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Patient Perspectives on Fixed Dose Combination Therapy for Pulmonary Arterial Hypertension: Exploratory Focus Group Research

Jean M. Elwing[1] | Stacey Barta[2] | Tim Smith[3] | Gabriela Gomez Rendon[4] | David Lopez[4] | Wesley Peters[5] | Marinella Sandros[4] | Akshay Muralidhar[6,7]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, University of Cincinnati, Cincinnati, Ohio, USA | [2]Pulmonary Hypertension Patient Engagement Research Council, Santee, California, USA | [3]Pulmonary Hypertension Patient Engagement Research Council, Scottsdale, Arizona, USA | [4]Actelion Pharmaceuticals US Inc., A Johnson & Johnson Company, Titusville, New Jersey, USA | [5]Evidera, Wilmington, North Carolina, USA | [6]Barrow Neurological Institute, Phoenix, Arizona, USA | [7]Arizona Pulmonary Specialists, Phoenix, Arizona, USA

Correspondence: Jean M. Elwing (elwingj@ucmail.uc.edu)

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ABSTRACT

Pulmonary arterial hypertension (PAH) requires lifelong medication, with patients taking an average of 12 tablets/day. Several chronic diseases can be treated with a fixed-dose combination (FDC) tablet, decreasing patient pill burden and increasing adherence. This exploratory research, conducted via focus groups, asked 13 patients with PAH for their insights about the use of FDC (2 PAH treatments in a single tablet), its potential benefits, and challenges to its use. At the time of the focus groups (July 2023), no FDC medications were available for PAH and the discussions were therefore hypothetical. Focus group transcripts were analyzed by a qualitative research specialist to identify key themes. Most participants were unfamiliar with FDC prior to taking part in the focus groups; however, during the engagement, 12/13 participants expressed interest in taking FDC as single-tablet therapy for their PAH. In general, participants saw the potential benefits as improved convenience, less time spent navigating insurance coverage, and improved adherence. Participants felt that reducing their tablet count by just one tablet would be meaningful to them. Concerns were raised about the potential difficulty with medication titration and challenges distinguishing between the side effects of two combined medications. This exploratory research provides insight into the perceptions of US patients on the utility of FDC in PAH and highlights an unmet need for patient education on medication adherence in PAH.

1 | Introduction

The benefits of targeting multiple pathways in pulmonary arterial hypertension (PAH) through initial or sequential combination therapy were first established by the SERAPHIN and AMBITION trials almost a decade ago [1, 2]. Following the inclusion of upfront combination therapy in the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) PAH guidelines, treatment practice evolved, with upfront double or triple therapy and sequential combination therapy becoming more common [3–7]. Based on current evidence, the latest ESC/ERS guidelines for PAH recommend initial double

Stacey Barta and Tim Smith: Patient Authors.

therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase 5 inhibitor (PDE5i) in all patients who have PAH without cardiopulmonary comorbidities and negative vasoreactivity testing; the guidelines also endorse initial triple therapy (including a prostacyclin analog) in high-risk patients or those at intermediate risk with severe hemodynamic impairment [8].

Despite guideline recommendations, there are practical challenges for combination therapy in PAH [9]. In routine clinical practice, adherence to PAH-specific therapy remains suboptimal and a systematic review of the literature suggests that ~40% of patients with PAH are not fully adherent with their medication [10]. Younger patients with PAH are at the highest risk of nonadherence [11]. Polypharmacy, comorbidities, complexity of combination therapy regimens, and cost can all pose barriers to adherence [11–13]. US claims data indicate that patients with PAH take a mean (standard deviation) of 11.8 (8.2) tablets/day [14]. Daily pill burden is known to impact quality of life in chronic diseases and adherence to therapy regimens [15]. Many specialty medications are sourced through specialty pharmacies and require prior authorization before a patient can start taking them, which means insurance providers must approve the medication as "medically necessary" before agreeing to cover any of the cost [16]. These processes create barriers by adding both cost and inconvenience for patients seeking PAH-specific therapies [13, 17]. Communicating with physicians, pharmaceutical companies, and insurance providers to guarantee access to multiple components of combination therapies can be time-consuming and stressful [17].

