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RESEARCH ARTICLE

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Impact of selexipag maintenance dose on persistence, adherence, and hospitalization in US patients with pulmonary arterial hypertension

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Abstract

Selexipag is an oral selective agonist of the prostacyclin receptor approved to treat adults with pulmonary arterial hypertension (PAH). Selexipag is initiated at a dose of 200 μg twice daily (bid) and usually titrated up by 200 μg bid weekly (per label) or more slowly (e.g., every other week in real-world clinical practice) to the highest tolerated individualized dose (ID) ranging from 200 to 1600 μg bid. In the Phase 3 GRIPHON trial, selexipag delayed disease progression and reduced risk of PAH-related hospitalization compared with placebo; the effect was consistent across three prespecified ID groups: low (200–400 μg bid), medium (600–1000 μg bid), and high (1200–1600 μg bid). This study evaluated patient outcomes across selexipag dose ranges in real-world practice. Data were analyzed from 1186 US adult patients with PAH on selexipag from the Komodo closed-claims database (2015–2022). Of these, 634 (53.5%) patients completed titration and reached their selexipag ID (43.8% high ID, 29.8% medium ID, 26.3% low ID). Subsequently, 72.4% of patients in the low ID group had dose adjustments compared with 61.9% (medium ID) and 34.5% (high ID; standardized mean difference 0.63). There were no significant differences in patient outcomes, i,e, persistence (time to discontinuation) and risk of all-cause and PAH-related hospitalization across ID groups. The findings in this diverse, real-world population of patients with PAH reinforced an individualized approach to the dosing scheme to maximize benefit-risk and achieve the highest tolerated dose with selexipag similar to findings from the GRIPHON trial and other studies.

KEYWORDS
claims, outcomes, real-world, tolerability

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, life-threatening disease characterized by a progressive increase in pulmonary vascular resistance, ultimately leading to right heart failure and death.[1,2] Compared with clinical trial participants, patients with PAH in real-world practice typically present with multiple comorbidities that contribute to poor clinical outcomes and poor response to treatment.[3] Medical therapies improving outcomes for patients with PAH have continued to advance, offering a range of different options. Current European Society of Cardiology/European Respiratory Society guidelines recommend treatment decisions be guided by a multiparameter risk assessment to determine the risk of deterioration or mortality for a patient with PAH.[4] These guidelines recommend consideration around the addition of selexipag to treatment with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 inhibitor (PDE5i) at first follow-up visit, to reduce the risk of clinical worsening in patients with idiopathic, heritable, or drug-associated PAH without cardiopulmonary comorbidities who remain at intermediate-low risk. Selexipag is also recommended for patients at intermediate-high or high risk as an addition in place of intravenous/subcutaneous prostacyclin analogs when the latter is unfeasible.[4]

Selexipag is an oral selective agonist of the prostacyclin receptor that is associated with lower risk of tachyphylaxis than prostacyclin analogs due to its property of partial antagonism.[5,6] The approval of selexipag was based on the results of the randomized Phase 3 GRIPHON trial, which showed that selexipag doses ranging from 200 to 1600 μg twice daily (bid), independent of background medication, were associated with delayed disease progression and reduced risk of PAH-related hospitalization versus placebo.[7,8] In patients with PAH, selexipag treatment is initiated at a dose of 200 μg bid and then increased, usually at weekly intervals, in increments of 200 μg bid to the highest tolerated dose (ranging from 200 to 1600 μg) to identify the post-titration individualized dose (ID).[7] This schedule for selexipag dose titration was assessed in GRIPHON. The treatment effect of selexipag on the primary morbidity and mortality composite endpoint was consistent across three prespecified dose groups: low ID (200–400 μg twice daily), medium ID (600–1000 μg bid), and high ID (1200–1600 μg bid).[8] The results were demonstrated in the context of a structured, well-monitored clinical trial. Nevertheless, there is limited evidence on how selexipag dose titration and maintenance treatment are implemented in a real-world clinical setting and whether there are differences in patient outcomes associated with different selexipag IDs. The current study aims to answer these questions using a large US claims data set, with the primary objective of examining the association between ID levels and time to selexipag maintenance discontinuation.

METHODS

Data source

This retrospective, observational, cohort study analyzed data from US adult patients with PAH. The data source was the Komodo closed-claims database, which comprises medical and prescription claims from 150 payers and an average of 330 million patients with insurance coverage, including Medicaid, commercial, and Medicare Advantage.[9] Closed claims were adjudicated by the insurance provider, with the payer directly entering health care encounters into the database (including full medical and/or prescription benefit information, insurance eligibility, and health care plan enrollment). The Komodo PAH cohort consists of approximately 8 million patients with at least one pulmonary hypertension (PH) diagnosis code or prescription drug that can be used to treat PAH recorded between January 1, 2015, and June 30, 2022. Data were deidentified, and no institutional review board approval was required.

Study design and patient eligibility criteria

The study design is shown in Figure 1. To be eligible, patients were required to be treated with selexipag during the identification period (December 15, 2015, to June 30, 2022), with at least one inpatient or two outpatient records with an International Classification of Diseases, Ninth or Tenth Revision (ICD9/ICD-10) diagnosis code for PH (on separate days; with at least one PH diagnosis occurring before the selexipag start date).

Patients were also required to be continuously enrolled with medical and pharmacy benefits during the 12 months (365 days) before the selexipag start date. Patients were excluded if they were aged < 18 years on the selexipag start date, had a diagnosis of chronic thromboembolic PH, or a procedure code for heart, lung, liver, or kidney transplantation at any time before the selexipag start date.

