DOI: 10.1002/pul2.12441

RESEARCH LETTER

Pulmonary Circulation Open Access | PVRI | WILEY

Practices affEcting macitentan and selexipag patient persistence Rates utilizing pulmonary arterial hypertension clinical Site and patIent perSpecTives (PERSIST): a US qualitative analysis

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Funding information
Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson

Abstract

This real-world study explored factors affecting persistence with macitentan and selexipag treatment from the perspective of 23 healthcare professionals (HCPs) and 134 patients with pulmonary arterial hypertension between 2019 and 2022. Continuous patient/HCP communication and education were key drivers of persistence, as were early discussion and management of side effects.

KEYWORDS

healthcare professional discussion tool, patient perspectives, pulmonary hypertension

INTRODUCTION

Medication persistence is the duration from therapy initiation to discontinuation.[1] Treatment persistence is important for patients with pulmonary arterial hypertension (PAH) to delay progression of this debilitating, life-limiting disease and maintain functional status.[2] Studies show adherence to and persistence with PAH medication can be suboptimal, yet limited data are available on treatment persistence and its factors among US patients with PAH.[2–7]

Macitentan and selexipag are oral PAH treatments that reduce the risk of disease progression and hospitalization.[2,8–10] We report findings from PERSIST (**P**ractices aff**E**cting macitentan and selexipag patient persistence **R**ates utilizing pulmonary arterial hypertension clinical **S**ite and pat**I**ent per**S**pec**T**ives), a US real-world study that explores factors affecting

macitentan and selexipag persistence from the perspective of healthcare professionals (HCPs) and patients with PAH.

METHODS

PERSIST was a cross-sectional quantitative and qualitative study evaluating HCP and patient perspectives on treatment persistence with macitentan and/or selexipag. The objective was to explore factors that modulate persistence by evaluating and comparing HCP and patient experiences via surveys and interviews.

The study was approved by the Advarra (Columbia, MD) Institutional Review Board and conducted in accordance with applicable regulatory requirements. All patients provided written informed consent, and HCPs verbally consented.

Patient eligibility and survey

Patients with PAH were recruited through the phaware® advocacy group,[11] social media advertisements, and direct-to-patient outreach (email, phone, or text). Eligible patients were aged ≥18 years with self-reported exposure to macitentan and/or selexipag for PAH treatment over the previous 12 months, meeting ≥1 of these criteria: persistent selexipag (stable maintenance dose for ≥1 month over the previous 12 months, without any interruptions of >30 days); persistent macitentan (≥3 months over the previous 12 months, without any interruptions of >30 days); discontinued (discontinued macitentan or selexipag for >30 days during the previous 12 months).

Eligible patients completed one 45-min online survey with closed-form questions (a set of predefined responses; Table S1). The questions assessed reasons for persisting on or discontinuing macitentan/selexipag, with separate sections for each medication (eligible patients completed surveys on both).

Patients received medication according to usual care in their treatment setting; the sponsor provided no medication. All treatment dosing and administration were at the treating physician's discretion.

HCP eligibility and survey

HCPs (advanced practice providers, nurse coordinators, or medical doctors) were recruited from sites with ≥10 patients prescribed macitentan or ≥8 prescribed selexipag for PAH treatment in a 12-month period. Site persistence rates were calculated based on specialty pharmacy medication shipment rates for the site. High- and low-persistence sites demonstrated >80% persistence and <40% persistence, respectively, over 12 months. Within each clinical site, an HCP familiar with clinical practice for macitentan/selexipag administration was chosen.

Semi-structured HCP interviews were conducted by experienced researchers. All HCPs were asked the same core, open-ended questions, plus additional elicitation questions based on responses. Interviews were audio-recorded and transcribed.

Statistical analyses details are in Supplementary Materials.

RESULTS

Surveys were conducted between November 2019 and August 2022. Twenty-three HCPs at 23 unique clinical sites responded (Figure S1); most were physicians ($n = 14$; 60.9%) or nurse practitioners ($n = 4$; 17.4%) (Table S2). Ninety-six patients provided 134 responses (macitentan alone = 40, selexipag alone = 18, both = 38; Figure S1); most were female (79.1%) and White (78.4%), and all were high-school graduates (79.9% had college education) (Table S3**)**.

