# Real-world experience of selexipag titration in pulmonary arterial hypertension

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**Abstract**

Selexipag is an oral selective prostacyclin receptor agonist, that was approved for use in patients with NYHA functional class II-III pulmonary arterial hypertension (PAH). In the GRIPHON study, selexipag demonstrated consistent efficacy for individualised doses in low, medium and high dose stratums. In order to better understand the real world approach to selexipag titration and to establish the individualised maintenance regimens used in our centre, we performed this retrospective study of the first 20 patients prescribed selexipag. Baseline characteristics differed from the GRIPHON study, with more combination therapy and comorbidities at baseline; however. Maintenance doses were stratified as low-dose in 10% (n=2), medium-dose in 70% (n=14) and high-dose in 20% (n=4). Furthermore, two of these patients were successfully transitioned from inhaled iloprost. This study demonstrates that selexipag can be safely initiated, titrated and transitioned in an outpatient setting to achieve an individualised dosing regimen.

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**Data availability statement:**

Data available on request from the authors

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**Introduction** :

Pulmonary arterial hypertension (PAH) is a devastating disease characterised by irreversible pulmonary vascular proliferation and remodelling resulting ultimately in right heart failure. Current therapy targets the nitric oxide, endothelin and prostacyclin pathways to promote pulmonary vasodilatation and reduce right ventricular afterload.[1, 2] Selexipag is an oral selective prostacyclin receptor agonist that is used in the treatment of PAH. In the GRIPHON trial the optimum dose of selexipag for maximum therapeutic benefit was determined to be the maximum tolerated dose for each individual patient. It is postulated that the

dose differs between patients due to variations in prostacyclin (IP) receptor expression and density.[3-5] The initiation dose of 200µg twice daily is prescribed and titrated weekly until a total daily dose of 3200µg is achieved or side effects become intolerable and an individual maximum tolerated dose is established. In the GRIPHON study this strategy demonstrated consistent efficacy for patients receiving low, medium or high selexipag doses.[6] In clinical trials selexipag demonstrated improvements in six minute walk distance (6MWD), n-terminal pro–brain natriuretic peptide (NT-proBNP), cardiac index (CI) and pulmonary vascular resistance (PVR), and a significant reduction was noted in the composite morbidity and mortality endpoint at a median of 70.7 weeks of treatment.[6, 7] In order to better understand the real world approach to selexipag titration we performed a retrospective analysis of the clinical and treatment characteristics of the first 20 patients prescribed selexipag in our centre.

**Aim** :

To perform a retrospective analysis of the clinical and treatment characteristics of the first 20 patients prescribed selexipag in our centre, with specific reference to drug titration and individualised maintenance doses.

**Materials and Methods** :

This study received ethical approval from the institutional ethical review board (IRB:1/378/2179 TMR). A retrospective search of the hospital database was performed to identify patients with confirmed PAH who commenced selexipag therapy, outside of a clinical trial, up until June 2020. Paper charts and the hospital information technology service (PatientCentre) were used to collect data that was subsequently fully anonymised. Patients were excluded if they were commenced on selexipag therapy in the context of a clinical trial, as their experience might not reflect 'real world' practice.

Data regarding patient demographics, PAH subtype, duration of PAH diagnosis, co-morbidities and regular medications were collected retrospectively. New York Heart Associated (NYHA) functional class (FC), patient risk stratification category (using the 2015 ESC/ERS PAH guidelines risk table) and 6MWD were also recorded.[2]. Details regarding selexipag indication, titration, maintenance doses, reported side effects and compliance were also recorded from patient records.

Statistical analysis was performed using GraphPad online statistical software. Fisher's exact test was employed to assess the statistical significance for categorical variables and t-test was used to calculate significance between means. A value $< 0.05$ was considered statistically significant ($P < 0.05$).

**Results** :

**Patient selection**

The first 20 patients prescribed selexipag in our centre, outside the setting of a clinical trial, were included in this analysis.

**Baseline characteristics**

Of the 20 patients, 65% (n=13) were female, the mean age was 55 ± 17 years, and 60% (n=12) had a diagnosis of Idiopathic PAH (IPAH), 30% (n=6) PAH associated with connective tissue disease (CTD-PAH) and 10%(n=2) were defined as other. Patients reported NYHA FC II symptoms in 50% (n=10) and FC III in 50% (n=10) at baseline. Baseline risk assessment was stratified as low in 25% (n=5), intermediate in 65% (n=13) and high risk in 10% (n=2). Dual combination therapy was prescribed in 90% (n=18) and triple combination therapy consisting of inhaled iloprost in 10% (n=2). Co-morbidities and additional baseline medications were common and are displayed in **Table 1** .