The index date was the date of selexipag ID, defined as receipt of the first maintenance selexipag dose pack that was used for >60 consecutive days (determined using days of supply without any gap in prescription covered days). Selexipag titration packs versus maintenance dose packs

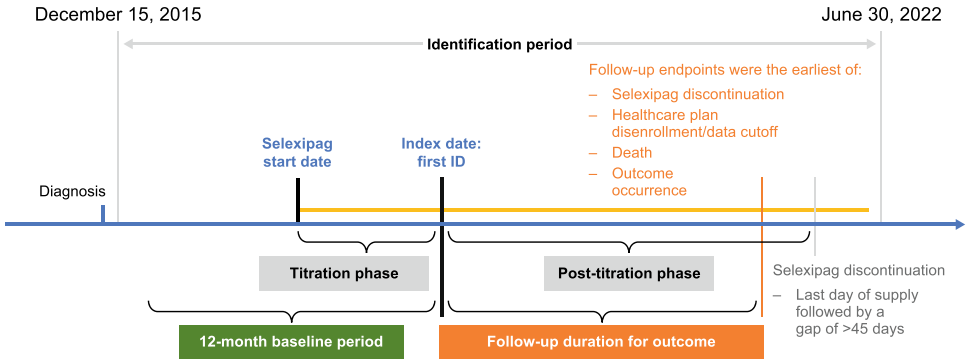

FIGURE 1 Study design. ID, individualized dose.

were discriminated using US National Drug Codes (Supporting Information S1: Table 1). Participants were required to be continuously enrolled during the titration phase, which ran from the date of the first selexipag prescription to the index date. For patients who did not reach the index date, the titration duration was from the first selexipag prescription date to the last consecutive selexipag titration pack prescription date plus the number of days of supply. Baseline was defined as the 12-month period before the index date. The post-titration phase (i.e., the duration or persistence of ID) ran from the index date to the earliest of selexipag discontinuation (defined as the last day of supply of selexipag refill followed by a gap of >45 days, regardless of dose adjustment), health care plan disenrollment/data cutoff, outcome occurrence, or death. For time-to-event outcomes (other than post-titration treatment duration and adherence), patients were followed up to the earliest of outcome occurrence, plan disenrollment/data cutoff, or death.

Study variables and outcome definitions

Patient demographic variables comprised baseline age at index, sex, US geographic region, and health care plan type. Variables captured during the baseline period included PAH-related comedications,[10] other non-PAH-related concomitant medications, Quan-Charlson Comorbidity Index score, individual comorbidities, PAH-related symptoms, and PAH-related procedures (Supporting Information S1: Tables 2 to 8). Patterns of selexipag dose changes were evaluated as the number of times a selexipag dose was increased or reduced over the post-titration phase; categories defined for selexipag dose changes were no change, increase or decrease by exactly 200 μg, and increase or decrease by ≥200 μg. The primary outcome was time from index date to the discontinuation of the first ID. Secondary outcomes included adherence to selexipag maintenance treatment, time to first all-cause hospitalization, and time to first PAH-related hospitalization, stratified according to ID level. Adherence to maintenance treatment was assessed as the proportion of days covered, calculated as the number of days of available selexipag maintenance medication divided by the duration of maintenance treatment. Treatment adherence was predefined as proportion of days covered ≥ 80%.

Statistical analyses

Variables were analyzed using descriptive statistics, both overall and stratified by ID level. Categorical data were reported as counts and percentages and continuous data as means ± standard deviations or medians with accompanying 25%–75% ranges (depending on the skewness of continuous data).

For comparative analyses, propensity score weighting was used to adjust for baseline confounding variables. Inverse probability of treatment weighting was created by regressing (using multinomial logistic model) ID levels on confounding/prognostic variables, including patient demographics and all clinical variables assessed during the baseline period.[11] The high ID stratum was set as the reference group because it had the largest sample size. The balance of baseline variables was assessed through the (global) standardized mean difference (SMD), with SMD <0.1 considered to indicate covariate balance across the three ID groups after propensity score weighting.[12] Weights were trimmed up to 2 percentiles if they were extremely small or large.[13,14] The effect of ID level on adherence to maintenance treatment was assessed using weighted logistical regression. The weighted Cox proportional hazard model was used to calculate the effect of ID level on all time-to-event outcomes. Weighted Kaplan–Meier curves were also plotted for all time-to-event variables, stratified by ID levels. A sensitivity analysis was performed by adjusting for covariates that did not

reach SMD <0.1 after weighting in the regression analyses.[15] The proportional hazards assumption was also empirically tested.[16,17] For the primary outcome, the alpha level was set to 0.025, to adjust for multiple testing issues.

RESULTS

Overall, 1186 patients with PAH met the key inclusion criteria for the study and initiated selexipag treatment (Supporting Information S1: Figure 1). Among these, 634 (53.5%) completed the titration phase and reached their selexipag ID, meaning they did not discontinue selexipag during their initial titration phase before achieving a stable dose (Figure 2). Supporting Information S1: Table 9 in the Supporting Information shows the baseline characteristics of patients who reached their ID compared to those who did not. Patients who did not reach their selexipag ID had a slightly higher burden of comorbidities (myocardial infarction, congestive heart failure, severe diabetes, coronary artery disease, chronic obstructive lung disease, and hypertension; Supporting Information S1: Table 9) and PAH-related symptoms, a higher rate of PAH associated with connective tissue disease or interstitial lung disease, and were hospitalized more often compared with patients who reached their selexipag ID (differences in covariates indicated by SMD >0.1). Both groups had a similar history of PAH therapy during the baseline period, with the exception that patients who reached their ID were slightly more likely to use selexipag as part of a combination therapy with either a PDE5i, ERA, and/or soluble guanylate cyclase stimulator (90.2% vs. 84.8% [SMD 0.24]).