Fixed-dose combination (FDC) therapy has been introduced for several chronic debilitating diseases, including hypertension and diabetes, with improvements noted in both adherence and outcomes [18–21]. Based on the findings from the A DUE trial [22], an FDC therapy of the ERA macitentan and PDE5i tadalafil has recently been approved in the United States as a once-daily tablet for the chronic treatment of PAH in adults with World Health Organization (WHO) Functional Class II–III [23]. Patients interviewed about taking the FDC tablet reported psychological benefits and reduced stress due to managing fewer tablets [24]. A simplified treatment may offer benefits in terms of convenience and improved adherence for patients with PAH. However, clinicians need to consider patient choice, clinical characteristics, and cost before prescribing any medication, including an FDC therapy [25].

This exploratory research, conducted via focus groups, aimed to ask patients with PAH how they felt about the use of FDC therapy, their perceptions of its potential benefits, and what they saw as challenges to its use and implementation. At the time this study was conducted (July 2023), there were no approved FDCs for PAH in the United States and focus group participants were not given any information about the proposed FDC composition. Most participants were unfamiliar with FDC; therefore, our research is intended to provide a sense of patients' perspectives around FDC in general, rather than an indication of how a particular FDC may fit into the PAH treatment paradigm.

2 | Methods

2.1 | Participants

Eligible participants were English-speaking US residents with PAH who were part of Johnson & Johnson's Pulmonary Hypertension (PH) Patient Engagement Research Council (PERC). Johnson & Johnson's PERC program spans more than 13 chronic disease states and includes patients and caregivers from a diverse group of ethnic and sociodemographic backgrounds. PERC participants volunteer to share their insights at specific focus groups, which have previously included topics such as barriers to trial participation, disease-specific outcome measures, and insurance copay card utilization and policies [26–29]. Participants provided written informed consent and were compensated for their time. This study was conducted in accordance with the Declaration of Helsinki (1964 and later amendments). The analysis was classified as market research and institutional review board approval was not required.

Participants were adults (aged $\geq$18 years) from Johnson & Johnson's PH PERC with a self-reported diagnosis of PAH; caregivers were not included. Individuals with sarcoidosis, pulmonary embolism, chronic thromboembolic PH, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, or pulmonary veno-occlusive disease were excluded.

2.2 | Research Design

Three virtual, 2-h focus group sessions were held in July 2023 to gather insights from participants about FDC for PAH (Figure 1). Each session was attended by four or five participants and at least one member of the sponsor's medical team. Sessions were moderated by a research specialist (from CorEvitas LLC) using a semi-structured discussion guide, interspersed with "show of hands" and formal polling questions with multiple-answer options. The semi-structured discussion guide included questions and prompts around how participants would have felt about starting double therapy with FDC if they had the option when they began treatment, the potential benefits, and any possible barriers or drawbacks. They were also asked to consider whether FDC would impact the process of escalating to triple therapy earlier in disease management. The FDC was defined in the focus groups as "single tablets that contain a combination of two or more active ingredients. The single-dose tablet may replace other individual medications, reducing the overall tablet count" [19]. The moderator explained that for triple therapy, the FDC would be a single tablet with two medications and the third medication would be an additional tablet or injection. Finally, participants' opinions were gathered on the potential impact of FDC on pill burden, adherence, access to medications, and costs. Each focus group session was audio-recorded and transcribed.

