Early initiation of oral selexipag for pulmonary arterial hypertension (PAH): real-world evidence from the EXPOSURE/EXTRACT studies

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Introduction

- Timely initiation of combination treatment in patients with pulmonary arterial hypertension (PAH) is associated with better long-term survival rates and outcomes.[1-3]
- Selexipag is an oral, selective prostacyclin receptor (IP) agonist indicated for the treatment of PAH.[4,5]
- Post-hoc analyses of PAH clinical trials including GRIPHON (NCT01106014) and TRITON (NCT02558231) have associated early initiation of selexipag (within ≤6 months of diagnosis) with improved long-term patient outcomes.[6,7]
- Further insights into the impact of timing of selexipag initiation on clinical outcomes of PAH in real-world settings are needed.

Objective

- To use real-world data from EXPOSURE and EXTRACT to describe the clinical characteristics, treatment patterns, and outcomes of patients with PAH based on timing of selexipag initiation relative to time from PAH diagnosis: ≤6 months or >6 months.

Methods

- Pooled data from EXPOSURE and EXTRACT were used for this analysis, which included patients initiating selexipag who had follow-up information up to data cut-off of July 2023.
  - EXPOSURE (EUPAS19085) (2017–ongoing): multicenter, prospective, observational study of patients with PAH initiating a new PAH-specific therapy in clinical practice, in Europe and Canada.
  - EXTRACT (EUPAS49227) (2016–2022): retrospective medical chart review of patients with PAH not eligible for enrollment in EXPOSURE due to initiating selexipag >30 days prior to the start of EXPOSURE.
- Patients were grouped by time from PAH diagnosis to selexipag initiation (baseline):
  - Earlier initiators (≤6 months)
  - Later initiators (>6 months)
- Patients were observed during the selexipag exposure period: from baseline to date of last available information, selexipag discontinuation (>7 days without selexipag therapy) or death, whichever occurred first.
- An outcome model for hospitalization was developed using a Poisson regression adjusted for selected covariates at selexipag initiation.
  - Covariates included: age, sex, country, World Health Organization functional class, 6-minute walk distance, PAH etiology, time since diagnosis, N-terminal pro-brain natriuretic peptide, mean right atrial pressure, cardiac index, mixed venous oxygen saturation, pericardial effusion, renal impairment, PAH-specific treatment regimen, and medical history of comorbidities/ cardiovascular risk factors.

Results

- As of July 2023, 154 (16%) patients initiated selexipag ≤6 months from PAH diagnosis (earlier initiators) and 822 (84%) initiated selexipag >6 months from PAH diagnosis (later initiators), all with follow-up information.
  - Among the 154 earlier initiators, 131 were from EXPOSURE and 23 from EXTRACT.
  - Among the 822 later initiators, 676 were from EXPOSURE and 146 from EXTRACT.

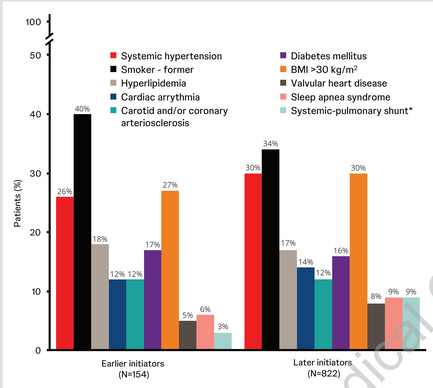
Table 1. Patient characteristics at baseline

	Earlier initiators N=154	Later initiators N=822
Age, median (Q1, Q3), years	58 (42, 70)	60 (46, 70)
Female, n (%)	106 (69)	596 (73)
Time since diagnosis, n Median (Q1, Q3), years	154 0.3 (0.1, 0.3)	756* 2.9 (1.2, 7.5)
PAH etiology, n Idiopathic/heritable, n (%) PAH-CTD, n (%) PAH-CHD, n (%) Other†, n (%)	154 85 (55) 47 (31) 8 (5) 14 (9)	822 466 (57) 201 (24) 115 (14) 40 (5)
WHO FC, n I, n (%) II, n (%) III, n (%) IV, n (%)	143 6 (4) 42 (29) 89 (62) 6 (4)	700 20 (3) 232 (33) 432 (62) 16 (2)
6MWD, n Median (Q1, Q3), m	103 362 (230, 426)	435 370 (281, 468)
NT-proBNP, n Abnormal‡, n (%) Median (Q1, Q3) for patients with abnormal values, ng/L	118 100 (85) 1065 (531, 2294)	569 427 (75) 955 (428, 2307)
Risk of one-year mortality§, n Low, n (%) Intermediate-low, n (%) Intermediate-high, n (%) High, n (%)	130 13 (10) 32 (25) 56 (43) 29 (22)	612 82 (13) 206 (34) 202 (33) 122 (20)
Right heart catheterization performed¶, n (%)	145 (95)	481 (59)
Pulmonary vascular resistance, n Median (Q1, Q3), Wood Units	137 10.0 (6.7, 14.0)	448 8.0 (5.9, 11.0)
Mean pulmonary arterial pressure, n Median (Q1, Q3), mmHg	140 49 (41, 58)	486 46 (40, 56)
Mean right atrial pressure, n Median (Q1, Q3), mmHg	133 9 (6, 12)	440 8 (5, 11)
Pulmonary capillary wedge pressure, n Median (Q1, Q3), mmHg	137 10 (7, 12)	454 10 (7, 13)
Mixed venous oxygen saturation, n >65%, n (%)	117 48 (41)	364 222 (61)
Cardiac index, n Median (Q1, Q3), L/min/m²	137 2.2 (1.7, 2.8)	438 2.6 (2.2, 3.2)
DLCO,** n Median (Q1, Q3), %	74 52 (35, 74)	209 46 (30, 65)
Pericardial effusion¶, n Yes, n (%)	154 30 (19)	820 98 (12)
Renal function impairment, n (%) Yes, n (%)	150 37 (25)	802 161 (20)