Patients' baseline characteristics according to selexipag ID level

Among the 634 patients who reached their selexipag ID, 43.8%, 29.8%, and 26.3% were in the high, medium, and low ID strata, respectively (Figure 2). Patient demographics were generally similar across the ID strata (Table 1). Overall, there was a higher proportion of females than males in the data set (72.4% female), with a lower proportion of females in the high ID group (69.4% vs. 77.8% in the medium ID group and 71.3% in the low ID group [SMD] 0.13). Patients in the high and medium ID groups were younger than those in the low ID group (mean age 51.7 years, 52.8 years, and 55.1 years, respectively [SMD 0.16]).

The baseline clinical characteristics of patients reaching their selexipag ID, overall and according to ID strata, are shown in Figure 3. Connective tissue disease/rheumatic disease was the most common PAH etiology (evaluable by claims data), followed by portal hypertension, with a similar frequency across the three ID groups (Figure 3a). Dyspnea was the most common PAH sign/symptom (44.0% overall) and was more common in patients reaching a high ID versus those in the medium and low ID strata (48.2% *vs.* 40.2% and 41.3% [SMD 0.11]) (Figure 3b; Supporting Information S1: Table 10). The overall pattern of comorbidities was similar across the selexipag ID strata (although there were some differences in frequency) (Figure 3c; Supporting Information S1: Table 11).

The pattern of PAH therapies (Figure 3d) and regimens (Figure 3e) was similar across the selexipag ID strata with the exception of prior prostacyclin/prostacyclin analog (PPA) use where a higher proportion

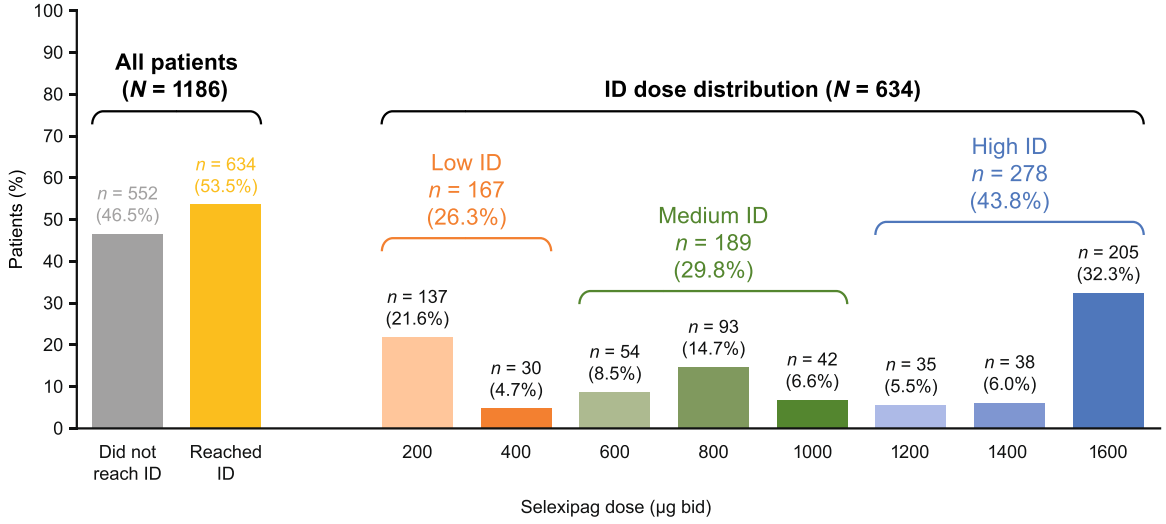

FIGURE 2 Proportion of patients reaching their selexipag ID. Patients were classified as "did not reach ID" if selexipag was discontinued during the initial titration phase before a stable dose was achieved. bid, twice daily; ID, individualized dose.

TABLE 1 Baseline demographics of patients reaching their selexipag ID: overall and according to ID.

Characteristic	All patients reaching selexipag ID ($N = 634$)	Low ID (selexipag 200–400 μg bid) ($n = 167$)	Medium ID (selexipag 600–1000 μg bid) ($n = 189$)	High ID (selexipag 1200–1600 μg bid) ($n = 278$)	SMD[a]
Age, mean years (SD)	53.0 (14.1)	55.1 (14.6)	52.8 (13.9)	51.7 (13.9)	0.16
Female, *n* (%)	459 (72.4)	119 (71.3)	147 (77.8)	193 (69.4)	0.13
US geographic region, *n* (%)					
Midwest	100 (15.8)	31 (18.6)	23 (12.2)	46 (16.5)	0.17
Northeast	90 (14.2)	23 (13.8)	28 (14.8)	39 (14.0)	
South	244 (38.5)	58 (34.2)	71 (37.6)	115 (41.4)	
West	192 (30.3)	53 (31.7)	64 (33.9)	75 (27.0)	
Unknown	8 (1.3)	2 (1.2)	3 (1.6)	3 (1.1)	
Health care plan type, *n* (%)					
HMO	329 (51.9)	96 (57.5)	93 (49.2)	140 (50.4)	0.21
PPO	181 (28.5)	33 (19.8)	60 (31.7)	88 (31.7)	
Other	58 (9.1)	15 (9.0)	17 (9.0)	26 (9.4)	
Unknown	66 (10.4)	23 (13.8)	19 (10.1)	24 (8.6)	

Abbreviations: bid, twice daily; HMO, Health Maintenance Organization; ID, individualized dose; PPO, Preferred Provider Organization; SD, standard deviation; SMD, standardized mean difference.