2.3 | Analysis

A trained qualitative research specialist summarized key themes from the focus group discussions, and a debrief session was held

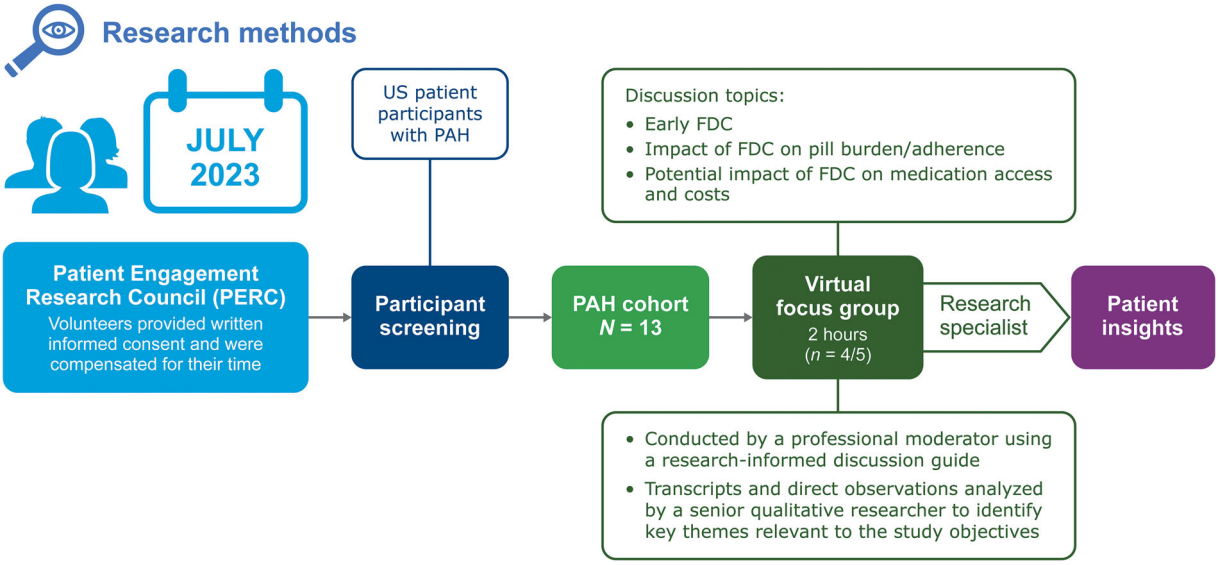

FIGURE 1 | Research design. FDC, fixed-dose combination; PAH, pulmonary arterial hypertension.

with the study sponsor during which the sponsor's medical team members added their observations on key themes identified during the discussions. Responses to polling questions were analyzed descriptively. Transcript analysis consisted of applying a narrative analysis framework to review and code written transcripts generated from audio-recordings and direct observations from the focus groups based on a priori topics and participants' experiences. Analysis was conducted using qualitative research analysis software (MAXQDA) to identify key themes. Research specialists analyzed the themes derived from transcript coding and sponsor review to synthesize findings in a written report.

3 | Results

3.1 | Participants

In total, 13 patients attended one of three 2-h virtual focus groups held in July 2023. The median (range) age of the participants was 51 (29–71) years, more than two-thirds (9/13) were female, and more than two-thirds (9/13) were White (Table 1). Many of the participants were highly educated—nine had a bachelor's or post-graduate degree—and had a good understanding of their disease and medication. More than half (8/13) had received triple therapy for their PAH (Table 1).

TABLE 1 | Participant demographics.

Characteristic	*N* = 13
Age, years, median (range)	51 (29–71)
Age category, years, *n* (%)	
18–34	2 (15)
34–54	6 (46)
55–64	3 (23)
≥ 65	2 (15)
Self-reported gender, *n* (%)	
Female	9 (69)
Male	4 (31)
Race/ethnicity, *n* (%)	
White	9 (69)
Black/African American	2 (15)
Hispanic/Latino	2 (15)
Highest level of education, *n* (%)	
Postgraduate education	5 (38)
Bachelor's degree	4 (31)
Trade school	2 (15)
Some college	1 (8)
High school	1 (8)
Previously taken triple therapy, *n* (%)	8 (62)

3.2 | Familiarity With and Receptiveness to FDC

Participants were advised that FDC therapy consists of a single tablet that contains a combination of two or more drugs. The FDC might replace the two individual drugs, thereby reducing the overall pill count. Participants were asked to consider a hypothetical FDC therapy for PAH that would be a single tablet with two medications. Most (11/13) participants were unfamiliar with FDC, but were receptive to the concept; 12 of 13 expressed an interest in taking FDC, with the remaining participant expressing skepticism about trying any medication that lacked a history of long-term real-world use.

