Selexipag in pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD): real-world evidence from EXPOSURE

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Introduction

- Patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) tend to have a worse prognosis than those with idiopathic PAH (IPAH)[1].
- Long-term studies assessing morbidity and mortality in PAH, including SERAPHIN and GRIPHON, have reported consistent treatment effects between PAH-CTD and IPAH patients[2–5].
- Selexipag is an oral, selective prostacyclin receptor (IP) agonist indicated for the treatment of PAH, including patients with PAH-CTD[6].
  - Treatment recommendations support adding selexipag at first follow-up to existing treatment regimens among patients who do not display excellent survival prospects, i.e., those who do not reach low risk status[7,8].
- Further insights into the clinical outcomes of selexipag-treated patients with PAH-CTD in real-world settings are needed.

Objective

- To describe the characteristics, treatment patterns, tolerability, and outcomes of patients with PAH-CTD treated with selexipag in clinical practice, using data from the EXPloratory Observational Study of Uptravi in Real-lifE (EXPOSURE) study.

Methods

- EXPOSURE (EUPAS19085): ongoing observational, multicenter, prospective study of PAH patients newly initiating PAH-specific therapy in clinical practice, in Europe and Canada.
- This analysis included consecutively enrolled PAH-CTD patients newly initiating selexipag and with follow-up information from Sep 2017 to Nov 2022.
- Patients were observed during the selexipag exposure period: from baseline (selexipag initiation) to date of last available information*.
- All analyses were descriptive; no formal statistical comparisons made.

*Or selexipag discontinuation (>7 days without selexipag therapy) or death, whichever occurred first.

Results

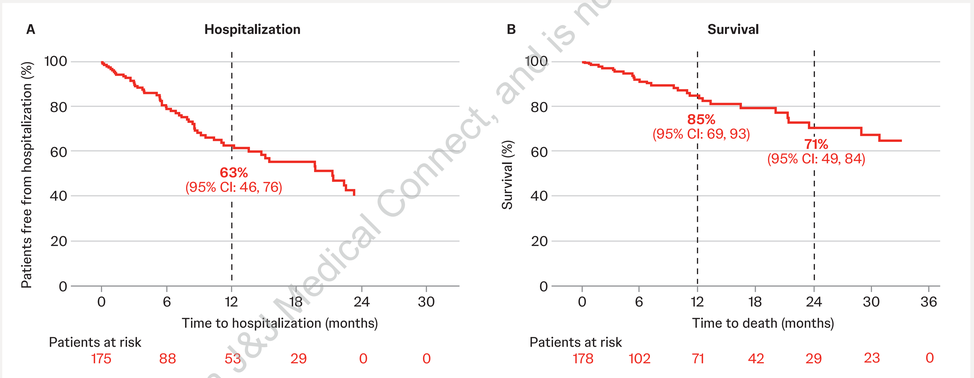
- As of November 2022 there were 178 (26%) PAH-CTD patients out of 698 PAH patients initiated on selexipag and with follow-up information.

Table 1. Patient characteristics at baseline

Characteristic at baseline	PAH-CTD N = 178
Age, median (Q1, Q3), years	68 (59, 74)
Female, n (%)	156 (88)
Time since diagnosis, n	172
Median (Q1, Q3), years	1.7 (0.6, 4.0)
CTD subgroup, n (%)	
Systemic sclerosis	127 (71)
Mixed CTD	15 (8)
Systemic lupus erythematosus	12 (7)
Rheumatoid arthritis	10 (6)
Sjogren's syndrome	8 (4)
Undifferentiated CTD	6 (3)
WHO functional class, n	152
I / II, n (%)	52 (34)
III / IV, n (%)	100 (66)
6-minute walk distance, n	106
Median (Q1, Q3), m	300 (236, 366)
NT-proBNP, n	133
Abnormal (per physician judgement), n (%)	111 (83)
Median (Q1, Q3) for patients with abnormal values, ng/L	1250 (531, 2747)
4-strata risk category*, n	138
Low, n (%)	7 (5)
Intermediate-low, n (%)	34 (25)
Intermediate-high, n (%)	55 (40)
High, n (%)	42 (30)
Right heart catheterization performed†, n (%)	124 (70)
Pulmonary vascular resistance, n	118
Median (Q1, Q3), Wood units	7.6 (5.4, 10.9)
Mean pulmonary arterial pressure, n	121
Median (Q1, Q3), mmHg	44 (37, 51)
Mean right atrial pressure, n	118
Median (Q1, Q3), mmHg	8 (5, 11)
Pulmonary arterial wedge pressure, n	118
Median (Q1, Q3), mmHg	10 (7, 12)
Mixed venous oxygen saturation, n	99
>65%, n (%)	53 (54)
Cardiac index, n	119
Median (Q1, Q3), L/min/m²	2.4 (2.0, 3.1)
DLCO‡, n	57
Median (Q1, Q3), %	32 (24, 46)
Pericardial effusion‡, n	178
Yes, n (%)	32 (18)