[a]SMD <0.1 predefined as indicating covariate balance between the cohorts (based on propensity score weighting/matching).

of patients in the high ID stratum had received a PPA during baseline versus the low and medium ID groups (23.0% vs. 11.6% and 7.8% [SMD 0.29]); this was most noticeable for intravenous PPA (13.3%, 2.6%, and 1.2%, respectively [SMD 0.329]). PAH-related laboratory tests and comedications used during baseline are shown in Supporting Information S1: Tables 12 and 13 in the Supporting Information. No extreme propensity score weights were observed (range, 0.04–1.79), and propensity score weighted covariate distribution is shown in Supporting Information S1: Table 14 in the Supporting Information. ERA use (SMD 0.118), cerebrovascular disease (SMD 0.116), congenital heart disease (SMD 0.199), and use of anti-anxiety (SMD 0.153) and anti-arrhythmia (SMD 0.116) comedications during baseline did not reach balance and were included as regression covariates in a sensitivity-adjusted analysis.

Selexipag maintenance dose patterns over time after patients reached ID

Figure 4 shows the pattern of selexipag dose adjustments occurring over time after the index date (when the ID was reached). Adjustments in selexipag dose occurred across the ID strata, but the patterns of dose adjustments varied. A higher proportion of patients in the high ID group remained at their initial ID with fewer dose adjustments over time compared with patients in the low and medium ID groups: maintenance dose adjustments occurred in 121 (72.5%) patients in the low ID group, 117 (61.9%) in the medium ID group, and 96 (34.5%) in the high ID group (SMD 0.63) (Table 2). Maintenance dose was increased by ≥200 μg at least once in 112 (67.1%) patients in the low ID group, 91 (48.1%) in the medium ID group, and 75 (27.0%) in the high ID group (SMD 0.69) (Table 2). Maintenance dose was decreased by ≥200 μg at least once in 93 (55.7%) patients in the low ID group, 79 (41.8%) in the medium ID group, and 58 (20.9%) in the high ID group (SMD 0.46) (Table 2). Overall, these results suggest that selexipag dose adjustments were implemented frequently in the patients in the low and medium ID strata, but that the higher doses were not sustained in many patients.

Selexipag adherence and discontinuation according to selexipag ID level

Analysis of adherence to selexipag (defined as the proportion of days covered ≥80%, with patients permitted an off-treatment period of up to 45 days) showed no statistically significant difference in adherence among the three ID strata. Compared with the high ID group, the weighted odds ratio (95% confidence interval [95% CI]) for adherence was 0.48 (95% CI 0.20, 1.45) in the low

