RESEARCH ARTICLE

Selexipag in patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD): Real-world experience from EXPOSURE

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Abstract

Selexipag is indicated for the treatment of pulmonary arterial hypertension (PAH), including PAH associated with connective tissue disease (CTD), and further insights into the management of selexipag-treated PAH-CTD patients in clinical settings are needed. These analyses of the ongoing, multicenter, prospective EXPOSURE (EUPAS19085) study describe characteristics, treatment patterns, tolerability, and outcomes of PAH-CTD patients initiating selexipag in Europe/Canada. All analyses were descriptive, with idiopathic PAH patients who typically display better prognosis included for context. Six hundred ninety-eight selexipag-treated patients had follow-up information; 178 (26%) had PAH-CTD. The median age was 68 years, patients were predominantly female (88%), and with WHO functional class III symptoms (63%); the median time since diagnosis was 1.7 years. There were 5% patients at low, 25% intermediate-low, 40% intermediate-high, and 30% high risk of 1-year mortality, according to the ESC/ERS 4-strata risk score. Most (80%) initiated selexipag as a triple oral therapy, and most of these (62%) remained on triple therapy 6 months post-baseline. Over a median (Q1−Q3) selexipag exposure period of 8.6 (2.5−17.2) months, 79 (44%) patients discontinued selexipag; 36 (20%) due to tolerability/adverse events. Sixty (34%) patients were hospitalized at least once; 120 hospitalizations occurred, with 49 (48%) deemed PAH-related. Survival at 1 year was 85%, and at 2 years was 71%; 29 (16%) patients died. These results describe the use of combination therapy with selexipag for patients with PAH-CTD. These findings suggest an opportunity to optimize the benefits of selexipag among patients with PAH-CTD by moving from escalating after years in response to clinical deterioration to escalating sooner to prevent clinical deterioration.

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Care of patients with pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) is particularly complex, and these patients tend to have a worse prognosis than those with idiopathic PAH (IPAH).[1–4] These patients are a prominent group among PAH and have typically been enrolled in randomized controlled trials (RCTs) of PAH patients. Earlier, short-term RCTs that assessed exercise capacity, suggested an attenuated treatment response to PAH-specific therapies among PAH-CTD populations.[5] However, more recent long-term studies designed to assess morbidity and mortality reported consistent positive treatment effects among PAH-CTD and IPAH/heritable PAH populations.[6–9] These studies include GRIPHON, the largest RCT in PAH, which enrolled 334 patients with PAH-CTD.[6,10] In GRIPHON, the treatment of PAH-CTD patients with the oral prostacyclin receptor agonist selexipag reduced the risk of disease progression by 41%, this reduction was consistent with the 39% seen in IPAH/heritable PAH patients.[6] Based on this evidence, PAH treatment recommendations support adding selexipag at first follow-up to existing treatment regimens in patients with PAH-CTD at intermediate-low risk and for those at intermediate-high or high risk for which parenteral prostacyclins are not feasible.[11,12]

Up to November 30, 2023, an estimated 46,452 PAH patients were exposed to commercial selexipag worldwide.[13] Assuming that there are 14%–39% of patients with PAH-CTD in the overall PAH population,[14–22] we estimate that between 6503 and 18,116 patients with PAH-CTD were exposed to selexipag during this time. The current analysis aims to describe the characteristics, treatment patterns, tolerability, and outcomes of PAH-CTD patients treated with selexipag in clinical practice, with IPAH patients included for context, using data from the EXPloratory Observational Study of Uptravi in Real-lifE (EXPOSURE) study.

METHODS

Study design

EXPOSURE (EUPAS19085) is an ongoing, multicenter, prospective, observational study of PAH patients initiating a PAH-specific therapy in Europe and Canada, started in 2017 and described in detail by Muller et al.[23] Patients ≥18 years old with Group 1 pulmonary hypertension (PAH) and initiating a new PAH-specific therapy, per decision of the treating physician, within 1 month of enrollment or at enrollment were eligible. Calcium channel blockers were not considered PAH-specific therapy in this study. Patients initiating a PAH-specific therapy must not have been previously treated with that same drug. Patient visits were not mandated and occurred as per clinical practice.

Patient population

This was an analysis of consecutively enrolled PAH-CTD patients initiating selexipag with a known selexipag initiation date and follow-up information between September 17, 2017, and November 30, 2022. IPAH patients meeting the same criteria were included for context. For the PAH-CTD group, patients with PAH associated with systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjogren's syndrome, mixed CTD, and undifferentiated CTD were included.

Analyses

Patients were observed during the selexipag exposure period, defined from the time of selexipag initiation (i.e., baseline) up to the date of last available information, selexipag discontinuation (>7 days without therapy), or death, whichever occurred first. All analyses were descriptive with no formal statistical comparisons made. Risk of 1-year mortality was calculated from baseline data using a minimum of two parameters: brain natriuretic peptide (BNP)/N-terminal (NT)-proBNP and either World Health Organization functional class (WHO FC) and/or 6-minute walk distance (6MWD), using the 4-strata risk score recommended by the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines.[11,12] For BNP/NT-proBNP, exact values were collected only for patients with "abnormal" values, as denoted in the electronic case report form. Patients with a "normal" BNP/NT-proBNP were categorized as low risk for this parameter. If the BNP/NT-proBNP value was missing for patients with an abnormal value, the risk score could not be calculated.