**Selexipag dosing**

Selexipag was commenced at 200 µg twice daily, following the protocol used in the GRIPHON study, increasing by 200 µg twice daily every seven days if side effects were tolerable.[6] The mean time to reach an individual maintenance dose was 67 days (± 26) and the mean total daily maintenance dose was 1830 µg

(± 548) at the end of the titration period. (**Table 2** ). Maintenance doses were stratified as low-dose in 10% (n=2), medium-dose in 70% (n=14) and high-dose in 20% (n=4). (**Table 3** ) Selexipag doses were reviewed at 6 months post initiation to ascertain if there were any subsequent dose titrations. These were not significantly different from individual maintenance doses established at the end of the titration period (p=0.699). (**Table 2** )

**Transitioning between prostacyclin therapies**

Two patients were prescribed triple combination therapy at baseline, including inhaled iloprost at doses of 5 µg six times a day. In both cases when selexipag was initiated at 200 µg twice daily, iloprost was simultaneously reduced to 5 µg four times a day by excluding the morning and the evening iloprost doses. Iloprost was then reduced to 5 µg twice daily in the second week, when selexipag was increased to 400 µg twice daily. This was well tolerated and inhaled iloprost was discontinued by week 3, with ongoing up titration of selexipag until individual maintenance doses were achieved. Final doses of 1200 µg twice daily and 1400 µg twice daily were achieved in these cases, which was significantly higher when compared to doses achieved by other patients in our centre. (p=0.037)

**Side effects and tolerance**

All patients reported side effects during selexipag titration. The most frequent reported side effects were nausea, gastroesophageal reflux (GERD) and vomiting in 65% (n=13), diarrhoea (65%, n=13) and headache in 65% (n=13). Jaw discomfort occurred in 45% (n=9). Clinical worsening occurred in 1 case, in a patient with CTD-PAH with FC III symptoms and high risk features at baseline, and required hospital admission for treatment of right heart failure. (**Table 4** ) No patients discontinued selexipag due to side effects or adverse events and there were no reported deaths. There was one reported case of new thyroid dysfunction (defined as subclinical hyperthyroidism).

**Discussion** :

The discovery of prostacyclin in 1976 and subsequent development of synthetic analogues revolutionised the field of PAH.[8, 9] These analogues include epoprostenol, iloprost and treprostinil, which target IP receptors to stimulate adenylate cyclase, increase cyclic adenosine monophosphate and promote beneficial downstream effects including pulmonary vasodilatation. Interestingly, these agents are not specific for the IP receptor and bind additional prostaglandin receptors that have diverse functions.[1, 10] Selexipag differs from these analogues, as it is structurally distinct from prostacyclin and is a selective agonist of the IP receptor.[6] In our centre, patients initiated on selexipag were more likely to be older (mean age 54± 16), with co-morbidities and additional baseline medications, when compared to patients included in the GRIPHON study. Additionally all patients were already on double combination therapy (90%, n=18) or triple therapy (10%, n=2) at baseline, reflective of current international best practice. These treatment characteristics emphasise the importance of clear guidelines on drug initiation and a standardised approach to transitioning between prostacyclin agents, as this is increasingly encountered in clinical practice.[11-17]

The TRANSIT-1 study was an open-label phase IIIb study that prospectively enrolled 34 patients with clinically stable PAH and assessed the transition from inhaled treprostinil to oral selexipag.[15] Dose reductions were implemented at the discretion of the investigators, highlighting that even in a controlled environment there can be considerable variability in titration approaches due to individual patient factors, including baseline prostacyclin requirements and reported side effects. In our centre two patients were transitioned from inhaled iloprost to oral selexipag. There is a paucity of published data limited to a case reports detailing the transition of iloprost to selexipag. [18] Iloprost is a stable analogue of prostacyclin, that can be administered via nebulisation six to nine times a day to preferentially vasodilate well-ventilated lung, with effects lasting 30 to 90 minutes.[19] Aerosolised iloprost is generally well tolerated as it typically avoids the systemic side effects of IV, subcutaneous or oral routes of prostacyclin administration, however there is some evidence that the cessation of iloprost overnight is associated with a deterioration in hemodynamic parameters.[20] In our cohort two patients transitioned from inhaled iloprost by reducing the frequency of drug administration, rather than reducing the dose administered or duration of treatment sessions. This method was well tolerated,

with complete drug cessation by week 3 in both cases. The final selexipag doses achieved in these two cases were significantly higher than those achieved by patients who were prostacyclin naïve, which one could speculate reflects iloprost associated IP receptor desensitisation or a higher tolerance of prostacyclin.