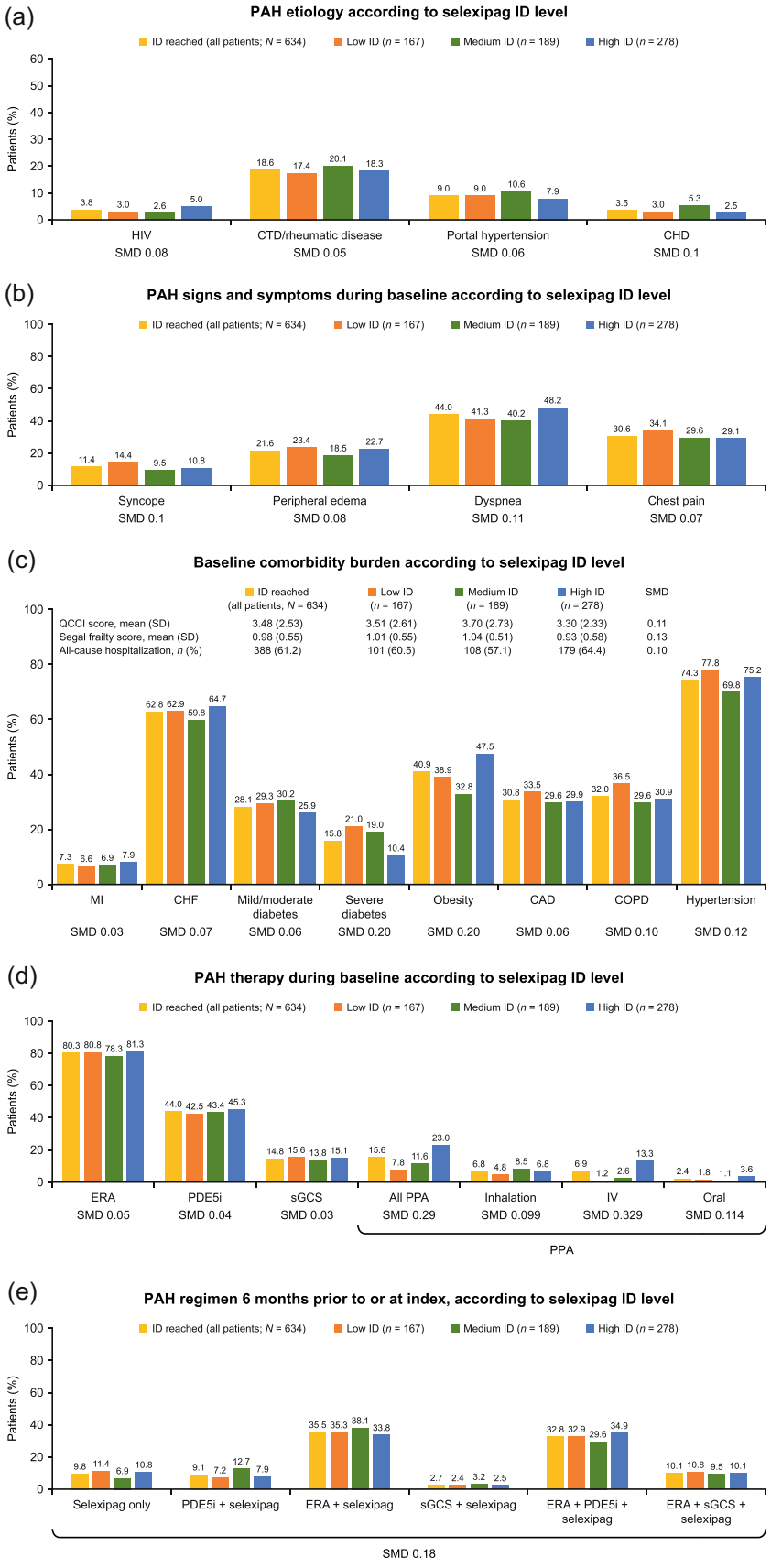

FIGURE 3 Baseline characteristics in PAH patients reaching their selexipag ID, according to ID level. ID levels: low (200–400 μg bid), medium (600–1000 μg bid), high (1200–1600 μg bid). SMD <0.1 predefined as indicating covariate balance between the cohorts (based on propensity score weighting/matching). Categories in panels (a–d) are not mutually exclusive, and patients can have multiple or none of the etiological categories, and percentages may not add up to 100%. Each indicator has an individual SMD. Categories in panel (e) are mutually exclusive, and one global SMD applies. CAD, coronary artery disease; CHD, congenital heart defect; CHF, congestive heart failure; COPD, chronic obstructive lung disease; CTD, connective tissue disease; ERA, endothelin receptor antagonist; HIV, human immunodeficiency virus; ID, individualized dose; ILD, interstitial lung disease; IV, intravenous; MI, myocardial infarction; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; PPA, prostacyclin/prostacyclin analog; QCCI, Quan-Charlson Comorbidity Index; SD, standard deviation; sGCS, soluble guanylate cyclase stimulator; SMD, standardized mean difference.

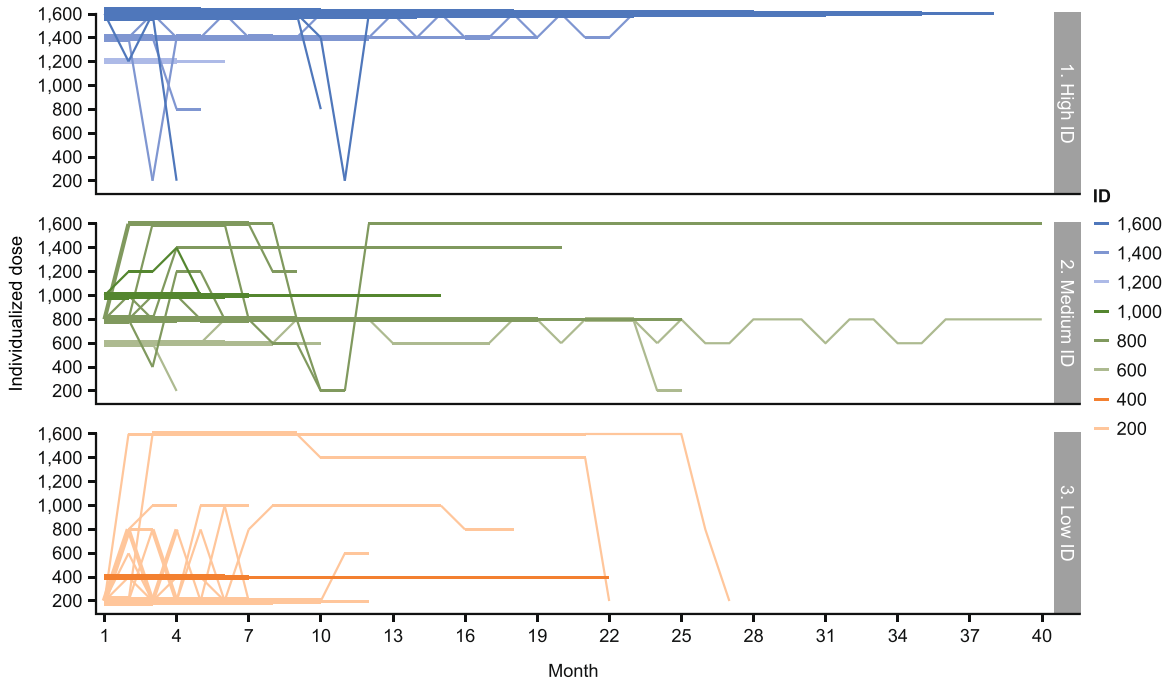

FIGURE 4 Selexipag dose pattern over time, according to ID level. The thickness of the line in the graph is proportional to the number of patients receiving each selexipag dose. ID levels: low (200–400 μg bid), medium (600–1000 μg bid), high (1200–1600 μg bid). ID, individualized dose.