Selexipag titration was conducted independently of the study design and per physician's judgment and

experience. For purposes of this analysis, the duration of selexipag titration and individualized dose were identified and defined in a stepwise manner for each patient. First, the highest dose taken within 24 weeks of selexipag initiation was identified. Second, the dose taken for ≥3 weeks after the intake of that highest dose was identified and defined as the individualized dose. Finally, the titration period was defined as the number of days from treatment initiation until intake of that individualized dose plus 7 days. To summarize the dose data, three dose groups were defined based on the patient's individualized dose at the end of titration: low dose group (200 or 400 μg twice daily [b.i.d]), medium dose group (600, 800, or 1000 μg b.i.d), and high dose group (1200, 1400, or 1600 μg b.i.d). Following titration, the number of dose adjustments, as well as selexipag discontinuations and reasons for discontinuation are described.

The treatment regimen was described as monotherapy for those treated with selexipag alone. The treatment regimen was described as combination therapy if concomitant PAH-specific therapy overlapped with selexipag for >1 day at baseline or within 30 days after baseline. If selexipag was taken in addition to one, two, or more concomitant PAH-specific therapies, the combination was described as double, triple, or other combination therapy, respectively. Treatment patterns were detailed using Sankey figures. At 6 and 12 months after baseline, patients with no observation data due to limited observation time, study discontinuation, or loss to follow-up were considered as "No observation".

Incidence rates for all-cause and PAH-related hospitalization and all-cause mortality rates were calculated as the number of patients experiencing an event after baseline divided by the overall sum of patients' exposure periods while at risk for an event. All-cause mortality rates were also calculated during the observation period, defined from selexipag initiation to the end of observation, regardless of whether patients remained on or discontinued selexipag. Rates were expressed as 100 person-years, with associated 95% confidence intervals (CI). Calculations were based on a Poisson distribution model with log (exposure time) as an offset. Kaplan−Meier (KM) estimates with 95% CIs were used to present time to the first event for hospitalizations and all-cause death during the selexipag exposure period. Each KM curve was cut at the first timepoint where <10% of patients in the group were at risk, as per Pocock's stopping rule.[24] For PAH-related hospitalizations and deaths, PAH-related status was based on physician's judgment.

The following frequently known adverse reactions associated with the mode of action of drugs targeting the prostacyclin pathway (headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia) were not reported as an adverse event unless they fulfilled at least one of the following: any seriousness criteria, lead to selexipag discontinuation or dose reduction, introduction of symptomatic treatment or reflective of an unusual pattern of severity based on physician's medical judgment.

Imputations were made for partially missing dates (i.e., day or/and month missing, year present) for start/end of hospitalization, start/discontinuation of PAH therapy, date of death, and date of PAH diagnosis. For completely missing dates, no imputations were made.

Monitoring and ethics statement

The study was conducted in compliance with the Declaration of Helsinki. The protocol was approved at each study site (and at the national level in Sweden) by an Institutional Review Board or Independent Ethics Committee, and the study was conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP)[25] and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.[26] For each patient, written informed consent was obtained.

RESULTS

Patient disposition

As of November 2022, EXPOSURE enrolled 2069 patients initiating a new PAH-specific therapy.[23] Of the 698 patients who initiated selexipag and had follow-up information reported, there were 178 (26%) patients with PAH-CTD and 362 (52%) with IPAH. Among the PAH-CTD population, 127 (71%) had SSc, 15 (8%) had mixed CTD, 12 (7%) had SLE, 10 (6%) had rheumatoid arthritis, 8 (4%) had Sjogren's syndrome, and 6 (3%) had undifferentiated CTD.

Demographics and patient characteristics at baseline (selexipag initiation)

Patients with PAH-CTD had a median age of 68 years, most were female (88%), and the median (Q1−Q3) time since diagnosis was 1.7 (0.6−4.0) years (Table 1). The median 6MWD was 300 m, 83% had abnormal NT-proBNP values (as per physician's judgment), and the majority were in WHO FC III (Table 1). Based on these parameters,[11,12] the

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TABLE 1 Patient characteristics at baseline.

Characteristic	PAH-CTD N = 178	IPAH N = 362
Age, median (Q1−Q3), years	68 (59−74)	61 (47−70)
Female, n (%)	156 (88)	232 (64)
Time since PAH diagnosis, n	172	339
Median (Q1−Q3), years	1.7 (0.6−4.0)	1.8 (0.7−5.2)
WHO FC, n	152	306
I, n (%)	2 (1)	9 (3)
II, n (%)	50 (33)	103 (34)
III, n (%)	95 (63)	183 (60)
IV, n (%)	5 (3)	11 (4)
6MWD, n	106	207
Median (Q1−Q3), m	300 (236−366)	386 (254−488)
NT-proBNP, n	133	268
Abnormal,[a] n (%)	111 (83)	202 (75)
Median (Q1−Q3) for patients with abnormal values, ng/L	1250 (531−2747)	805 (392−2134)
RHC performed,[b] n (%)	124 (70)	264 (73)
Pulmonary vascular resistance, n	118	249
Median (Q1−Q3), WU	7.6 (5.4−10.9)	8.3 (6.1−11.5)
Mean pulmonary arterial pressure, n	121	258
Median (Q1−Q3), mmHg	44 (37−51)	47 (40−56)
Mean right atrial pressure, n	118	238
Median (Q1−Q3), mmHg	8 (5−11)	8 (5−12)
Pulmonary arterial wedge pressure, n	118	249
Median (Q1−Q3), mmHg	10 (7−12)	10 (8−13)
SvO$_2$, n	99	200
n (%), >65%	53 (54)	109 (55)
Cardiac index, n	119	242
Median (Q1−Q3), L/min/m^2	2.4 (2.0−3.1)	2.5 (2.0−3.1)
Pericardial effusion,[c] n	178	362
Yes, n (%)	32 (18)	42 (12)

TABLE 1 (Continued)

Characteristic	PAH-CTD N = 178	IPAH N = 362
DLCO,[c] n	57	127
Median (Q1−Q3), %	32 (24−46)	51 (34−68)
4-strata risk category,[d] n	138	273
Low, n (%)	7 (5)	44 (16)
Intermediate-low, n (%)	34 (25)	88 (32)
Intermediate-high, n (%)	55 (40)	86 (32)
High, n (%)	42 (30)	55 (20)

Abbreviations: 6MWD, 6-minute walk distance; BNP, brain natriuretic peptide; DLCO, diffusing capacity of lung for carbon monoxide; IPAH, idiopathic PAH; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; Q1−Q3, interquartile range; RHC, right heart catheterization; SvO$_2$, mixed venous oxygen saturation; WHO FC, World Health Organization functional class; WU, Wood units.