Any changes to baseline PAH therapy, including the initiation of oral prostacyclin therapy, should involve careful patient selection and multiparametric risk assessment.[2] All patients selected for selexipag therapy in this study were prevalent patients, with a mean time since diagnosis of 4 years, which may have implications for treatment response, as a post hoc analysis of patients included in the GRIPHON study demonstrated more pronounced treatment effects in patients who initiated therapy closer to their PAH diagnosis.[21] The importance of patient selection, individual assessment and consideration of hemodynamic parameters was highlighted by Yanaka et al in a study of 8 patients transitioned from IV epoprostenol to oral selexipag.[16] At evaluation approximately 4.4 months post selexipag transitioning, there was a significant reduction in cardiac index in these patients.[22] To address the knowledge gaps surrounding patient selection for oral prostacyclin therapy, an expert consensus statement on the treatment of PAH with oral prostacyclin agents was published.[23] This suggested 13 specific situations where oral selexipag may be suitable, with reference to patients with IPAH and CTD-PAH, with NYHA FC II-III and associated low to intermediate risk features. Parenteral prostacyclin was recommended for patients with high-risk hemodynamics or with NYHA FC IV symptoms.

Selexipag initiation was accompanied by extensive patient education of anticipated side effects during the titration period and comprehensive supervision by experienced PH nurse specialists who were familiar with individual patients. Individual maintenance doses were established by 67 days on average. In our study the majority of patients (73%, n=16) achieved maintenance doses in the medium-dose stratum, with fewer individual maintenance doses categorized in the high-dose stratum when compared to the GRIPHON study. This is likely multifactorial in nature and reflects differences in patient demographics and baseline characteristics, including older age, more comorbidities and additional baseline medications in our cohort. Prostacyclin-type side effects are common and led to drug discontinuation in twice as many participants when compared to placebo in the GRIPHON study.[6] Interestingly there were no cases of drug discontinuation in our cohort. Interestingly selexipag does not appear to lead to IP receptor desensitization over time, potentially due to partial antagonism of the IP receptor, and therefore future titrations are generally not be required once a maintenance dose is established.[24, 25] In our cohort, there was no significant difference between maintenance doses at the end of the titration period and doses at 6 months post drug initiation; however this is a relatively short interval and extended follow-up would be required to support this.

Important limitations of this study include its retrospective descriptive nature and the absence of long-term follow up. Due to the COVID-19 pandemic a considerable proportion of clinical assessments were performed using telemedicine technology and therefore hemodynamic data was not included. Nevertheless this study reflects 'real-world' experience of selexipag and helps to highlight appropriate patient selection for oral prostacyclin therapy and an approach to transitioning between prostacyclin agents. Additionally as selexipag titration was safely performed in an outpatient setting, guided by experienced PAH nurse specialists, this has important implications for resource utilisation and patient autonomy.

**Conclusion:**

This study of the first 20 patients prescribed selexipag in our centre demonstrates that selexipag can be safely initiated, titrated and transitioned in an outpatient setting to achieve an individualised dosing regimen. Prostacyclin side effects were common, but improved in the maintenance phase. There were no drug discontinuations or deaths in this study, but close observation and consideration of clinical, biochemical and hemodynamic parameters are recommended following any changes in drug therapy.

**References** :

1. Lang IM and Gaine SP. Recent advances in targeting the prostacyclin pathway in pulmonary arterial hypertension. *Eur Respir Rev* 2015; 24: 630-641. 2015/12/02. DOI: 10.1183/16000617.0067-2015.

2. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *The European respiratory journal* 2015; 46: 903-975. 2015/09/01. DOI: 10.1183/13993003.01032-2015.

3. Rajkumar R, Konishi K, Richards TJ, et al. Genomewide RNA expression profiling in lung identifies distinct signatures in idiopathic pulmonary arterial hypertension and secondary pulmonary hypertension. *Am J Physiol Heart Circ Physiol* 2010; 298: H1235-H1248. 2010/01/15. DOI: 10.1152/ajpheart.00254.2009.

4. Menyhart K and Nayler O. Influence of IP Receptor Density on Agonist Activity of ACT-333679, the Active Metabolite of Selexipag. *A66 PH: MOLECULES, CELLS AND ANIMAL MODELS* . pp.A2239-A2239.

