Real-world clinical outcomes according to individualised selexipag dose in pulmonary arterial hypertension (PAH)

Lange TJ[1,2], Escribano-Subias P[3], Borissoff JI[4], Fernandes CC[4], Fontana M[5], Venkatesh A[4], Söderberg S[6], Gaine S[7]

[1]Department of Pulmonology, Kreisklinik Bad Reichenhall, Bad Reichenhall, Germany; [2]Faculty of Medicine, Department Internal Medicine II, Regensburg University, Regensburg, Germany; [3]Pulmonary Hypertension Unit, Cardiology Department, CIBERCV, Hospital 12 de Octubre, Madrid, Spain; [4]Johnson & Johnson, Allschwil, Switzerland; [5]Johnson & Johnson, Milan, Italy; [6]Department of Public Health and Clinical Medicine, Medicine, Umeå University, Umeå, Sweden; [7]National Pulmonary Hypertension Unit, Mater Misericordiae University Hospital, Dublin, Ireland.

PA5156

Introduction

- Selexipag is an oral, selective prostacyclin receptor (IP) agonist indicated for the treatment of pulmonary arterial hypertension (PAH).[1,2]
- The recommended starting dose of selexipag is 200 µg twice daily (b.i.d.).[1,2]
  - To optimise efficacy while minimising side effects, selexipag is titrated in 200 µg increments to a patient's maximally tolerated dose (their individualised dose [up to a maximum dose of 1600 µg b.i.d.]).
  - If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.
- In the real-world, the observed median individualised dose for selexipag was:
  - 1100 µg b.i.d. in the SPHERE study (NCT03278002).[3]
  - 800 µg b.i.d. in the EXPOSURE study (EUPAS19085).[4]
- Similar outcomes across different selexipag dose groups (low, medium, high)* were observed in GRIPHON (NCT01106014)[5] and its open-label extension (NCT01112306).[6]
  - Real-world data supported these findings with similar survival up to 18 months observed in the SPHERE registry and similar all-cause and PAH-related hospitalisations reported from US claims data across different dose groups.[3,7]
- Further insights into the impact of individualised dose of selexipag on clinical outcomes in patients with PAH in real-world settings would be of interest.

* Dose groups in GRIPHON: low (200, 400 µg b.i.d.), medium (600, 800, 1000 µg b.i.d.) and high (1200, 1400, 1600 µg b.i.d.); Dose groups in SPHERE: low (200–400 µg b.i.d.), medium (600–1000 µg b.i.d.) and high (>1200 µg b.i.d.); Dose groups from US claims data: low (200–400 µg b.i.d.), medium (600–1000 µg b.i.d.) and high (1200–1600 µg b.i.d.).

Objective

- To use real-world data from EXPOSURE and EXTRACT to describe the clinical characteristics, treatment patterns, and outcomes of patients with PAH, categorised based on median individualised dose of selexipag.

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): multicentre, 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 enrolment in EXPOSURE due to initiating selexipag >30 days prior to the start of EXPOSURE.
- The median individualised dose of selexipag in EXPOSURE[4] and this pooled dataset was 800 µg b.i.d; this was used to group patients into those receiving a lower individualised dose (≤800 µg b.i.d.) or a higher individualised dose (>800 µg b.i.d.) to allow for sufficient patients in each group to run the outcome model.
- Patients were observed during the first selexipag exposure period: from selexipag initiation to date of last available information, or selexipag discontinuation (>7 days without selexipag therapy) or death, whichever occurred first.
- Clinical worsening was defined as all-cause death, first PAH-related hospitalisation, initiation of parenteral prostacyclin therapy or registration to lung transplantation list.
- An outcome model for clinical worsening 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 (6MWD), PAH aetiology, time since diagnosis, N-terminal pro-brain natriuretic peptide (NT-proBNP), mean right atrial pressure, cardiac index, mixed venous oxygen saturation, pericardial effusion, body mass index, renal impairment, PAH-specific treatment regimen and medical history of comorbidities/cardiovascular risk factors.
  - For missing categorical variables, values were categorised as 'Missing/Unknown' and included as such in the analyses. For missing continuous variables, multiple imputation was applied.
- All other data are descriptive.

Results

- As of July 2023, 492 (59%) patients received a lower dose of selexipag (≤800 µg b.i.d.) and 341 (41%) a higher dose (>800 µg b.i.d.), all with follow-up information.