3.2.1 | Early Double Therapy With FDC

Participants were asked to think back to when they started their PAH treatment and consider how they would have felt starting double therapy with FDC early in the disease course. Responses were divided; roughly half the group (7/13) believed that this would have impacted them positively and the remaining

participants (6/13) highlighted that the benefits of early FDC might not apply to all patients with PAH, particularly those at lower risk. These six participants were more receptive to the idea of initiating treatment with separate tablets to distinguish side effects between medications (especially during titration) before switching to FDC.

> *You could see which [tablet's] giving you bad side effects. If you take a [double], you wouldn't know which one it was.*

Perceived benefits of early FDC on adherence were considered important, particularly for those newly diagnosed with PAH. One participant recalled their own struggle to comply with a medication regimen during their youth, highlighting an unmet need for patient education around combination therapy in general.

> *I was young, barely 18: the definition of 'not adherent.' Having two different pathways in one ... would've really, really, really helped me be able to tackle that. I didn't even know about triple pathways yet ... and my specialists weren't talking about it.*

Four of the participants felt that FDC could serve as an opportunity to teach those newly diagnosed with PAH about the importance of adherence, with FDC being a "reward" after demonstrating adherence with separate tablets.

> *It's a great communication tactic: 'Here's these two different pathways or whatever; we're gonna start you on the [separate tablets,] and if you respond well, you're taking them every day ... we can work towards the goal of the one tablet.'*

3.2.2 | Escalation to Triple Therapy While on FDC

In total, 8/13 participants had received triple therapy. These eight participants were asked how they would have felt about escalating to triple therapy while taking FDC, four indicated they would have been comfortable with this due to their need for immediate therapy and desire to avoid multiple prior authorizations. The remaining four would have preferred to start on separate tablets until side effects were identified and resolved before switching to FDC.

3.3 | Perceived Benefits of FDC

3.3.1 | Overall Health

Participants were asked whether using multiple medications affects the way they think about their overall health and to consider whether FDC would affect that perception. Seven participants did not respond, while three participants said that taking FDC would be no different than taking two separate medications, and three others believed fewer tablets would help improve their perception of their overall health.

> *The visualization of ... the more you see, the more [tablets], you feel like you're [doing] worse. So, the less you see, you start feeling better, at least for me, speaking personally.*

3.3.2 | Overall Convenience

Participants considered convenience (reduced tablet count/administration frequency and, potentially, less time dealing with prior authorization issues) to be the most compelling benefit of FDC (Table 2).

3.3.3 | Reduced Tablet Count and Improved Convenience

All of the focus group participants viewed the reduced tablet count and improved convenience of FDC positively. They agreed that simplifying therapy from two tablets to one with FDC would have a positive impact on the way they perceived their pill burden. Even those participants who took a high number of tablets suggested that taking just one less tablet a day would make a difference to them.

> *It'd be nice to just take 1 [tablet] instead of keep taking [tablets] all the time or a handful of them. I took 16 of them for breakfast this morning.*

One participant commented that a reduced pill count would also make sorting medication an easier task.

> *It takes me about 45 minutes to an hour to sort out medication every Sunday. ... [With FDC] it would be one less [tablet] I had to sort.*

There was general agreement that the reduced tablet number could improve adherence, with most (10/13) participants believing that they would be less likely to miss doses of medication with FDC.

> *When I was new and on [double] therapy, I had to take one [tablet] twice and another thrice [daily]. It would make me panic whether I took it. If it was combined, it would make it so much easier.*

However, two participants were worried that forgetting to take a tablet would have a greater impact with FDC.

3.3.4 | Fewer Doses per Day

The potential to reduce the number of times tablets are taken each day was seen as a key benefit of FDC.

> *This is the most important benefit we've discussed—more exciting than reducing the pill burden.*

> *I would pay more for the convenience. I'm less apt to miss any doses, and I know how my mind works.*

TABLE 2 | Summary of participants' perceived benefits of FDC in PAH.