[a]As per physician's judgment.

[b]RHC was performed within 12 months of baseline.

[c]DLCO and presence of pericardial effusion assessed within 3 months before or at baseline.

[d]4-strata risk scores calculated for patients who had data available for BNP/NT-proBNP and WHO FC and/or 6MWD.[11,12]

distribution of patients by 1-year mortality risk according to the ESC/ERS 4-strata risk score was low 5%, intermediate-low 25%, intermediate-high 40%, and high 30%. Median (Q1−Q3) for the following hemodynamic parameters was: pulmonary vascular resistance 7.6 (5.4−10.9) Wood units, right atrial pressure 8 (5−11) mmHg, and cardiac index 2.4 (2.0−3.1) L/min/m^2. Of the patients with available data, 54% (n = 53) had a mixed venous oxygen saturation >65%, and 18% (n = 32) had pericardial effusion. The most frequently reported cardiovascular risk factors were being a former smoker (38%), systemic hypertension (31%), and obesity (body mass index >30 kg/m^2) (22%) at baseline (Figure 1). Demographics and baseline characteristics for patients with IPAH are provided in Table 1 and Figure 1.

Selexipag titration, dosing, and treatment patterns

The median (Q1−Q3) duration of selexipag titration was 1.5 (0.7−2.8) months and, at the end of the observation period for this analysis, 151 (85%) patients had completed their titration, 10 (6%) were ongoing, and 17 (10%) had discontinued selexipag (Table 2). Among those who completed titration, the median (Q1−Q3) selexipag individualized dose was 600 (400−1000) μg b.i.d (Table 2). The distribution by dose group was low (200

FIGURE 1 History of cardiovascular risk factors at baseline. *Systemic-pulmonary shunts were recorded as cardiac shunts in the case report form. BMI, body mass index; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease.
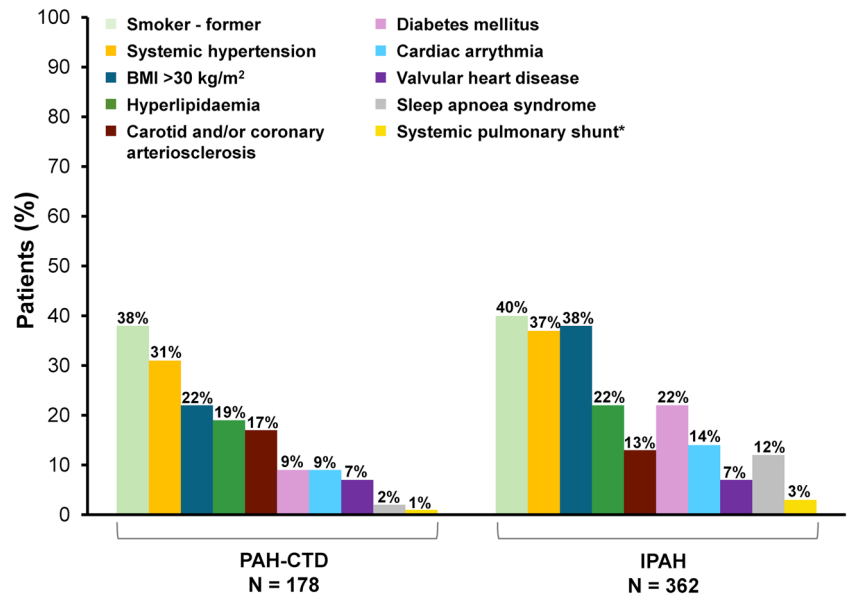
TABLE 2 Selexipag titration and dosing.

	PAH-CTD N = 178	IPAH N = 362
Titration duration, median (Q1−Q3), months	1.5 (0.7−2.8)	1.8 (0.9−3.0)
Titration status at data cut-off, n (%)		
Completed	151 (85)	314 (87)
Discontinued	17 (10)	29 (8)
Ongoing	10 (6)	19 (5)
Individualized dose, n	151	314
Median (Q1−Q3), µg b.i.d	600 (400−1000)	800 (400−1200)
Patients with further dose adjustments post-titration, n/N (%)	43/151 (28)	104/314 (33)

Abbreviations: b.i.d, twice daily; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; Q1−Q3, interquartile range.

or 400 µg b.i.d.): 45 (30%), medium (600, 800, or 1000 µg b.i.d.): 61 (41%), and high (1200, 1400, or 1600 µg b.i.d.): 34 (23%). It was observed that 11 patients received a dose not consistent with the defined dose groups and reasons for this were not captured in EXPOSURE. The distribution of dose groups is shown in Supporting Information S1: Table 1. Post-titration, 43/151 (28%) patients had further adjustments in their dose (Table 2) during the median (Q1−Q3) 3.9 (1.4−12.1) months.