The surveyed HCPs ($n = 23$) reported the most common reasons for patient non-persistence as side effects or tolerability (87.0%), treatment cost (82.6%), and perceived inadequate efficacy (69.6%; Figure S2a). At low-persistence sites ($n = 11$), HCP perception of persistence differed from actual persistence according to medication shipment rates (85.6% vs <40%, respectively); at high-persistence sites ($n = 13$), no such discrepancy existed (88.1% vs ≥80%). HCPs recommended educating patients about PAH and its treatment (73.9%) as the key strategy to improve persistence; reviewing test data with patients (26.1%), discussing treatment expectations upfront (26.1%), and managing side effects (26.1%) were also considered important (Figure S2b).

Of the 134 patient responses, 112 were considered persistent and 22 discontinued. Ninety-three (83.0%) persistent and 10 (45.5%) discontinued patients self-reported that they always took their PAH medication as prescribed. In persistent patients, the most common reasons for not taking PAH medication as prescribed were forgetfulness (13.4%), high cost (8.0%), and fear of side effects (6.3%); in discontinued patients, reasons cited were fear of side effects (36.4%), high cost (22.7%), and forgetfulness (13.6%) (Figure S3a). The most frequently cited reasons for taking PAH medication in persistent and discontinued patients were symptom improvement (70.5% vs 45.5%, respectively), feeling better (58.9% vs 31.8%), HCP instruction

(52.7% vs 54.5%), and fear of getting sick (44.6% vs 27.3%) (Figure S3b).

Overall, most patients (≥95%) received information about PAH from their HCP (Table S4). The next most common information sources were websites (50%) and social media (36.6%) (Table S4). Discontinued patients were more likely than persistent patients to obtain information from websites (63.6% vs 47.3%, respectively) or social media (45.5% vs 34.8%).

The patient survey identified insights in three key areas: most felt they were involved in decision-making on treatment, received clear instructions and information about medication, and felt comfortable calling their HCP or asking questions (Figure 1). However, approximately one-third did not receive sufficient resources to understand their medication or anticipate when they might feel better. Just under half felt comfortable disagreeing with HCP recommendations. Based on these insights, Figure 1 proposes an HCP discussion tool to support conversations with patients.

DISCUSSION

Our survey shows differences in HCP and patient perspectives on persistence with PAH treatment. Issues related to side effects were the most frequent reason for non-persistence identified by HCPs and patients who discontinued treatment; both groups also identified treatment costs as a persistence barrier. The most common reasons for persisting with PAH treatment cited by patients were that it "improves my symptoms" and "makes me feel better." A greater proportion of persistent patients cited "I fear getting sick if I stop," which may reflect greater awareness than discontinued patients of these treatments' long-term potential to delay disease progression. Among low persistence sites, HCPs perceived persistence to be higher than indicated by medication shipment data, possibly because patients under-report non-persistence to their provider team or due to pharmacy–provider communication delays, among other possibilities. As low persistence may impact patient outcomes,[2,3,6] this disconnect warrants further investigation.

The surveyed HCPs recognized the importance of educating patients on PAH and its treatment. Although most patients had discussed treatment choices with their HCP, some were uncomfortable asking questions and only half felt "very/extremely comfortable" disagreeing with HCP recommendations. Most patients reported receiving information on PAH and their treatment from their HCPs, but many also sought information from social media and the internet, suggesting the need for better access to reputable PAH educational materials. This was evidenced by discontinued patients indicating that their information needs were not fully met by their HCP interactions, highlighting the importance of HCPs directing patients to validated online information and the role of patient advocacy partners in disseminating reliable materials to meet educational needs.