*Patients that did not have time from diagnosis information available were assigned to the later initiators group. †Includes patients with drug- and toxin-induced PAH, PAH associated with portal hypertension, HIV infection or schistosomiasis, or pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis. ‡Per physician judgment. §4-strata risk scores calculated for patients who had data available for BNP/NT-proBNP and WHO FC and/or 6MWD[1,2]. ¶Performed within 12 months prior to or at baseline. **Assessed within 3 months prior to or at baseline.

6MWD: 6-minute walk distance; BNP: brain natriuretic protein; CHD: congenital heart disease; CTD: connective tissue disease; DLCO: diffusing capacity of the lungs for carbon monoxide; HIV: human immunodeficiency virus; NT-proBNP: N-terminal proBNP; PAH: pulmonary arterial hypertension; Q1, Q3: interquartile range; WHO FC: World Health Organization functional class.

Figure 1. Cardiovascular risk factors



Patients may have had more than one cardiovascular risk factor. *Systemic-pulmonary shunts were recorded as cardiac shunts in the case report form. BMI: body mass index.

Table 2. Selexipag titration and dosing

	Earlier initiators N=154	Later initiators N=822
Exposure duration, median (Q1, Q3), months	12.8 (4.1, 28.4)	13.0 (4.1, 29.0)
Titration duration, median (Q1, Q3), months	2.1 (1.0, 3.2)	1.8 (1.0, 3.0)
Titration status at cut-off*, n (%) Completed Discontinued Ongoing	135 (88) 11 (7) 7 (5)	721 (88) 57 (7) 31 (4)
Individualized dose†, n Median (Q1, Q3), µg b.i.d.	135 800 (400, 1400)	721 800 (400, 1200)
Patients with further dose adjustments post-titration, n/N (%)	38/135 (28)	250/721 (35)

*During titration, the highest dose taken during the first 24 weeks was identified and titration was considered completed once a stable dose was taken for ≥3 weeks after the start of the highest dose. †Individualized dose was the first dose started after the highest dose in 24 weeks that lasted for ≥3 weeks without dose interruption and/or dose change. b.i.d.: twice daily; Q1, Q3: interquartile range.

Table 3. Treatment patterns at baseline

	Earlier initiators N=154	Later initiators N=822
Monotherapy, n (%) Selexipag	**5 (3)** 5 (3)	**14 (2)** 14 (2)
Double combination therapy, n (%) ERA + selexipag PDE5i + selexipag Other double combination therapies*	**26 (17)** 13 (8) 12 (8) 1 (<1)	**90 (11)** 42 (5) 42 (5) 6 (<1)
Triple combination therapy, n (%) ERA + PDE5i + selexipag ERA + sGC stimulator + selexipag Other triple combination therapies*	**115 (75)** 108 (70) 7 (5) 0	**666 (81)** 613 (75) 50 (6) 3 (<1)
>3 PAH therapies, n (%)	**5 (3)**	**31 (4)**
Unknown†, n (%)	**3 (2)**	**21 (3)**

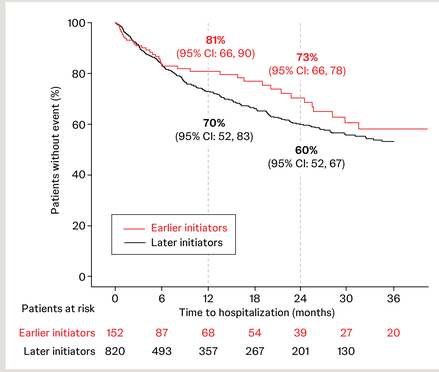
*Other double combination: PGI_2 + selexipag (Earlier: n=0; Later: n=3), sGC stimulator + selexipag (Earlier: n=1; Later: n=3); Other triple combination: ERA + PGI_2 + selexipag (Earlier: n=0; Later: n=1), PDE5i + PGI_2 + selexipag (Earlier: n=0; Later: n=2). †Includes patients with therapies that have missing start and end dates and those for whom it cannot be determined if some treatments are prior or current. ERA: endothelin receptor antagonist; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase 5 inhibitor; PGI_2: prostacyclin and its analogs; sGC: soluble guanylate cyclase.