5. Farber HW and Gin-Sing W. Practical considerations for therapies targeting the prostacyclin pathway.*European Respiratory Review* 2016; 25: 418-430. DOI: 10.1183/16000617.0083-2016.

6. Sitbon O, Channick R, Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension.*New England Journal of Medicine* 2015; 373: 2522-2533. DOI: 10.1056/NEJMoa1503184.

7. Simonneau G, Torbicki A, Hoeper MM, et al. Selexipag: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. *European Respiratory Journal* 2012; 40: 874-880. DOI: 10.1183/09031936.00137511.

8. Gomberg-Maitland M and Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. *European Respiratory Journal* 2008; 31: 891-901. DOI: 10.1183/09031936.00097107.

9. Surveillance for respiratory hazards in the occupational setting [American Thoracic Society].*Am Rev Respir Dis* 1982; 126: 952-956. 1982/11/01.

10. Kingman M, Archer-Chicko C, Bartlett M, et al. Management of prostacyclin side effects in adult patients with pulmonary arterial hypertension. *Pulm Circ* 2017; 7: 598-608. 2017/07/11. DOI: 10.1177/2045893217719250.

11. Galiè N, Barberà JA, Frost AE, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *New England Journal of Medicine* 2015; 373: 834-844. DOI: 10.1056/NEJMoa1413687.

12. Sitbon O and Gaine S. Beyond a single pathway: combination therapy in pulmonary arterial hypertension.*European Respiratory Review* 2016; 25: 408-417. DOI: 10.1183/16000617.0085-2016.

13. Sofer A, Ryan MJ, Tedford RJ, et al. A systematic review of transition studies of pulmonary arterial hypertension specific medications. *Pulm Circ* 2017; 7: 326-338. 2017/06/10. DOI: 10.1177/2045893217706357.

14. Chakinala MM, Feldman JP, Rischard F, et al. Transition from parenteral to oral treprostinil in pulmonary arterial hypertension. *J Heart Lung Transplant* 2017; 36: 193-201. 2016/07/30. DOI: 10.1016/j.healun.2016.06.019.

15. Frost A, Janmohamed M, Fritz JS, et al. Safety and tolerability of transition from inhaled treprostinil to oral selexipag in pulmonary arterial hypertension: Results from the TRANSIT-1 study. *J Heart Lung Transplant* 2019; 38: 43-50. 2018/11/06. DOI: 10.1016/j.healun.2018.09.003.

16. Yanaka K, Guillien A, Soumagne T, et al. Transition from intravenous epoprostenol to selexipag in pulmonary arterial hypertension: a word of caution. *European Respiratory Journal* 2020; 55: 1902418. DOI: 10.1183/13993003.02418-2019.

17. Pan IZ, Carey JR, Jacobs JA, et al. Transitioning Between Prostanoid Therapies in Pulmonary Arterial Hypertension. *Front Med (Lausanne)* 2020; 7: 81-81. DOI: 10.3389/fmed.2020.00081.

18. Bhura S and Gibbons W. TRANSITIONING FROM INHALED ILOPROST TO ORAL SELEXIPAG: A CASE REPORT.*Chest* 2019; 156: A741. DOI: 10.1016/j.chest.2019.08.714.

19. Olschewski H, Simonneau G, Galiè N, et al. Inhaled Iloprost for Severe Pulmonary Hypertension. *New England Journal of Medicine* 2002; 347: 322-329. DOI: 10.1056/NEJMoa020204.

20. Nakayama K, Emoto N, Tamada N, et al. The optimization of iloprost inhalation under moderate flow of oxygen therapy in severe pulmonary arterial hypertension. *Pulm Circ* 2018; 8: 2045894018781537-2045894018781537. 2018/05/21. DOI: 10.1177/2045894018781537.

21. Gaine S, Sitbon O, Channick RN, et al. The Impact of Time from Diagnosis at Baseline on Long-Term Outcome in the GRIPHON Study: Selexipag in Pulmonary Arterial Hypertension. *A105 GLORY DAYS: THE LATEST CLINICAL RESEARCH IN PAH* . pp.A2502-A2502.

22. Holthaus N, Prins K, Rose L, et al. EXPRESS: Transition from Parental Prostacyclin to Selexipag: A Case Series of Five Pulmonary Arterial Hypertension Patients. *Pulm Circ* 2019: 2045894019862167. 2019/06/20. DOI: 10.1177/2045894019862167.

23. McLaughlin VV, Channick R, De Marco T, et al. Results of an Expert Consensus Survey on the Treatment of Pulmonary Arterial Hypertension With Oral Prostacyclin Pathway Agents. *Chest* 2020; 157: 955-965. 2019/11/19. DOI: 10.1016/j.chest.2019.10.043.