Continuous engagement with patients, improved patient and HCP two-way communication to overcome patients' reluctance to raise issues, and disease and treatment education are needed to facilitate persistence. Proactive discussion about side effects and their management, as well as patients' fear of side effects, is a key intervention to support treatment persistence. Our findings indicate current engagement processes might not always meet patient needs, and new ways to engage with low-persistent patients are needed. To support better communication, we developed a simple discussion tool for HCPs to use with patients, based on insights gained from patient surveys. Best-practice guidelines recommend patients with PAH be managed by a multidisciplinary team, including social workers to provide wider support and case managers to coordinate care and help with financial resources.[2] Pharmacists can also play an important role in mitigating barriers to adherence and managing treatment costs.[6] Our findings support previous observations that partnership and improved communication between provider teams, patients, and specialty pharmacies would facilitate early identification of non-persistence.[7] We also heard from patients that advocacy groups can educate providers and communicate patient needs and fears.

Patient survey limitations include the small sample size and disproportionately low number of discontinued versus persistent patients, which precludes statistical analysis; a lack of patient demographic diversity, including race/ethnicity, making it difficult to compare data and draw firm conclusions; potential patient selection bias; and recall bias. Patient participants were highly educated; the time required to complete the survey may have biased toward educated respondents. Study enrollment was open longer than expected (3 years vs 3 months) and could have been impacted by the COVID-19 pandemic. Geographic information was not collected, and surveyed patients and HCPs were not necessarily from the same sites, which may have contributed to differences between HCP and patient perspectives. To further improve applicability to the wider PAH community, future surveys should be designed to include wider patient diversity and inclusion.

In summary, our study highlights the importance of continuous patient engagement and improvement of patient–HCP communication, with education on the disease and treatment. Early discussion and management of side effects is important in patients with PAH.