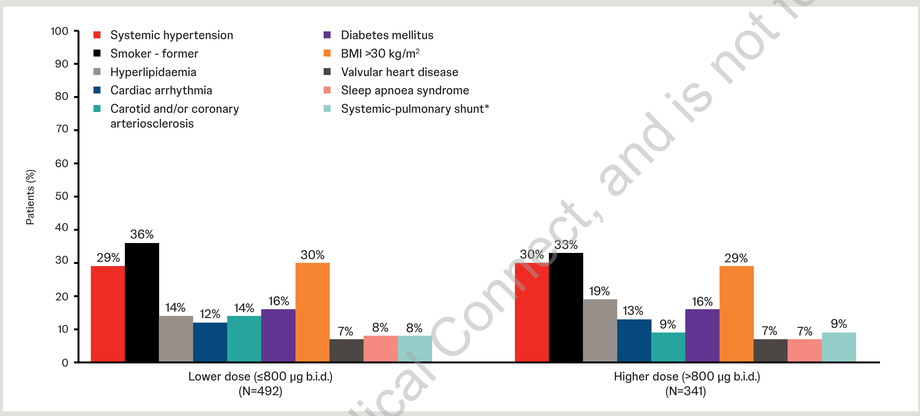
Table 1. Patient characteristics at selexipag initiation

	Lower dose ≤800 µg b.i.d. (n=492)	Higher dose >800 µg b.i.d. (n=341)
Age, median (Q1, Q3), years	60 (47, 71)	58 (44, 68)
Female, n (%)	360 (73)	231 (68)
Time since diagnosis, n Median (Q1, Q3), years	456 2.4 (0.8, 6.4)	323 1.8 (0.7, 5.9)
PAH aetiology, n (%) Idiopathic/heritable PAH-CTD PAH-CHD Other*	 270 (55) 141 (29) 53 (11) 28 (6)	 201 (59) 72 (21) 49 (14) 19 (6)
WHO FC, n I, n (%) II, n (%) III, n (%) IV, n (%)	423 8 (2) 130 (31) 277 (65) 8 (2)	303 12 (4) 112 (37) 173 (57) 6 (2)
6MWD, n Median (Q1, Q3), m	265 360 (244, 451)	192 400 (311, 483)
BMI, n Median (Q1, Q3), kg/m²	426 26 (22, 31)	302 27 (24, 31)
NT-proBNP, n Abnormal†, n (%) Median (Q1, Q3) for patients with abnormal values, ng/L	377 268 (76) 997 (427, 2386)	261 188 (78) 862 (466, 1958)
Risk of 1-year mortality‡, n Low, n (%) Intermediate-low, n (%) Intermediate-high, n (%) High, n (%)	376 54 (14) 113 (30) 125 (33) 84 (22)	262 31 (12) 97 (37) 89 (34) 45 (17)
Right heart catheterisation performed§, n (%) **Pulmonary vascular resistance,** n Median (Q1, Q3), Wood Units **Mean pulmonary arterial pressure,** n Median (Q1, Q3), mmHg **Mean right atrial pressure,** n Median (Q1, Q3), mmHg **Pulmonary capillary wedge pressure,** n Median (Q1, Q3), mmHg **Mixed venous oxygen saturation,** n >65%, n (%) **Cardiac index,** n Median (Q1, Q3), L/min/m²	311 (64) 284 8.2 (6.1, 12.1) 296 48 (40, 57) 279 8 (5, 12) 286 10 (8, 12) 235 121 (51) 283 2.5 (2.0, 3.0)	220 (65) 214 8.3 (6.5, 11.8) 216 48 (42, 57) 204 8 (5, 11) 213 10 (7, 13) 171 100 (58) 206 2.5 (2.0, 3.2)
DLCO¶, n Median (Q1, Q3), %	146 46 (30, 65)	97 56 (36, 70)
Pericardial effusion‖, n Yes, n (%)	491 54 (11)	341 54 (16)
Renal function impairment, n Yes, n (%)	476 100 (21)	338 70 (21)

*Includes patients with drug- or toxin-induced PAH, PAH associated with portal hypertension, HIV infection, schistosomiasis, or pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis. †Per physician judgement. ‡4-strata risk scores calculated for patients who had data available for BNP/NT-proBNP and WHO FC and/or 6MWD.[8,9] §Performed within 12 months prior to or at selexipag initiation. ¶Assessed within 3 months prior to or at selexipag initiation.

6MWD: 6-minute walk distance; b.i.d.: twice daily; BMI: body mass index; BNP: brain natriuretic peptide; 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 pro-BNP; PAH: pulmonary arterial hypertension; Q1, Q3: interquartile range; WHO FC: World Health Organization functional class.

Figure 1. Cardiovascular risk factors at selexipag initiation



*Systemic-pulmonary shunts were recorded as cardiac shunts in the case report form. b.i.d.: twice daily; BMI: body mass index.

Table 2. Selexipag titration and dosing

	Lower dose ≤800 µg b.i.d. (n=492)	Higher dose >800 µg b.i.d. (n=341)
Exposure duration, median (Q1, Q3), months	13.0 (4.5, 28.2)	21.0 (9.1, 33.3)
Titration duration*, median (Q1, Q3), months	1.2 (0.6, 2.3)	2.7 (1.9, 3.9)
Individualised dose† Median (Q1, Q3), µg b.i.d.	600 (300, 800)	1400 (1200, 1600)
Patients with further dose adjustments post-titration, n/N (%)	157/492 (32)	123/341 (36)

*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. †Individualised 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.