Among PAH-CTD patients, 80% initiated selexipag as a triple oral therapy, almost all in combination with both

an endothelin receptor antagonist (ERA) and a phosphodiesterase 5 inhibitor (PDE5i) (Figure 2a). The majority of PAH-CTD patients initiating triple oral combination therapy were escalated from double oral combination therapy, and most had been on double therapy for at least 1 year before treatment escalation with selexipag (Figure 3a). For the patients with PAH-CTD that were on triple therapy at 6 months post-baseline (n = 91), 89 patients remained on triple therapy from baseline, and two patients escalated from double therapy at baseline. While some de-escalation from triple to double combination therapy was observed 6 months post-baseline (n = 21/143; 15%), most patients (n = 89/143; 62%) remained on triple therapy. The majority of patients also maintained their treatment regimen at 12 months post-baseline, albeit with fewer follow-up observations at this timepoint (n = 122; Figure 3a). Details for patients with IPAH are outlined in Table 2 and Figures 2b and 3b.

Long-term outcomes and safety

Over a median (Q1−Q3) selexipag exposure duration of 8.6 (2.5−17.2) months, 34% of patients with PAH-CTD were hospitalized at least once. Of the 102 hospitalizations that occurred in total, 49 (48%) were considered PAH-related as per physician's judgment (Table 3). The incidence rate for PAH-related hospitalizations was 18.5 (95% CI: 12.6−26.2) per 100 person-years, indicating that for 100 patients over a period of 1 year, 18.5 will have a first occurrence of PAH-related hospitalization and 81.5 will be free from PAH-related hospitalization (Table 3). The proportion of patients who were free from any hospitalization was 63% at 1 year (Figure 4a).
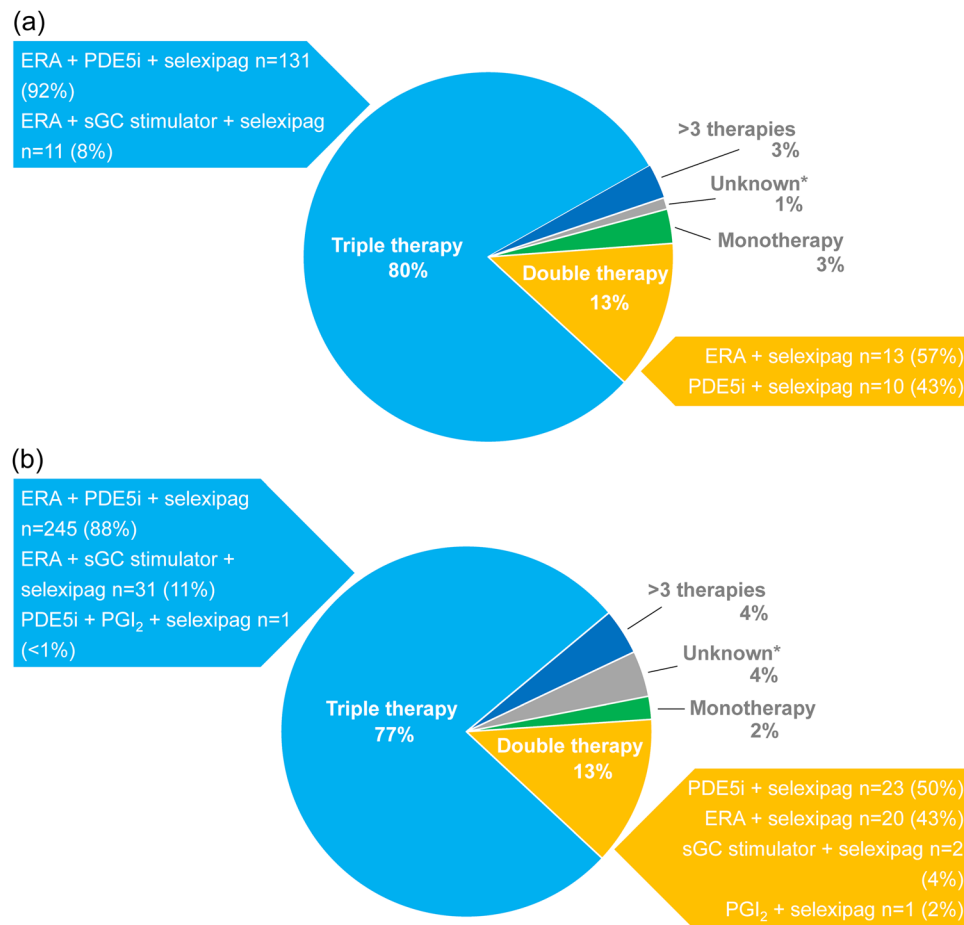
FIGURE 2 Treatment patterns at baseline for (a) PAH-CTD ($N = 178$) and (b) IPAH patients ($N = 362$). Calcium channel blockers were not considered as PAH-specific therapy in EXPOSURE. Baseline was defined as the time of selexipag initiation. *Includes patients with therapies that have missing start and end dates and those for whom it cannot be determined if some treatments are prior or current. ERA, endothelin receptor antagonist; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; PDE5i, phosphodiesterase 5 inhibitor; PGI_2, prostacyclin and its analogs; sGC, soluble guanylate cyclase.

There were 29 (16%) deaths among patients with PAH-CTD during a median exposure of 8.6 months, and of these, 83% were considered PAH-related as per physician's judgment (Table 3). The mortality rate was 15.5 (95% CI: 10.4−22.2) per 100 person-years during selexipag exposure (Table 3). Mortality rates during the total observation period are shown in Supporting Information S1: Table 2. The 1- and 2-year KM estimates of survival were 85% and 71%, respectively (Figure 4c). The main cause of death, as per physician's judgment, was disease progression/PAH worsening.

There were 79 (44%) PAH-CTD patients who discontinued selexipag (Table 4). Reasons for discontinuation were mainly due to tolerability/adverse events ($n = 36$; 20%), death ($n = 29$; 16%), or PAH disease progression ($n = 8$; 4%). From all adverse events reported, the most frequent were diarrhea, and headache, and were consistent with the mode of action of selexipag

(Table 4). Hospitalization and survival data for patients with IPAH are presented in Table 3 and Figure 4b,d, and selexipag discontinuation and safety data are in Table 4.