Perceived benefit	Participant insights	Individual perspectives
Reduced pill count and improved adherence	Even a small reduction in daily pill count was considered meaningful in terms of convenience and making adherence easier, particularly for new patients	*"There's less to worry about. There's less of a burden, and then there's less to think about as far as maintaining to [adherence]."*
Fewer doses per day	The potential to eliminate a dose, especially in the afternoon, was considered helpful	*"When I first started having this disease 15 years ago, I missed so many pills, so many afternoon doses. … If you could take one pill away and make it easier on a patient, that's great."*
Less time spent navigating access	Fewer potential prior authorizations could reduce the stress and time spent dealing with insurance issues	*"I wouldn't have … 3 months wait for this and 3 months wait for that and try to get prior auth [orization] for two things. … It just takes that much longer if you're trying to do that with two separate tablets versus one going out of two pathways. I just think that would have been amazing."*
Potential cost savings	While FDC may be expensive as it is a new medication, there could be potential for "2 for the price of 1" deals that could mean cost savings	*"You don't have to manufacturer two separate things"*

Abbreviations: FDC, fixed-dose combination; PAH, pulmonary arterial hypertension.

Participants said they believed individuals newly diagnosed with PAH would find it easier to remain adherent if they could take medication less frequently. They also saw benefits of fewer doses per day for "veteran" patients. Several individuals (4/13) indicated that they sometimes forgot or skipped their afternoon dose if they were napping or if they did not have food readily available to prevent nausea.

> *I need food in my stomach. I get nauseous and feel bad [without it]. If I don't eat, I make a decision to delay or not take the [afternoon] dose.*

3.3.5 | Reduced Time Navigating Access Issues

Participants expressed frustration at the administrative burden of dealing with prior authorization requests and renewals for each of their PAH medications.

> *The fact that I have to go through this at least once a year is very frustrating.*

All of the participants received their medications from a specialty pharmacy via mail order and described this process as being time-consuming.

> *All my PH meds are mail order but I spend so much time on the phone.*

Most (9/13) participants thought going through a prior authorization just the once (as opposed to several times for multiple tablets) would make it easier to navigate the insurance process, while three participants said it would be more difficult to go through a single prior authorization and one thought there would be no change in ease or difficulty from their current process. Those who felt a single prior authorization would be easier saw potential for fewer phone calls, less time spent, and reduced stress.

> *Specialty pharmacy mails me everything, but even if I have two different medications at the same specialty pharmacy, I have to call at different times because of their rules. This would be amazing—reduce the phone calls.*

The majority (12/13) of participants agreed or strongly agreed that obtaining FDC from one specialty pharmacy would be more convenient and give them confidence that they could fill their medication on time, compared with getting multiple medications from different pharmacies.

> *Just [helpful] for management. I have multiple pharmacies for my meds, and it would be nice to have everything on one app, and I can look at it and see what needs to be refilled without having to do a research project.*

3.3.6 | Potential Cost Savings

The cost of FDC was an important consideration. Most (8/13) participants thought that FDC might be more expensive than separate medications as it is a newer concept.

> *They'll compare the one [tablet] versus the other. Not both. They don't think big picture.*

Four participants said the cost of FDC would be similar to their current medications due to consistent copays, and one thought that a potential "2 for the price of 1" deal might lead to cost savings. In response to a poll, 11 participants indicated that they