ID group and 0.47 (95% CI 0.20, 1.08) in the medium ID group (Table 3). A sensitivity analysis adjusting for five baseline covariates differing between the ID groups (SMD >0.1) showed similar results.

Violation of the proportional hazard assumption was not detected for time-to-event outcomes (all $p > 0.20$). Compared with the high ID group, the weighted hazard ratio (95% CI) with respect to time to selexipag discontinuation was 1.00 (95% CI 0.65, 1.55) for the low ID stratum and 0.88 (95% CI 0.57, 1.36) for the medium ID stratum (Figure 5a and Table 3). A sensitivity analysis adjusting for five baseline covariates differing between the ID groups showed similar results to the main analyses (Table 3).

Time to first hospitalization during follow-up according to selexipag ID level

Adjusted Kaplan–Meier analysis showed that the risks of first all-cause hospitalization (Figure 5b) and first PAH-related hospitalization (Figure 5c) were similar during the follow-up period for patients in the three ID strata. A sensitivity analysis adjusting for five baseline covariates differing between the ID groups (SMD >0.1) showed similar results for all-cause hospitalization and PAH-related hospitalization as the weighted-only analysis (Table 3).

DISCUSSION

Selexipag targets the prostacyclin pathway, and the approach to dosing is consistent with other therapies available in this class where the patient's individual therapeutic dose is determined through titration. The goal of selexipag titration is to achieve a therapeutic dose of selexipag at the highest tolerable level for each patient and to maintain that dose level for as long as possible to increase the chances of a clinical response and optimize long-term outcomes.[17] Following this approach, selexipag demonstrated efficacy in the GRIPHON trial.[8] In the present study, nearly half the patients initiating selexipag did not achieve an ID. The data suggested that these patients tended to have slightly higher comorbidity scores and baseline hospitalization rates, fewer prior ERA exposures, and a PAH etiology more likely to be associated with connective tissue disease compared with patients who reached their ID. However, the claims data do not contain critical contextual information that would allow us to understand the reasons for selexipag discontinuation. For example, physician experience, PAH care settings (e.g., academic vs. community, primary care physician vs. specialist), and the availability of titration protocol and nursing support could all affect the decision to discontinue titration early.

Among patients reaching their ID, the distribution of the three ID strata was highly consistent with that

TABLE 2 Selexipag dose adjustments, overall and according to initial ID reached.

Parameter	All patients reaching selexipag ID ($N = 634$)	Low ID (selexipag 200– 400 μg bid) ($n = 167$)	Medium ID (selexipag 600– 1000 μg bid) ($n = 189$)	High ID (selexipag 1200–1600 μg bid) ($n = 278$)	SMD[a]
Number of times maintenance dose was adjusted, *n* (%)					
None	300 (47.3)	46 (27.5)	72 (38.1)	182 (65.5)	0.63
1	135 (21.3)	32 (19.2)	51 (27.0)	52 (18.7)	
≥2	199 (31.4)	89 (53.3)	66 (34.9)	44 (15.8)	
Number of times maintenance dose was increased by 200 μg, *n* (%)					
None	514 (81.1)	119 (71.3)	133 (70.4)	262 (94.2)	0.46
1	78 (12.3)	28 (16.8)	39 (20.6)	11 (4.0)	
≥2	42 (6.6)	20 (12.0)	17 (9.0)	5 (1.8)	
Number of times dose was decreased by 200 μg, *n* (%)					
None	516 (81.4)	124 (74.3)	144 (76.2)	248 (89.2)	0.31
1	83 (13.1)	26 (15.6)	30 (15.9)	27 (9.7)	
≥2	35 (5.5)	17 (10.2)	15 (7.9)	3 (1.1)	
Number of times dose was increased by ≥200 μg, *n* (%)					
None	356 (56.2)	55 (32.9)	98 (51.9)	203 (73.0)	0.69
1	157 (24.8)	43 (25.7)	55 (29.1)	59 (21.2)	
≥2	121 (19.1)	69 (41.3)	36 (19.0)	16 (5.8)	
Number of times dose was decreased by ≥200 μg, *n* (%)					
None	404 (63.7)	74 (44.3)	110 (58.2)	220 (79.1)	0.46
1	129 (20.3)	33 (19.8)	52 (27.5)	44 (15.8)	
≥2	101 (15.9)	60 (35.9)	27 (14.3)	14 (5.0)	

Abbreviations: bid, twice daily; ID, individualized dose; SMD, standardized mean difference.

[a]SMD <0.1 predefined as indicating covariate balance between the cohorts.

reported in the GRIPHON trial (42.9%, 31.2%, and 23.2%, respectively, in the high, medium, and low ID groups)[8] and very similar to that in the SPHERE study, a US registry of patients initiating selexipag (40.8%, 31.4%, 15.0%, and 12.8%, respectively, in high, medium, low, and other ID groups).[18,19] However, it should be noted that the GRIPHON protocol excluded patients with prior non-selexipag PPA exposure while SPHERE and the current study did not. In the current study, patients' baseline characteristics, PAH etiology, and comorbid conditions did not appear to be related to the ID levels reached. This suggests that the ID appropriate for each patient is independent of background patient characteristics and may be largely determined by their prostacyclin receptor density, as suggested by preclinical evidence.[20] There were, however, some differences in prior PAH treatments, with a higher proportion of patients in the high ID stratum having prior intravenous or oral PPA treatment (23.0%) compared with patients in the medium and low ID groups (11.6% and 7.8%, respectively). These proportions were consistent with those reported in SPHERE, where, at the time of selexipag initiation, 19% of patients were already receiving non-selexipag PPA.[19] In a Phase 3b trial of patients who switched to selexipag from inhaled treprostinil, a higher proportion of patients reached the high ID stratum (62.5%) than the medium or low ID strata (34.4% and 3.1%, respectively).[21] These findings suggest that previous PPA exposure might select a group of patients who are inherently more tolerant to selexipag and its prostacyclin-related side effects.

