10-year data on oral selexipag: Long-term survival, safety, and dosing insights in pulmonary arterial hypertension (PAH) from the GRIPHON study and its open-label extension (OLE)

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Introduction

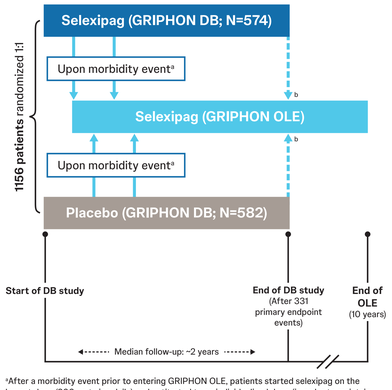
- Selexipag, an oral selective IP prostacyclin receptor agonist, significantly reduced morbidity/mortality risk by 40% versus placebo in the pivotal GRIPHON study[1]
  - The treatment effect of selexipag was consistent whether used as monotherapy, as part of double combination therapy, or as part of triple therapy,[1] and across different risk categories[2–4]
- Results from GRIPHON and its open-label extension (OLE)[5] have guided the use of selexipag in pulmonary arterial hypertension (PAH) clinical practice[6,7]

These analyses from GRIPHON and its OLE report survival among patients treated with selexipag for up to 10 years, including post hoc survival assessments by individual maintenance dose, risk category, background therapy, and time from diagnosis

Methods

- Patients were randomized to selexipag and titrated to individualized doses in GRIPHON (double-blind study; NCT01106014); those who entered its OLE (NCT01112306) were followed for adverse events and survival up to the end of the study (**Figure 1**)
- Assessments included patient characteristics, Kaplan–Meier survival estimates (assessed in the overall population, by individual maintenance dose, by risk category, and by background therapy and time from diagnosis), and safety and tolerability
- All analyses, including for subgroups, are descriptive only:
  - Survival analyses were post hoc, and baseline characteristics were not balanced
  - Subgroups were based on characteristics at selexipag initiation or start of individualized maintenance dose
  - Changes in patient characteristics over the long-term follow-up could not be accounted for

FIGURE 1: Study design



[a]After a morbidity event prior to entering GRIPHON OLE, patients started selexipag on the lowest dose (200 µg twice daily) and uptitrated to an individualized dose (in order to maintain integrity of the DB study). [b]At the end of GRIPHON DB, patients randomized to selexipag entered GRIPHON OLE at the same dose received at the end of the study, and patients randomized to placebo started selexipag at the lowest dose (200 µg twice daily) and uptitrated to their individualized dose. Individualized maintenance dose corresponds to the individual maximum tolerated dose.

DB, double-blind; **OLE**, open-label extension.

Results

Patient demographics and baseline characteristics

- Patient demographics and baseline characteristics are presented in **Table 1**

TABLE 1: Demographics and baseline characteristics

	ITT-selexipag population (N=574)
Female, n (%)	457 (80)
Age, years, mean ± SD	48 ± 15
Time from PAH diagnosis[a], years, median (Q1, Q3)	0.9 (0.3, 2.9)
PAH classification, n (%)	
Idiopathic PAH	312 (54)
Heritable PAH	13 (2)
PAH associated with connective tissue disease	167 (29)
PAH associated with congenital heart disease	60 (10)
PAH associated with HIV	5 (1)
Drug- or toxin-induced PAH	17 (3)
6MWD, m, mean ± SD	359 ± 76
WHO FC, n (%)	
I	4 (1)
II	273 (48)
III	294 (51)
IV	3 (1)
4-strata risk category[b], n (%)	
Low	118 (21)
Intermediate-low	266 (46)
Intermediate-high	177 (31)
High	7 (1)
Background PAH therapy, n (%)	
ERA and PDE5i combination therapy	179 (31)
ERA monotherapy	94 (16)
PDE5i monotherapy	189 (33)
None	112 (20)

Percentages are rounded and may not add up to 100.

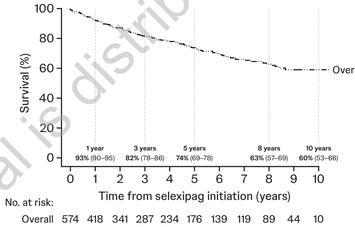
[a]PAH diagnosis confirmed by right heart catheterization. [b]Risk of 1-year mortality calculated according to the 4-strata risk score recommended by the 2022 ESC/ERS guidelines,[6,7] based on at least two of 6MWD, BNP/NT-proBNP, or WHO FC at GRIPHON DB baseline; six patients did not have data available for risk assessment.

6MWD, six-minute walk distance; **BNP/NT-proBNP**, brain natriuretic peptide/N-terminal pro-BNP; **ERA**, endothelin receptor antagonist; **ERS**, European Respiratory Society; **ESC**, European Society of Cardiology; **HIV**, human immunodeficiency virus; **ITT**, intention-to-treat; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor; **Q1**, **Q3**, interquartile range; **SD**, standard deviation; **WHO FC**, World Health Organization functional class.

Overall survival

- The Kaplan–Meier estimates of overall survival rate were 93% at 1 year, 82% at 3 years, 74% at 5 years, 63% at 8 years, and 60% at 10 years (**Figure 2**)

FIGURE 2: Kaplan–Meier curve for time from selexipag initiation to death up to end of treatment + 30 days: Overall survival

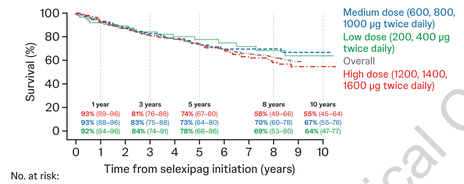


Kaplan–Meier survival estimates (95% confidence intervals) are shown.