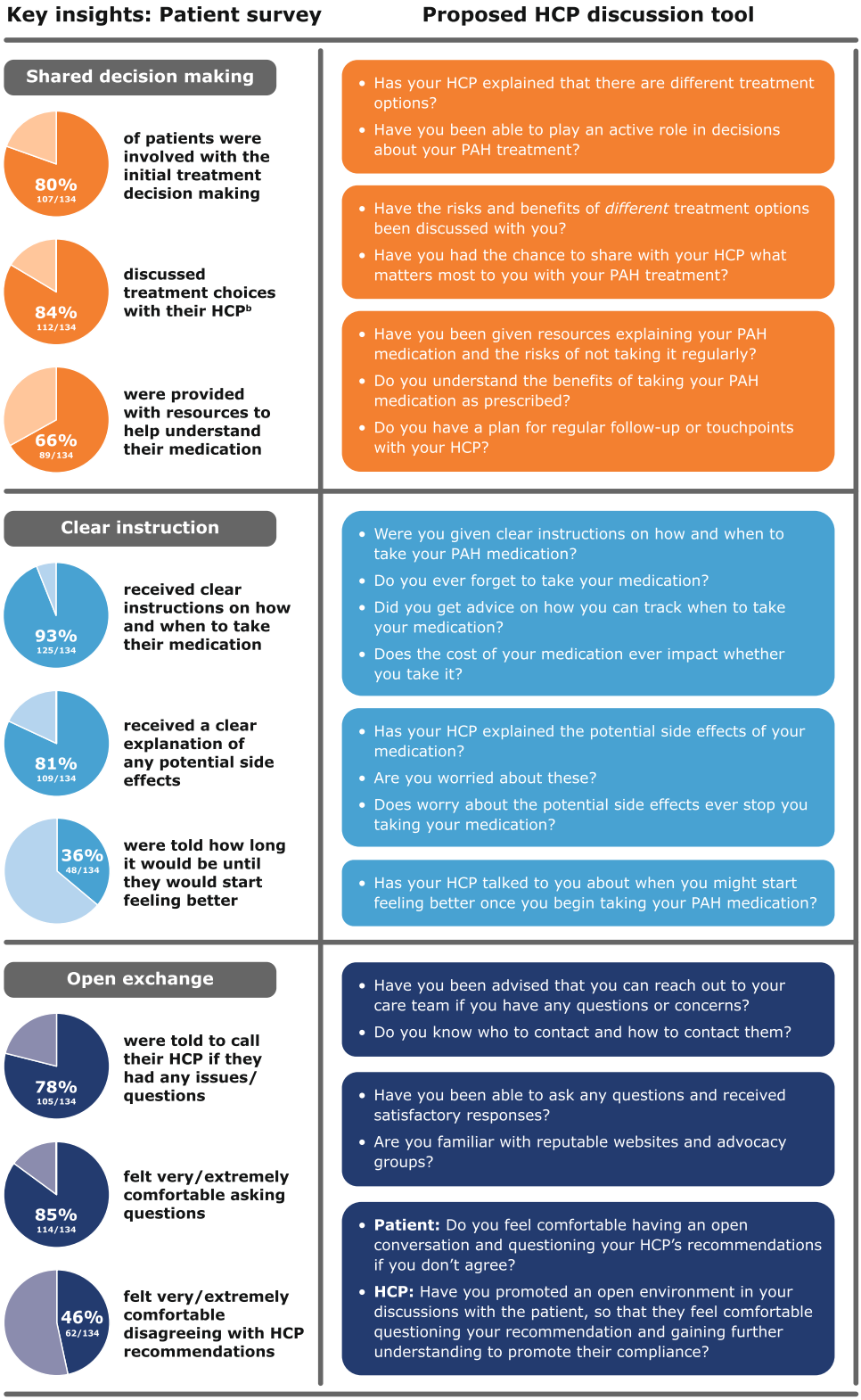

FIGURE 1 HCP discussion tool to enhance patients' engagement with their PAH treatment: based on key insights on discussions of treatment choice, shared decision-making, and comfort in asking questions from the patient survey ($N = 134$[a]). [a] Data were missing for 1 patient. [b] In the past 12 months. Abbreviations: HCP, healthcare professional; PAH, pulmonary arterial hypertension.

CONFLICTING INTERESTS

OA Shlobin has served on advisory boards for Johnson & Johnson, United Therapeutics, Merck, and Gossamer Bio and served as a Consultant for United Therapeutics, Altavant, and Gossamer Bio. C. McEvoy has served on advisory boards for Janssen and United Therapeutics and served as a Consultant for United Therapeutics. F. Rogers has served on the speakers bureau for United Therapeutics, served as a Consultant for Actelion, and served on advisory boards for Johnson & Johnson, United Therapeutics, Merck, and Gossamer Bio. S. Studer, T. Tobore, G. Gomez-Rendon, and M. Rahman are employees of Actelion Pharmaceuticals US, Inc., Titusville, New Jersey. M. Kingman has received consulting fees from and served on the advisory boards and speakers bureaus for Bayer, Gilead, Johnson & Johnson, United Therapeutics, and Arena Pharmaceuticals.

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AUTHOR CONTRIBUTION

Gabriela Gomez-Rendon, Tobore Tobore, and Mohammad Rahman were involved in the conception and design of the study. Gabriela Gomez-Rendon, Mohammad Rahman, Tobore Tobore, and Colleen McEvoy conducted data acquisition, analysis, and interpretation. All authors helped to develop the manuscript, critically reviewed, and approved the final article for publication.

ACKNOWLEDGMENTS

This work was sponsored by Actelion Pharmaceuticals US, Inc., a Johnson & Johnson company. Medical writing support was provided by Ify Sargeant, DPhil, and Kathryn Quinn, PhD, on behalf of Twist Medical, and was funded by Actelion Pharmaceuticals US, Inc., a Johnson & Johnson company. This study was funded by Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson. SS, TT, GG-R, and MR are employees of the funding organization and as study contributors were involved in the collection of data, its analysis and interpretation, and had the right to approve or disapprove publication of the finished manuscript.

ETHICS STATEMENT

The study protocol was reviewed by Advarra Institutional Review Board (Columbia, MD; Approval number MOD01212373), and the study was conducted in accordance with the protocol and applicable regulatory requirements.

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SUPPORTING INFORMATION

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

How to cite this article: Shlobin OA, Bruce G, Gomez-Rendon G, Kingman M, Rahman M, Rogers F, Studer S, Tobore T, McEvoy C. Practices affEcting macitentan and selexipag patient persistence Rates utilizing pulmonary arterial hypertension clinical Site and patIent perSpecTives (PERSIST): a US qualitative analysis. Pulm Circ. 2024;14:e12441. https://doi.org/10.1002/pul2.12441