DISCUSSION AND CONCLUSIONS

Patients with PAH-CTD are a large and important subset of PAH patients, comprising 14%−39% of patients in contemporary European disease registries.[14–22] While their management is complicated by their underlying CTD and associated comorbidities, evidence-based recommendations for PAH-specific therapy in these patients are aligned with that of IPAH. In our study, we followed, over a period of several years, 178 patients with PAH-CTD who were prevalent at the time of selexipag initiation and predominantly with PAH-SSc (Graphical Abstract; Supporting Information S1: Figure 1). Our data
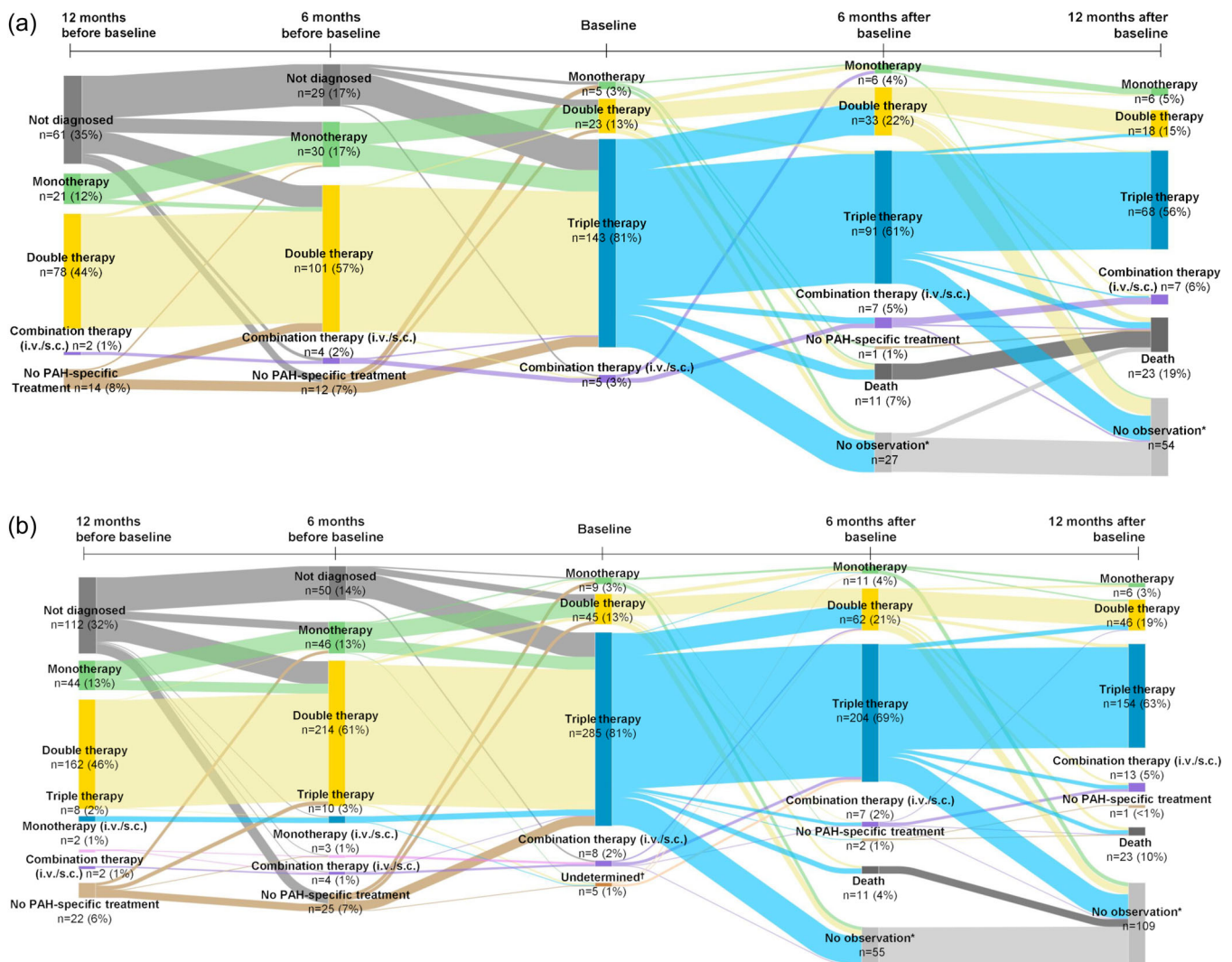
FIGURE 3 Treatment patterns over time during the selexipag exposure period for (a) PAH-CTD ($N = 176$) and (b) IPAH patients ($N = 352$). Calcium channel blockers were not considered as PAH-specific therapy in EXPOSURE. Two PAH-CTD patients and 10 IPAH patients were excluded due to missing PAH-specific therapy start date. Some patients were receiving PAH-specific therapy before baseline/diagnosis due to the date of right heart catheterization occurring after patients were enrolled. *Includes patients with <6 months of observation after baseline in the study. †Includes patients for whom the PAH-specific treatment combination at initiation was unknown. IPAH, idiopathic PAH; i.v., intravenous; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; s.c., subcutaneous.

provide a unique opportunity to characterize patients with PAH-CTD initiating triple oral therapy and describe selexipag dosing, treatment patterns, and outcomes of these patients over the long term.