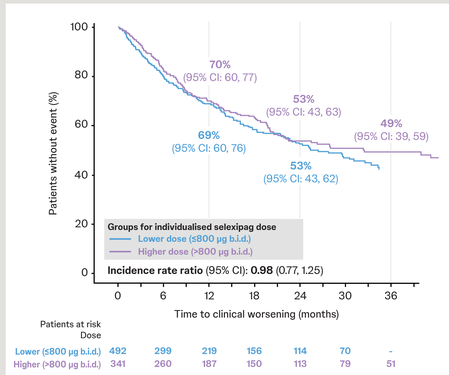
Table 3. Treatment patterns at selexipag initiation

	Lower dose ≤800 µg b.i.d. (n=492)	Higher dose >800 µg b.i.d. (n=341)
Monotherapy, n (%) Selexipag	8 (2) 8 (2)	7 (2) 7 (2)
Double combination therapy, n (%) ERA + selexipag PDE5i + selexipag sGC stimulator + selexipag	63 (13) 29 (6) 31 (6) 3 (1)	35 (10) 18 (5) 16 (5) 1 (<1)
Triple combination therapy, n (%) ERA + PDE5i + selexipag ERA + sGC stimulator + selexipag ERA + PGI_2 + selexipag	404 (82) 366 (74) 37 (8) 1 (<1)	279 (82) 261 (77) 17 (5) 0
>3 PAH therapies, n (%)	3 (1)	14 (4)
Unknown‡, n (%)	14 (3)	6 (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.

b.i.d.: twice daily; ERA: endothelin receptor antagonist; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase 5 inhibitor; PGI_2: prostacyclin and its analogues; sGC: soluble guanylate cyclase.

Figure 2. Time to clinical worsening during the selexipag exposure period



Time to clinical worsening during the selexipag exposure period illustrated using KM curves. Each curve is cut at the first timepoint where <10% of patients in the group are left at risk. KM estimates (95% CI) shown at 12, 24 and 36 months. For the lower dose group, patient numbers were insufficient at 36 months to calculate a KM estimate. b.i.d.: twice daily; CI: confidence interval; KM: Kaplan-Meier.

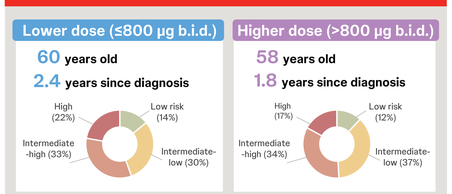
Table 4. Selexipag discontinuations and adverse events during exposure period

	Lower dose ≤800 µg b.i.d. (n=492)	Higher dose >800 µg b.i.d. (n=341)
Patients who discontinued selexipag, n (%)	218 (44)	113 (33)
Reasons for discontinuation, n (%) Tolerability/adverse event Death PAH disease progression Administrative Unknown Treatment non-compliance Missing	 99 (20) 70 (14) 27 (5) 8 (2) 8 (2) 6 (1) 0	 20 (6) 39 (11) 39 (11) 10 (3) 3 (1) 1 (<1) 1 (<1)
Patients with an adverse event*, n (%) **Most frequent adverse events†,** n (%) Headache Diarrhoea Nausea	236 (48) 73 (15) 65 (13) 36 (7)	173 (51) 48 (14) 55 (16) 21 (6)

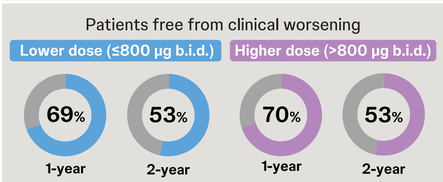
*The following frequently known adverse reactions associated with the mode of action of selexipag (headache, diarrhoea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia) were only collected or reported on an adverse event/adverse drug reaction form if they fulfilled any of 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 judgement. †Occurring in >7% of patients in any group. b.i.d.: twice daily; PAH: pulmonary arterial hypertension.

Key Takeaways

>800 patients with PAH treated with selexipag were included in this analysis, with up to 3 years of follow-up data



>80% initiated selexipag as part of triple oral therapy



These real-world data suggest no differences in clinical worsening between groups when patients were titrated to their individualised selexipag dose

Conclusions

- At selexipag initiation, patients in both groups were predominantly prevalent, with the majority starting treatment as part of triple combination therapy.
- The lower dose group had a slightly longer time since diagnosis, a higher proportion of patients with connective tissue disease, higher NT-proBNP levels and a lower 6MWD.
- The time to clinical worsening was similar between the groups when adjusted for characteristics at the time of selexipag initiation.
  - The proportion of patients free from clinical worsening events was approximately 70% at 1 year and 53% remained event-free at 2 years for both groups.
- Patients in the lower dose group had a shorter selexipag exposure duration and were more likely to discontinue selexipag due to tolerability. This suggests that there may be an opportunity to optimise selexipag titration, including proactive management of side effects, so patients can receive their maximally tolerated dose.
- These real-world data suggest no differences in time to clinical worsening between groups when patients were titrated to their individualised dose, supporting the individualised dosing approach for selexipag.

Disclosures

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