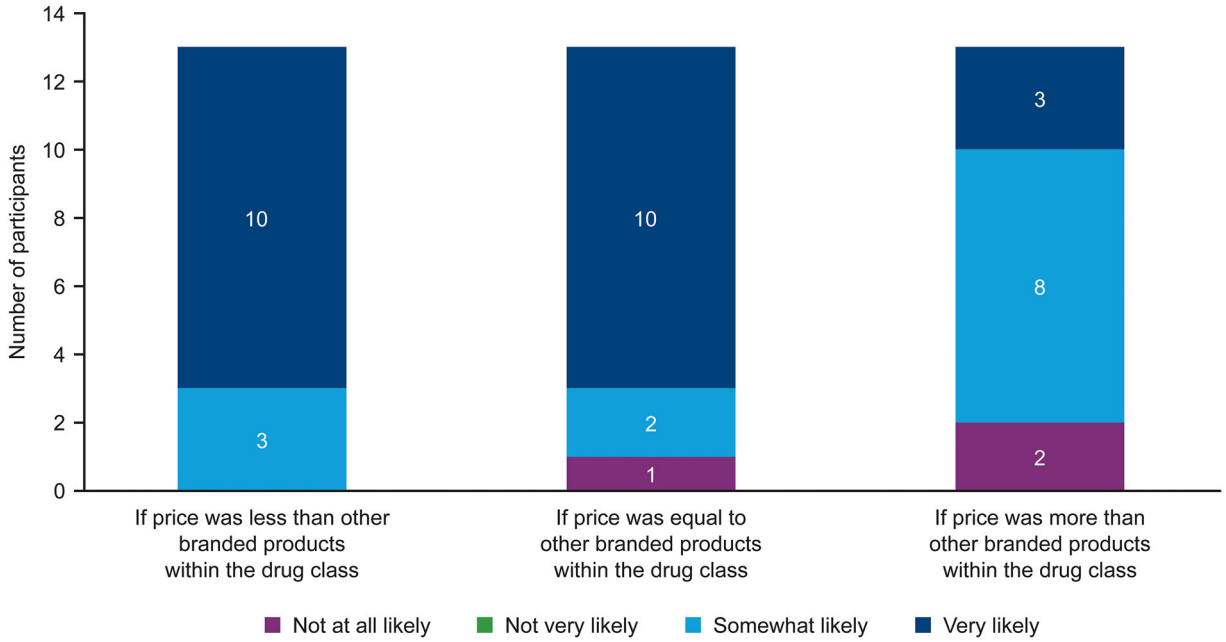

FIGURE 2 | Participants' likelihood of considering FDC according to different cost scenarios. They were asked how likely they would be to consider single-tablet combination therapy if the price was less than, equal to, or more than other PAH products. FDC, fixed-dose combination; PAH, pulmonary arterial hypertension.

would be somewhat or very likely to consider FDC, even if the price was higher than for other branded products within the drug class, while two indicated they would not be willing to pay significantly more just for convenience (Figure 2).

3.4 | Hesitations and Concerns Around FDC

The focus group participants anticipated difficulty with accessing FDC through their insurance provider as it will be a new medication and likely more expensive than existing options. While they expected to pay a similar amount in copay, they suspected that insurance providers would be likely to deny FDC, preferring the separate components already in the market.

> *It's going to be a brand new, specialty medication, and insurance won't understand why you need it, and there are generics that do the same thing.*

Despite these concerns, participants believed that most PAH medical teams would fight for their patients to get access to the medication they need. One participant mentioned receiving assistance to navigate insurance issues from an industry program when they were prescribed a new specialty medication.

While the convenience of FDC was compelling for some participants, others wanted to see evidence of equal or superior efficacy to existing options.

> *I know it's a hassle to take so many medications, but I'm not going to pay a significant amount of money extra just for convenience. It's not worth it.*

Three participants expressed concerns about FDC, such as how large the tablet would be, the ability to titrate separate medications within the same tablet, complex dosing schedules, cost, and potential issues with distinguishing side effects from each component. Another three participants were worried that their medication might be less efficacious when combined.

> *I wonder about the potency of it because I think about a multivitamin, and I always wonder with those if they're as potent as when you take individual vitamins.*

4 | Discussion

This exploratory research was conducted to gain a sense of patients' perspectives around FDC for PAH. Despite most participants being unfamiliar with FDC, all but one expressed an interest in taking it. In general, most participants considered FDC to be a good option for making double therapy easier. They saw potential benefits in terms of improved convenience (through a simplified number of tablets/daily doses and less time spent dealing with prior authorization issues) and the possibility of improved adherence.