Establishing a patient on selexipag typically requires titration from 200 μg b.i.d., in 200 μg increments, to an individualized dose (maximum 1600 μg b.i.d.) based on the patients' tolerability.[27] In GRIPHON, the selexipag pivotal trial,[10] the initial 12 weeks were defined per protocol as the titration phase, and this "titration phase", along with a cadence of dose increases "usually weekly", is reflected in the prescribing information.[27,28] In GRIPHON, patients' individualized dose was noted at the end of the 12-week titration period, as per study protocol. While this was necessary for the clinical trial, it

is less suitable to summarize data from clinical practice. Therefore, we characterized selexipag titration using a stepwise approach considering dose and time to dose for each patient within a time frame of 24 weeks. Contrasting the individualized doses of PAH-CTD patients in our study with those of the pivotal trial, we observed 30% with low dose selexipag, 41% with medium dose, and 23% with high dose; as compared with 24%, 27%, and 45% for PAH-CTD patients in GRIPHON.[6] The slight shift toward lower doses may suggest a less stringent approach to dosing and dose adjustments in clinical practice. In EXPOSURE, individualized doses were reached in a median of 6 weeks. At first glance this appears short, however considering the dose distribution, we can infer that in clinical practice, the incremental increases in

TABLE 3 Hospitalizations and mortality during selexipag exposure.

	PAH-CTD $N = 178$	IPAH $N = 362$
Exposure duration, median (Q1−Q3), months	8.6 (2.5−17.2)	11.1 (3.8−25.5)
Patients hospitalized after baseline, n (%)	60 (34)	98 (27)
Time to first hospitalization, median (Q1−Q3), days	202 (92−358)	152 (64−477)
Total number of hospitalizations,[a] n	120	193
After baseline, n (%)	110 (92)	169 (88)
PAH-related hospitalization, n/N,[b,c] (%)	49/102 (48)	104/159 (65)
Incidence rate per 100 person-years (95% CI), n	175	362
All hospitalizations after baseline	41.6 (31.1−54.1)	24.8 (19.8−30.6)
PAH-related hospitalizations after baseline[b]	18.5 (12.6−26.2)	17.3 (13.6−21.7)
Mortality		
Total all-cause deaths, n (%)	29 (16)	34 (9)
PAH-related deaths,[b] n	23	25
Yes, n (%)	19 (83)	15 (60)
No, n (%)	4 (17)	10 (40)
Unknown, n	6	9
Mortality rate per 100 person-years (95% CI)	15.5 (10.4−22.2)	7.2 (5.0−10.1)
Main cause of death, n (%)		
Disease progression/PAH worsening	9 (5)	11 (3)
Right heart failure	5 (3)	1 (<1)
Sudden death/sudden cardiac arrest	3 (2)	4 (1)
Arrhythmia	1 (1)	0
Stroke	0	2 (<1)
Other causes (occurring in ≤7% of patients)	8 (4)	8 (2)
Unknown cause of death	3 (2)	8 (2)

Abbreviations: CI, confidence interval; IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; Q1−Q3, interquartile range.

[a]Patients could have been hospitalized multiple times.

[b]As per physician's judgment.

[c]The PAH-related status was unknown for eight hospitalizations in the PAH-CTD group and 10 hospitalizations in the IPAH group.

selexipag doses are also being made in intervals of greater than 1 week. In addition, we observed flexibility in the approach to selexipag dosing after titration, with approximately 30% of patients having dose adjustments post-titration. The safety profile of selexipag was in line with the safety profile established during the randomized clinical studies of adult PAH patients, as provided in the approved product information documents.[27,28] Patients mainly discontinued selexipag due to tolerability/adverse events and at a similar rate to that observed in GRIPHON (20% vs. 19%, respectively).[6] Adverse events were also similar to those described previously.[6,10]

