutics. **L.H.** has served as a Scientific Committee member for Johnson & Johnson, Gossamer Bio and Lung Biotechnology; has received research grants from Johnson & Johnson; has received speaker's fees from Bayer PLC, Johnson & Johnson and Merck; has received support for attending meetings and/or travel from Johnson & Johnson; has been a member of an advisory board for Acceleron, Johnson & Johnson and Merck and is a shareholder in iOWNA and Circular. **J.E.** has received research grant support from Acceleron/Merck, Aerovate, Altavant, Gossamer Bio, Pharmosa/Liquidia, Johnson & Johnson, Lung LLC and Pulmovant, and serves on the consultant or advisory board of United Therapeutics, Aerovate, Gossamer Bio, Liquidia, Merck, Insmed, Pulmovant and Johnson & Johnson. **M.S.** is an employee of Johnson & Johnson. **C.C.F.** and **P.S.** are employees of Johnson & Johnson and hold stock and/or shares in Johnson & Johnson. **S.G.** has had relations, such as funding, with the following subjects that have commercial interests in the pharmaceutical and medical field: Aerovate Therapeutics, Acceleron, Altavant, Bayer, Gossamer Bio, Johnson & Johnson, MSD and United Therapeutics. **N.G.** has served as a Scientific Committee member for Johnson & Johnson; has received grant support, personal fees, and non-financial support from Johnson & Johnson, and has received grant support and personal fees from Bayer Healthcare, Pfizer and GlaxoSmithKline. **R.J.O.** has received consulting, paid speaking or honoraria from Johnson & Johnson, Medtronic, Merck, Respira and United Therapeutics, and has received grant support from Johnson & Johnson, Merck, Respira and Altavant. **S.S.** has served as a Scientific Committee member for Johnson & Johnson; has been a member of advisory boards for MSD and Bayer and has received speaker fees from Orpha Swiss. **Y.T.** has served as a Scientific Committee member for Johnson & Johnson and has received research grants from Nippon Shinyaku. **N.H.K.** has served as a Scientific Committee member for Johnson & Johnson; has received research grants/support from Johnson & Johnson, Bellerophon, Eiger, Gossamer Bio, Lung Biotechnology, SoniVie, and Altavant; has received consultant fees from Bayer, Merck, United Therapeutics, Pulnovo, and Polarean; and speaker fees from Johnson & Johnson and Bayer.

## Data Availability Statement

The data sharing policy of Johnson and Johnson is available online.[30] Requests for access to the study data can be submitted through the Yale Open Data Access project.[31]

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.healun.2025.11.007.

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