Individualized maintenance dose by dose stratum

- The Kaplan–Meier survival estimates for individual maintenance dose by dose stratum are presented in **Figure 3**

FIGURE 3: Kaplan–Meier curve for time from selexipag initiation to death up to end of treatment + 30 days: Individualized maintenance dose by dose stratum

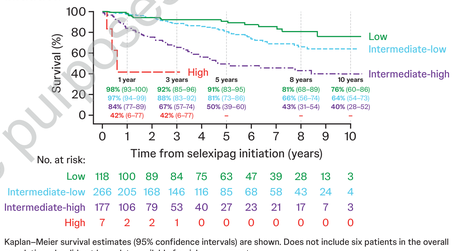


Kaplan–Meier survival estimates (95% confidence intervals) are shown. Does not include eight patients in the overall population who were on an individualized maintenance dose of selexipag <200 µg twice daily and one patient whose individualized maintenance dose of selexipag (700/900 µg twice daily) did not meet the criteria for "medium" dose.

4-strata risk category at selexipag initiation

- The Kaplan–Meier survival estimates for the 4-strata risk category at selexipag initiation are presented in **Figure 4**

FIGURE 4: Kaplan–Meier curve for time from selexipag initiation to death up to end of treatment + 30 days: 4-strata risk category at selexipag initiation

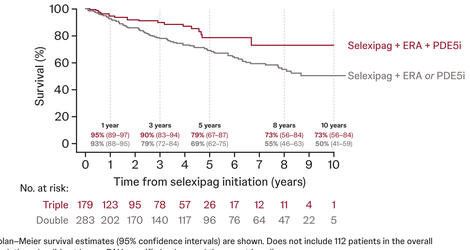


Kaplan–Meier survival estimates (95% confidence intervals) are shown. Does not include six patients in the overall population who did not have data available for risk assessment.

PAH-specific combination therapy regimen at selexipag initiation

- The Kaplan–Meier survival estimates for the PAH-specific combination therapy regimen at selexipag initiation are presented in **Figure 5**

FIGURE 5: Kaplan–Meier curve for time from selexipag initiation to death up to end of treatment + 30 days: PAH-specific combination therapy regimen at selexipag initiation



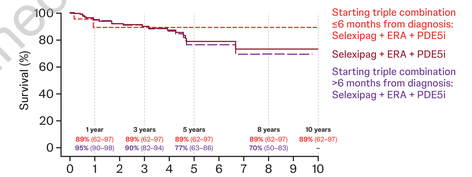
Kaplan–Meier survival estimates (95% confidence intervals) are shown. Does not include 112 patients in the overall population who did not have a PAH-specific background therapy at baseline.

ERA, endothelin receptor antagonist; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor.

Triple combination therapy and time from diagnosis

- The Kaplan–Meier survival estimates for the triple combination therapy and time from diagnosis are presented in **Figure 6**

FIGURE 6: Kaplan–Meier curve for time from selexipag initiation to death up to end of treatment + 30 days: Triple combination therapy and time from diagnosis



Kaplan–Meier survival estimates (95% confidence intervals) are shown. Does not include 112 patients in the overall population who did not have a PAH-specific background therapy at baseline.

ERA, endothelin receptor antagonist; **PAH**, pulmonary arterial hypertension; **PDE5i**, phosphodiesterase type 5 inhibitor.

Safety and exposure

- Median selexipag exposure, total selexipag exposure, and the incidence of adverse events are reported in **Table 2**
  - Median follow-up time from selexipag initiation in GRIPHON was 54 months
  - In total, 176 (31%) patients had been receiving selexipag for ≥5 years
  - Ten (2%) patients had been receiving selexipag for ≥10 years

TABLE 2: Safety and exposure

	ITT-selexipag population (N=574)
Selexipag exposure, months, median (range)	35.8 (0.0–126)
Total selexipag exposure, patient-years	2105.5
Adverse events, n (%)	
Patients with ≥1 adverse event	572 (100)
Patients with ≥1 serious adverse event	368 (64)
Patients with ≥1 adverse event leading to selexipag discontinuation[a]	223 (39)
Patients with ≥1 prostacyclin-associated adverse event leading to selexipag discontinuation	47 (8)
Most frequent adverse events[b], n (%)	
Headache	390 (68)
Diarrhea	265 (46)
Nausea	209 (36)
Pulmonary arterial hypertension worsening	203 (35)
Pain in jaw	156 (27)
Death[c], n (%)	126 (22)

[a]All adverse events leading to discontinuation of selexipag are reported here and not only those considered the primary reason for discontinuation. [b]Occurring in ≥25% of patients. [c]Up to end of treatment + 30 days; most common (>1%) reasons for death were PAH worsening (6%), right ventricular failure (4%), sudden death (2%), and cardiac arrest (1%).

ITT, intention-to-treat; **PAH**, pulmonary arterial hypertension.

Conclusions

- **In the overall population treated with selexipag, 10-year survival was 60% and was consistent across dose groups**
- **These 10-year data provide valuable insights, while earlier timepoints facilitate their contextualization with other datasets.[8,9] We observed 5-year survival of 74% including:**
  - **>80% survival when selexipag was initiated in patients at low and intermediate-low risk, and ~50% survival when it was initiated in intermediate-high risk patients**
  - **~80% survival when selexipag was initiated as part of triple therapy with an endothelin receptor antagonist and a phosphodiesterase type 5 inhibitor, and ~90% survival when this triple therapy regimen was initiated within 6 months of diagnosis**
- **The safety profile of selexipag over this extended period was consistent with previous observations**
- **Despite limitations inherent to long-term, open-label studies, these findings represent the most comprehensive safety, tolerability, and survival data for selexipag and the longest follow-up in a clinical study of any PAH therapy**

Acknowledgments

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