At selexipag initiation, the vast majority of PAH-CTD patients were being escalated to triple oral therapy with selexipag, an ERA, and a PDE5i, and were diagnosed with PAH-CTD for almost 2 years. Other demographics were typical for this PAH subset, with patients tending to be older and more predominantly female than their IPAH counterparts. Assessment of 1-year mortality risk can be used as an indication of PAH severity. In EXPOSURE, PAH-CTD patients had a greater PAH severity at selexipag initiation compared with the EXPOSURE IPAH population: 70% of PAH-CTD patients were at intermediate-high or high risk, compared with
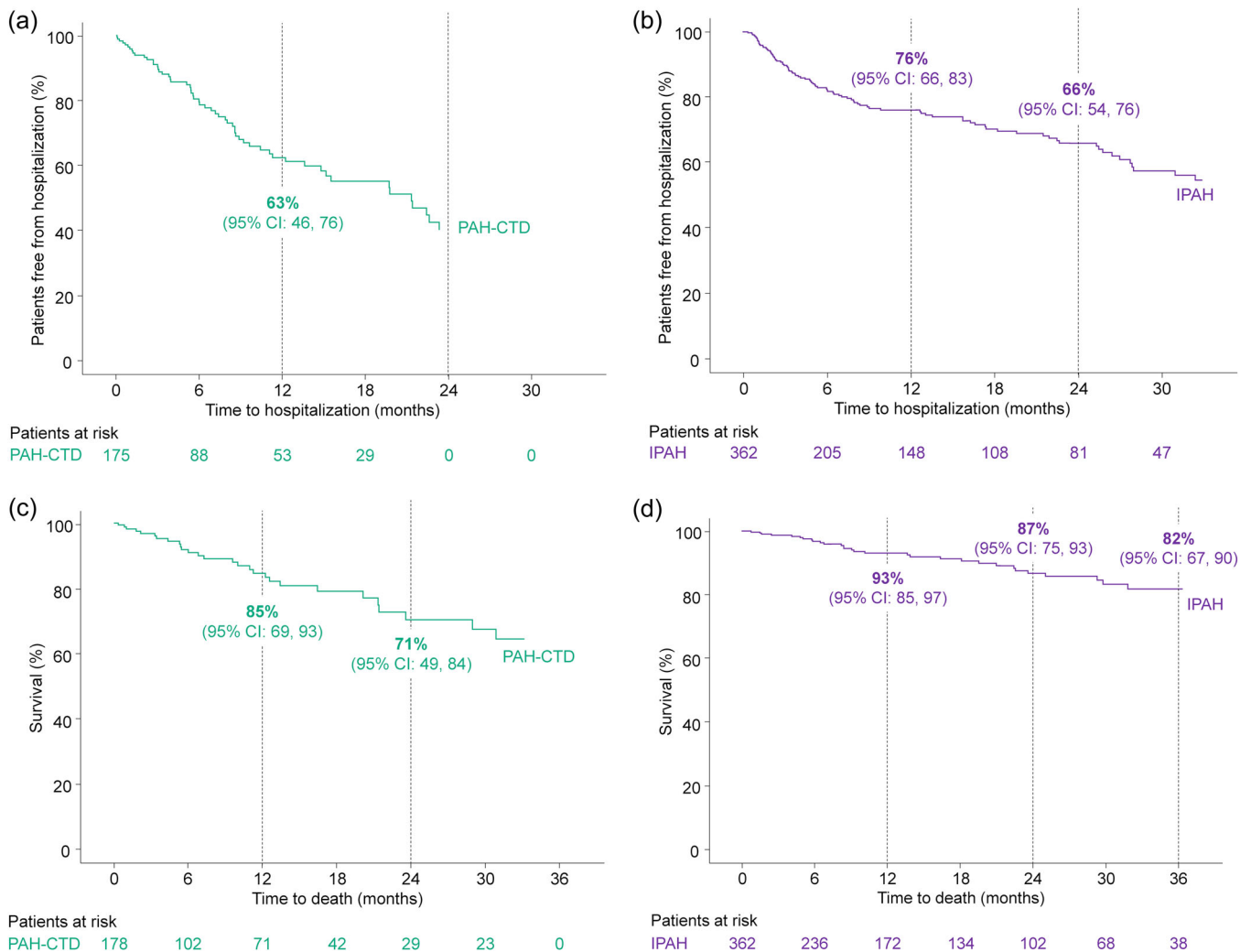
FIGURE 4 Time to first all-cause hospitalization for (a) PAH-CTD and (b) IPAH patients and time to all-cause death for (c) PAH-CTD and (d) IPAH patients during selexipag exposure illustrated using KM curves. KM estimates (95% CI) are shown at 12, 24, and 36 months. Each curve is cut at the first timepoint where <10% of patients in the group are left at risk. CI, confidence interval; IPAH, idiopathic PAH; KM, Kaplan−Meier; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease.

~50% of IPAH patients. The greater proportion of patients with PAH-CTD at higher risk versus those with IPAH observed in EXPOSURE could be attributed to the fact that the ESC/ERS 4-strata risk score is based on WHO FC, NT-proBNP and 6MWD,[11,12] as some populations/studies suggest that patients with PAH-CTD tend to have worse values for these parameters.[1,3,8,29] Of note, values for hemodynamic parameters for patients with PAH-CTD in our analysis align more toward the lower end of the defined thresholds for intermediate risk[11,12] and are similar to those observed for patients with IPAH.

Comorbidities are of particular concern among patients with PAH-CTD, and consistent with disease registries,[15,17] our patients displayed notable cardiovascular comorbidities, the most common being systemic

hypertension and obesity. Taken together, the characterization of our PAH-CTD cohort suggests that triple oral therapy is reserved for patients in whom considerable severity of underlying PAH-CTD has evolved over a period of years. These results are consistent with those from recent disease registries, where the majority of PAH-CTD patients are initiated on monotherapy and experience stepwise treatment escalation after years, prompted by clinical deterioration.[17]

Examination of the temporal trends showed that escalation to triple oral therapy typically occurred after an extended period on double oral therapy (median 1.7 years), and that patients persisted on triple oral therapy with selexipag. These observations were similar in the EXPOSURE IPAH patient population and are

TABLE 4 Selexipag discontinuation and adverse events.

	PAH-CTD $N = 178$	IPAH $N = 362$
Exposure duration, median (Q1−Q3), months	8.6 (2.5−17.2)	11.1 (3.8−25.5)
Patients who discontinued selexipag, n (%)	79 (44)	134 (37)
Time to discontinuation, median (Q1−Q3), months	4.3 (1.2−11.1)	4.9 (1.2−13.6)
Reasons for discontinuation, n (%)		
Tolerability/adverse event	36 (20)	55 (15)
Death	29 (16)	34 (9)
PAH disease progression	8 (4)	32 (9)
Administrative	4 (2)	4 (1)
Treatment noncompliance	1 (<1)	2 (<1)
Unknown	1 (<1)	7 (2)
Patients with an adverse event,[a] n (%)	70 (39)	135 (37)
Most frequent adverse events,[b] n (%)		
Diarrhea	20 (11)	29 (8)
Headache	13 (7)	28 (8)
Dyspnea	9 (5)	10 (3)
Nausea	6 (3)	14 (4)
Pain in jaw	6 (3)	8 (2)
Dizziness	5 (3)	10 (3)
Arthralgia	5 (3)	7 (2)
Myalgia	5 (3)	5 (1)
Cardiac failure	4 (2)	10 (3)
Peripheral edema	2 (1)	11 (3)

Abbreviations: IPAH, idiopathic PAH; PAH, pulmonary arterial hypertension; PAH-CTD, PAH associated with connective tissue disease; Q1−Q3, interquartile range.

[a]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 judgment.