24. Hardin EA and Chin KM. Selexipag in the treatment of pulmonary arterial hypertension: design, development, and therapy. *Drug Des Devel Ther* 2016; 10: 3747-3754. DOI: 10.2147/DDDT.S103534.

25. Gatfield J, Menyhart K, Wanner D, et al. Selexipag Active Metabolite ACT-333679 Displays Strong Anticontractile and Antiremodeling Effects but Low β-Arrestin Recruitment and Desensitization Potential. *J Pharmacol Exp Ther*2017; 362: 186-199. 2017/05/10. DOI: 10.1124/jpet.116.239665.

**Tables:**

**Tables 1:**

Table 1 describes the baseline characteristics of patients, prior to the initiation selexipag.

*Note data regarding 6MWD (N=16).

| Characteristics | N=20 (%) |
|---|---|
| Gender- Male / Female: no. (%) | 7(35) / 13(65) |
| Age: Mean (years) ± SD | 55 ± 17 |
| Time since PAH diagnosis - yr | 4 ± 4 |
| PAH classification | |
| IPAH | 12 (60) |
| CTD-PAH | 6 (30) |
| Group 5 PH (Sarcoid) | 1 (5) |
| Mixed disease | 1 (5) |
| WHO functional class – no. (%) | |
| I | 0 |
| II | 10 (50) |
| III | 10 (50) |
| IV | 0 |
| 6-Minute walk distance* – Mean (meters) ± SD | 331 ± 165 |
| Risk stratification | |
| Low risk | 5 (25) |
| Intermediate risk | 13 (65) |
| High risk | 2 (10) |

| Characteristics | N=20 (%) |
|---|---|
| Baseline medications for PAH – no. (%) | |
| ERA+ PD5 inhibitors | 17 (85) |
| ERA + sGC stimulator | 1 (5) |
| ERA+ PD5 inhibitors + PGI2 therapy | 2 (10) |
| Baseline medications (excluding targeted PAH med.) – no. (%) | |
| None | 1 (5) |
| 1-2 | 10 (50) |
| 3-6 | 7 (35) |
| >7 | 2 (10) |
| Co-morbidities | |
| None | 3 (15) |
| Respiratory | 11 (55) |
| Cardiovascular | 4 (20) |
| Gastrointestinal | 4 (20) |

**Table 2** :

Table 2 demonstrated the characteristics of selexipag titration and maintenance doses at the end of the titration period and at 6 months post selexipag initiation.

| Selexipag dosing | |
|---|---|
| Titration period – mean (days) ± SD | 67 ± 26 |
| Maintenance dose post titration – mean daily dose (μg) ± SD | 1830 ± 548 |
| Subsequent dose changes at 6 months – no. (%) | |
| No change | 15 (75) |
| Dose increase | 2 (10) |
| Dose reduction | 2 (10) |
| Data missing | 1 (5) |
| Drug discontinuation | 0 |
| Maintenance dose at 6 months – mean daily dose (μg) ± SD | 1758 ± 620 |

**Table 3** :

Table 3 describes the maintenance dose ranges obtained at the end of the initial titration period, which are classified as low (200-400 μg twice daily) medium (600– 1,000 μg twice daily) and high (1,200–1,600 μg twice daily). Low, nedium and high dose definitions are derived from the GRIPHON Study protocol.

| Maintenance doses (n=20) | Twice-daily dose (μg) | Patients N (%) |
|---|---|---|
| Low-dose stratum | 200 | 0 |
| | 400 | 2 (10) |
| Medium-dose stratum | 600 | 1 (5) |
| | 800 | 6 (30) |
| | 1000 | 7 (35) |
| High-dose stratum | 1200 | 2 (10) |
| | 1400 | 2 (10) |
| | 1600 | 0 |

**Table 4:**

Side effects reported during selexipag titration. 3 patients classified as "other" reported increased thirst (n=1), insomnia (n=1) and cold intolerance (n=1).

| Side effects | N=20 (%) |
|---|---|
| Nausea, GERD, Vomiting | 13 (65) |
| Diarrhoea | 13 (65) |
| Headache | 13 (65) |
| Jaw discomfort | 9 (45) |
| Myalgia, arthralgia | 7 (35) |
| Abdominal cramps | 3 (15) |
| Weight loss | 2 (10) |
| Flushing | 2 (10) |
| Clinical worsening of PAH | 1 (5) |
| Other | 3 (15) |