Table 4. Selexipag discontinuations and adverse events during exposure period

	Earlier initiators N=154	Later initiators N=822
Patients who discontinued selexipag, n (%)	49 (32)	349 (42)
Reasons for discontinuation, n (%) Tolerability / adverse event Death PAH disease progression Treatment non-compliance Administrative Unknown Missing	 24 (16) 16 (10) 6 (4) 0 3 (2) 0 0	 143 (17) 99 (12) 65 (8) 11 (1) 18 (2) 12 (2) 1 (<1)
Patients with an adverse event*, n (%) **Most frequent adverse events†,** n (%) Diarrhea Headache Nausea	63 (41) 12 (8) 11 (7) 7 (5)	390 (47) 115 (14) 127 (15) 62 (8)

*The following frequently known adverse reactions associated with the mode of action of selexipag (headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia) were only collected or reported on an adverse event / adverse drug reaction form if they fulfilled any of the following: any seriousness criteria; lead to selexipag discontinuation or dose reduction, or introduction of symptomatic treatment; or reflect an unusual pattern of severity based on prescriber's / investigator's medical judgment. †Occurring in >7% of patients in any group. PAH: pulmonary arterial hypertension.

Figure 2. Outcomes during selexipag exposure: first all-cause hospitalization



KM curves illustrating time to all-cause hospitalizations during the selexipag exposure period. KM estimates (95% CI) shown at 12 and 24 months. Patients with a hospitalization ongoing at baseline were excluded from the KM analysis. Each curve is cut at the first timepoint where <10% of patients in the group are left at risk. CI: confidence interval; KM: Kaplan-Meier.

Table 5. Hospitalizations and mortality during the selexipag exposure period

	Earlier initiators N=154	Later initiators N=822
Exposure duration, median (Q1, Q3), months	12.8 (4.1, 28.4)	13.0 (4.1, 29.0)
Patients hospitalized, n (%)	38 (25)	253 (31)
Number of hospitalizations*, n PAH-related†, n/N (%)	85 28/65 (43)	477 245/412 (59)
Hospitalization incidence, per 100-person years (95% CI) All-cause hospitalization PAH-related hospitalization	 19.5 (13.3, 27.4) 10.0 (6.3, 15.2)	 25.3 (22.0, 29.0) 15.2 (13.0, 17.7)
All-cause hospitalization – Earlier vs Later initiators Incidence rate ratio (95% CI)‡	0.69 (0.45, 1.04)	
All-cause deaths, n (%)	16 (10)	100 (12)
Mortality rate, per 100-person years (95% CI) All-cause death PAH-related death	 6.7 (3.9, 10.9) 4.2 (2.0, 7.7)	 8.2 (6.7, 10.0) 4.5 (3.4, 5.9)

*Hospitalizations ongoing at selexipag initiation and during the exposure period; patients could have experienced more than one hospitalization during the exposure period. †The PAH-related status was unknown for 9 hospitalizations in the earlier initiators and 25 hospitalizations in the later initiators. ‡Incidence rate ratio (95% CI) obtained using Poisson model estimates for all 10 imputations and adjusted for selected covariates at selexipag initiation. Earlier initiators exposure: 194.7 person-years. Later initiators exposure: 998.6 person-years. CI: confidence interval; PAH: pulmonary arterial hypertension; Q1, Q3: interquartile range.

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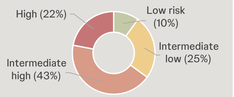
Key Takeaways

~150 (16%) patients initiated selexipag within 6 months of PAH diagnosis

58 years old

0.3 years since diagnosis



75% on triple oral therapy

16% discontinued selexipag due to AE/tolerability

Hospitalization free

Trend for **30% reduction of incidence rate of hospitalization** vs later initiators

These real-world data suggest a trend favoring better outcomes for PAH patients treated with selexipag within 6 months of PAH diagnosis

Conclusions

- Earlier initiators started selexipag treatment a median of ~3 months after their PAH diagnosis.
  - At baseline, earlier initiators had higher risk of 1-year mortality (65% higher risk groups) vs later initiators (53%), and worse hemodynamics.
  - Selexipag was predominantly initiated as part of triple combination in both groups.
- While discontinuations due to an adverse event were similar between the groups, a lower proportion of earlier initiators discontinued selexipag compared to later initiators.
  - Overall, the safety and tolerability profile of selexipag was generally consistent between the groups, and the most frequent adverse events were associated with the mode of action of selexipag.
- There was a trend for a lower rate of hospitalization for earlier initiators compared to those starting later.
  - Mortality rates for all-cause and PAH-related deaths were similar between the groups.
- These contemporary real-world findings complement existing clinical data and support the benefit of early selexipag initiation in optimizing long-term patient outcomes.

Disclosures

- The study was funded by Johnson & Johnson.
- Stefan Söderberg has had relations, such as funding, with the following subjects that have commercial interests in the pharmaceutical and medical field: Johnson & Johnson and MSD.

Acknowledgements

- Medical writing support was provided by Elizabeth Oliver, PhD (Cactus Life Sciences, Meggen, Switzerland) and funded by Johnson & Johnson.

Poster presented at the ISHLT 45th Annual Meeting & Scientific Sessions on 27–30th April 2025, Boston, MA, USA.

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