The pattern of dose adjustments during selexipag maintenance treatment in the present study showed that patients in the high ID stratum more frequently remained at a stable maintenance dose over time and required fewer dose adjustments compared with the patients in the low and medium ID strata. This may be partially explained by the fact that a higher proportion of these patients had prior PPA medication use. In contrast,

TABLE 3 Outcome measures during follow-up, according to ID level.

Parameter	Low ID (selexipag 200–400 μg bid) ($n = 167$)	Medium ID (selexipag 600–1000 μg bid) ($n = 189$)	High ID (selexipag 1200–1600 μg bid) ($n = 278$)
Adherence to selexipag (defined as the proportion of days covered ≥80%)			
Weighted OR (95% CI)	0.48 (0.20, 1.45)	0.47 (0.20, 1.08)	Reference
Weighted + adjusted[a] OR (95% CI): sensitivity analysis	0.52 (0.22, 1.23)	0.51 (0.22, 1.17)	Reference
Selexipag discontinuation after index date			
Weighted HR (95% CI)	1.00 (0.65, 1.55)	0.88 (0.57, 1.36)	Reference
Weighted + adjusted[a] HR (95% CI): sensitivity analysis	1.15 (0.77, 1.73)	0.99 (0.65, 1.53)	Reference
All-cause hospitalization			
Weighted HR (95% CI)	1.11 (0.84, 1.47)	1.04 (0.81, 1.35)	Reference
Weighted + adjusted[a] HR (95% CI): sensitivity analysis	1.14 (0.86, 1.52)	1.07 (0.82, 1.39)	Reference
PAH-related hospitalization			
Weighted HR (95% CI)	1.19 (0.85, 1.66)	1.18 (0.87, 1.59)	Reference
Weighted + adjusted[a] HR (95% CI): sensitivity analysis	1.23 (0.89, 1.70)	1.19 (0.88, 1.61)	Reference

Abbreviations: bid, twice daily; CI, confidence interval; ERA, endothelin receptor antagonist; HR, hazard ratio; ID, individualized dose; OR, odds ratio; SMD, standardized mean difference.

[a]Additionally adjusted for the following baseline covariates with SMD >0.1: ERA use (SMD 0.118), cerebrovascular disease (SMD 0.116), congenital heart disease (SMD 0.199), and use of anti-anxiety (SMD 0.153) and anti-arrhythmia (SMD 0.116) comedications.

patients receiving a low ID showed a pattern of frequent dose increases followed by dose reduction, presumably due to tolerability issues. This suggests that clinicians continue to try to increase the selexipag dose despite evidence that a patient has reached their highest tolerated dose.

Analysis of outcomes in the patients across the different dose strata showed that patients reaching a low, medium, or high ID had similar persistence (time to discontinuation) and a similar risk of all-cause and PAH-related hospitalizations. These findings are reassuring and support that consistent outcomes are achieved across the three ID levels in this diverse real-world population of patients with PAH. The findings also reinforced the consistency in efficacy across the three stratified ID groups observed in a recent meta-analysis, which included data from trials and other observational studies.[8,18,19,22]

Study strengths and limitations

The major strength of this study is the breadth of data for a rare condition like PAH captured in the Komodo Health database, which includes health insurance claims data from an average of 330 million individuals (including 8 million patients with at least one PH diagnosis or prescription drug that can be used to treat PAH). The closed claims have undergone insurance adjudication.

The study results should be interpreted alongside a few caveats. First, there are some limitations introduced by the use of data from a health care claims database, including the potential for minor coding errors and inconsistencies; data may not be generalizable to the overall US population; the presence of a claim for a dispensed prescription does not indicate that the medication was taken as prescribed; the prescription claim date is the date a medication was dispensed and not necessarily the date a patient begins treatment; over-the-counter medications and those administered in the inpatient setting are not captured in the database; there is potential for misclassification for PAH-related hospitalization identified through claims; important PAH-related clinical data such as functional class and risk stratification are unavailable; and important aspects such as adverse events that lead to discontinuation were not captured and therefore not available to be analyzed. Secondly, even though the current study is large in sample size among studies investigating the same research question, the given sample size only allows us