[b]Occurring in >3% of patients in any group.

consistent with trends observed in other registries of PAH patients.[17] These findings highlight an opportunity for earlier escalation to triple oral therapy, as the GRIPHON study indicated more pronounced improvements in long-term outcomes when selexipag was added within 6 months of diagnosis and in less severe

patients.[10,30] The need to pursue better outcomes through proactive treatment escalation is particularly relevant for patients with PAH-CTD patients, for whom prognosis tends to be poorer.[1-3]

Contemporary disease registries report survival estimates among incident PAH-CTD patients of 82%–88% at 1 year and 57%–67% at 3 years.[17,20] The survival data from IPAH patients in EXPOSURE also provide context, confirming poorer prognosis among PAH-CTD compared with IPAH patients. Despite the availability of these data, it is challenging to provide context for the survival estimates among PAH-CTD patients in our study (85% at 1-year and 71% at 2-years), as all patients in our study were enrolled at a time of treatment escalation. Our data suggest that this treatment decision is being taken for these patients at a time of clinical deterioration, as 70% of our population have characteristics indicative of intermediate-high or high risk of death at 1-year, despite extended use of double combination therapy. While recent evidence from RCTs in the general PAH population does not favor initial triple oral combination therapy at baseline,[31] it does describe excellent survival, 96% at 1-year and 93% at 2-years, when selexipag is provided as triple oral combination therapy within 6 months from diagnosis.[32] Further improvements for patients in real-world settings may be observed if greater weight is placed on the relevance of timing in treatment escalation, ideally before disease progression occurs, for the long-term management of PAH.

Real-world evidence regarding hospitalizations in PAH is very limited and hospitalization data have not been reported from European PAH disease registries. A number of reports are available based on administrative hospital records and health insurance databases and these highlight hospitalization as a significant burden among PAH patients and a financial burden to health care systems.[33,34] In our data set, the burden of underlying CTD and its associated complications, including PAH is also evident. One-third of PAH-CTD patients were hospitalized over the exposure period of approximately 9 months, and the 1-year KM estimate for PAH-CTD patients free from hospitalization was 63%. A more detailed view of the individual hospitalizations revealed that while all-cause hospitalization rates were greater among PAH-CTD patients as compared with IPAH, the rates of PAH-related hospitalizations were similar between these groups, even with the higher proportion of PAH-CTD patients at highrisk. This suggests that the greater overall hospitalization rates in PAH-CTD patients may be driven by hospitalizations for reasons other than PAH, that could include the underlying CTD, other comorbidities or preexisting diseases, or the higher age of these patients compared to IPAH. As discussed above, the ESC/ERS 4-strata risk score

used for this analysis may be categorizing patients with PAH-CTD at higher risk than they are in reality, supported by the less severe hemodynamic profile observed for these patients, one that is more aligned with patients with IPAH. In such a case, the similar rates of PAH-related hospitalization between patients with PAH-CTD and IPAH reported here may not be unexpected.

This analysis of PAH-CTD patients in EXPOSURE is subject to limitations. In EXPOSURE, the underlying disease was predominantly SSc (71%), providing limited insights into patients with other CTD types. A greater diversity of CTD subtypes was observed in GRIPHON, where almost a quarter of patients had PAH-SLE, and selexipag reduced the risk of disease progression by 34% versus placebo in this CTD subgroup.[6]

Conclusion

This analysis highlights the important role of combination therapy in the management of patients with PAH-CTD in the clinical setting, including patients with comorbidities, which is an important consideration in this specific patient population. The majority of PAH-CTD patients initiated selexipag as part of triple combination therapy and across all four strata of 1-year mortality risk. The safety and tolerability profile for PAH-CTD patients was consistent with that observed in the IPAH population treated with selexipag. Taken together, our findings on survival, treatment patterns, tolerability, and patient characterization suggest an opportunity to further improve outcomes for patients with PAH-CTD by early treatment escalation at intermediate-high, intermediate-low, or even low risk rather than escalation after a prolonged period of time in reaction to PAH disease clinical deterioration (Graphical Abstract; Supporting Information S1: Figure 1).

AUTHOR CONTRIBUTIONS
Sean Gaine, Pilar Escribano-Subias, Catarina C. Fernandes, Tatiana Remenova, Stefan Söderberg, and Tobias J. Lange: Conceptualization; writing—original draft and writing—reviewing and editing. **Audrey Muller**: Conceptualization; data curation; formal analysis; methodology; writing—original draft and writing—reviewing and editing of the manuscript. **Martina Fontana**: Data curation; formal analysis; validation; writing—original draft and writing—reviewing and editing.

CONFLICTS OF INTEREST STATEMENT
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, Gossamer Bio, Johnson & Johnson, MSD, and United Therapeutics. P. E. S. has received grants/research support from Ferrer and GlaxoSmithKline, consulting fees from Johnson & Johnson, Acceleron, Ferrer, and MSD, payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Johnson & Johnson, MSD, Ferrer and AOT, has received support from Johnson & Johnson and MSD for attending meetings and/or travel and has participated on a Data Safety Monitoring Board or Advisory Board for Johnson & Johnson, MSD, Ferrer, Gossamer and AOT, Acceleron and GlaxoSmithKline. A. M. is an employee of Johnson & Johnson and has Johnson & Johnson shares. C. C. F. is an employee of Johnson & Johnson. M. F. is an employee of Johnson & Johnson and has Johnson & Johnson shares. T. R. is an employee of Johnson & Johnson. S. S. has received speaker and consultancy fees, and financial support for participation in scientific events from Johnson & Johnson. T. J. L. 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.

DATA AVAILABILITY STATEMENT
These data are not currently publicly available for sharing. Requests for sharing can be sent to the Corresponding Author and will be evaluated on an individual basis.

ETHICS STATEMENT

The study was conducted in compliance with the Declaration of Helsinki. The protocol was approved at each study site (and at the national level in Sweden) by an Institutional Review Board or Independent Ethics Committee, and the study was conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. For each patient, written informed consent was obtained.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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