*4-strata risk scores calculated for patients who had data available for BNP/NT-proBNP and WHO FC and/or 6MWD[7,8]. †Performed within 12 months of baseline. ‡Assessed within 3 months prior to or at baseline. BNP: brain natriuretic peptide; DLCO: diffusing capacity of lung for carbon monoxide; NT-proBNP: N-terminal pro-BNP; PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease; WHO: World Health Organization.

Figure 1. Outcomes during selexipag exposure: A) first all-cause hospitalization and B) all-cause death



KM estimates (95% CI) shown at 12 months. The KM curve is cut at the first timepoint where <10% of patients in the group are left at risk. CI: confidence interval; KM: Kaplan-Meier; PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease.

Table 2. Selexipag titration and dosing

	PAH-CTD N = 178
Exposure duration, median (Q1, Q3), months	8.6 (2.5, 17.2)
Titration duration, median (Q1, Q3), months	1.5 (0.7, 2.8)
Titration status at cut-off*, n (%)	
Completed	151 (85)
Discontinued	17 (10)
Ongoing	10 (6)
Individualized dose†, n	151
Median (Q1, Q3), µg b.i.d	600 (400, 1000)
Patients with further dose adjustments post-titration, n/N (%)	43/151 (28)

*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; PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease; Q1, Q3: interquartile range.

- 80% (n=142) of patients initiated selexipag as triple oral therapy, mostly (92%; n=131) in combination with both an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor.
- The majority (69%) of patients initiating triple oral combination therapy were escalated from double oral combination therapy, and most (>75%) had been on double therapy for at least one year prior to treatment escalation with selexipag.

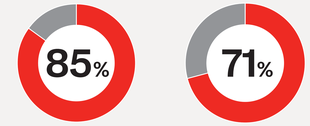
Table 3. Selexipag discontinuations and adverse events

	PAH-CTD N = 178
Exposure duration, median (Q1, Q3), months	8.6 (2.5, 17.2)
Patients who discontinued selexipag, n (%)	79 (44)
Time to discontinuation, median (Q1, Q3), months	4.3 (1.2, 11.1)
Reasons for discontinuation, n (%)	
Tolerability / adverse event	36 (20)
Death	29 (16)
PAH disease progression	8 (4)
Administrative	4 (2)
Treatment non-compliance	1 (<1)
Unknown	1 (<1)
Patients with an adverse event*, n (%)	70 (39)
Most frequent adverse events†, n (%)	
Diarrhea	20 (11)
Headache	13 (7)
Dyspnea	9 (5)

*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 not collected nor reported on an adverse event / adverse drug reaction form, unless 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 ≥5% of patients. PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease; Q1, Q3: interquartile range.

Key takeaway

Encouraging survival outcomes for PAH-CTD patients treated with selexipag



The time since diagnosis and disease severity at selexipag initiation suggest an opportunity for earlier escalation

- 1.7 years since diagnosis
- 70% Intermediate-high risk or High risk

80% Initiated selexipag as part of **triple oral therapy** and across all risk categories

20% Selexipag discontinuations due to tolerability/AEs

Conclusions

- The majority of patients with PAH-CTD initiated selexipag as part of triple oral combination therapy and across all four strata of one-year mortality risk.
- The 1-year and 2-year Kaplan-Meier survival estimates were 85% and 71%, respectively.
- The safety and tolerability of selexipag were consistent with the known profile of selexipag and no new safety signals were observed.
- Our findings suggest an opportunity to optimize the benefits of selexipag among patients with PAH-CTD by moving away from escalation in response to clinical deterioration, towards sooner escalation to prevent clinical deterioration.

Authors relevant interests

Sean Gaine has had relations, such as funding, with the following subjects that have commercial interests in the pharmaceutical and medical field: Aerovate Therapeutics, Acceleron Pharma Inc, Altavant, Gossamer Bio, Johnson & Johnson, MSD and United Therapeutics. Tobias J Lange has received speaker fees and/or consultancy fees and/or financial and non-financial support for participation in scientific events and/or participated on a Data Safety Monitoring Board or Advisory Board for Acceleron Pharma, AOP orphan pharmaceuticals, Bayer, BMS, Böhringer Ingelheim, CGI medicare, Ferrer, Gossamer Bio, Johnson & Johnson, MSD, and Pfizer.

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Disclosures

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