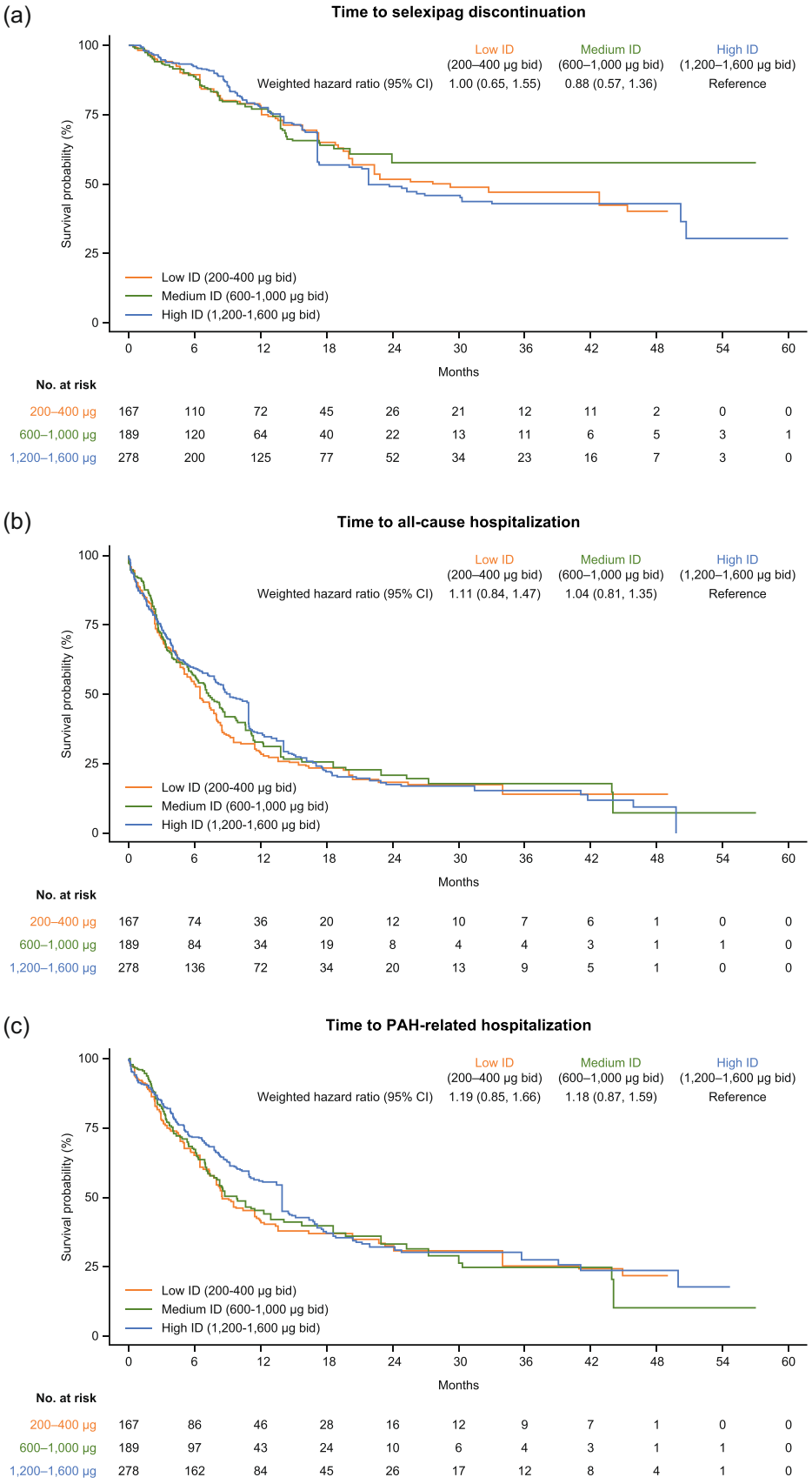

FIGURE 5 Kaplan–Meir curves for time to selexipag discontinuation (a), all-cause hospitalization (b) and PAH-related hospitalization (c) during the follow-up period, according to ID level. bid, twice daily; CI, confidence interval; ID, individualized dose.

to narrow down the possible range of relative risks that the data are comparable with. For example, when comparing the risk of selexipag discontinuation between low versus high ID groups, we cannot rule out a decreased hazard ratio of 0.65 and an increased hazard ratio of 1.55. Future studies with greater sample size and power should be conducted as replication and further narrow down the possible range of relative risks.

CONCLUSIONS

In routine clinical practice, selexipag initiation following the prescribed dose titration schema allows the selexipag maintenance dose to be optimized for each patient with PAH. Patients reaching their ID were distributed across dose ranges, but were mostly in the high ID stratum. These patients required fewer maintenance dose adjustments than those with a lower ID, likely due to their inherent ability to tolerate higher doses. Treatment persistence and hospitalization outcomes (including time to all-cause and PAH-related hospitalization) were similar irrespective of ID group. Future studies should evaluate the same outcomes within other databases (e.g., claims, electronic health records, Medicare) with greater study power.

AUTHOR CONTRIBUTIONS

Charles D. Burger, Wenze Tang, Yuen Tsang, and Sumeet Panjabi contributed to the study development and design. Charles D. Burger, Wenze Tang, and Yuen Tsang were involved in the acquisition of data, analysis, and interpretation of results. Charles D. Burger, Wenze Tang, Yuen Tsang, and Sumeet Panjabi were involved in all stages of manuscript development, writing, and revision.

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CONFLICT OF INTEREST STATEMENT

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Actelion Pharmaceuticals US, Inc., a Johnson & Johnson company, sponsored this study. Wenze Tang, Yuen Tsang, and Sumeet Panjabi are employees of Actelion Pharmaceuticals US, Inc. and may own stocks. The study sponsor was involved in all aspects of the research, including the collection of data, its analysis and interpretation, and approval of the final manuscript for publication. Charles D. Burger provided consulting services to Janssen, LLC.

DATA AVAILABILITY STATEMENT

The authors had full permission from a commercial data source to access the data sets and use them for this study. However, restrictions apply to the dissemination of these data, which were used under license for the current study; thus, these data are not publicly available.

ETHICS STATEMENT

This retrospective study used secondary, deidentified US health insurance claims data from Komodo Health, accessed via a data licensing agreement. The study did not involve the collection, use, or transmission of any identifiable patient data. Thus, institutional review board/ethical approval and informed consent were not required.

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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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