In light of research suggesting that ~40% of patients are not fully adherent with their PAH medication [10] due to high pill burden and other contributing factors [11, 13], simplified dosing regimens (e.g., FDC) offer an opportunity to reduce the number of tablets and doses per day. Participants in our research felt that even a reduction of one tablet or elimination of one daily dose would be meaningful in terms of improving adherence. These findings echo the results of a discrete choice experiment where patients with PAH rated the ability to take fewer tablets as the top benefit of FDC, followed by spending less time managing prescriptions [30]. In line with research indicating younger patients with PAH are at the highest risk of nonadherence [11], some participants described not fully

understanding the importance of adherence when they were younger and first diagnosed with PAH. A survey of 134 responses from patients with PAH identified continuous healthcare provider–patient communication and education as key drivers of patients remaining on their medication [31]. These findings suggest that newly diagnosed patients in particular may benefit from the improved convenience of FDC.

Copays can be another barrier to medication adherence. Individuals with higher copays have been shown to have decreased adherence to combination therapy in PAH than those with lower copays [32]. Most participants in our research expected they would pay a similar amount in copay for FDC compared with existing treatment options, although there was an expectation that FDC would present some challenges when dealing with insurance companies because it is a new and potentially more expensive medication. In the United States, each specialty PAH medication needs a prior authorization obtained by the prescribing physician before insurance providers will pay their portion of the medication cost. Each prior authorization is dealt with separately by a specialty pharmacy. This can be a time-consuming and stressful process involving separate phone calls for each medication, particularly for any parenteral medications where additional supplies must also be ordered. Additionally, specialty pharmacies generally operate during standard business hours, which can be inconvenient for night shift workers or those unable to make or receive calls during the day. Notably, participants thought FDC might reduce the time and stress associated with navigating insurance issues. Participants said they believe PAH medical teams will fight for patients to access the medication they need, illustrating hope for potential access to FDC; however, time spent by physicians and PH coordinators dealing with prior authorizations may reduce time devoted to patient care [33].

While improved convenience and adherence were considered important by most participants in our research, others wanted more compelling motivations to consider FDC. In the United States, patients are increasingly wary of any changes to their medications, and the current study participants expressed concern around the potency and efficacy of FDC compared with existing options, as well as potential issues with distinguishing side effects from each component when starting FDC upfront. These comments highlight the need for further education on the potential benefits of FDC for patients and likely reflect growing interest from patients to engage in shared decision-making and become more knowledgeable about their treatments.

Participant feedback on triple therapy indicated that they felt dual therapy with FDC would be beneficial and may facilitate escalation to triple therapy; however, they also noted titration management would still be important. At the time our research was conducted, the A DUE study results had not been published in full [22] and Johnson & Johnson's OPSYNVI [23] was not yet approved in PAH. Participants discussed FDC as a general concept and had not been provided with information about potential active ingredients. Patient perspectives may have differed had an FDC therapy containing an ERA and a PDE5i been available to be discussed in the focus groups.

This study has additional limitations. This qualitative exploratory research was performed in a sample of self-selected patients with PAH and is subject to inherent observation and selection biases. Participants were recruited from an existing PERC and were highly educated with strong awareness of their disease and medications, as observed with other patient engagement research of this nature [26–29]. As such, our findings may not be generalizable to all patients with PAH.

In conclusion, this exploratory research provides insight into the perceptions of 13 US patients on the utility of an FDC therapy in PAH. Overall, FDC was viewed as a good option to make double therapy easier, with perceived improvements in convenience and adherence that may be particularly relevant for newly diagnosed patients. Our findings have implications for the benefits of optimizing shared decision-making in PAH regarding combination therapy and highlight an unmet need for patient education around medication options and the importance of adherence in patients with PAH.

Author Contributions

Jean M. Elwing, Stacey Barta, Tim Smith, Marinella Sandros, and Akshay Muralidhar analyzed and interpreted the data, and reviewed and critically revised the manuscript. Gabriela Gomez Rendon and David Lopez contributed to the study design, analyzed and interpreted the data, and reviewed and critically revised the manuscript. Wesley Peters contributed to the study design, collected the data, analyzed and interpreted the data, and reviewed and critically revised the manuscript. All authors approved the final version for publication and agree to be accountable for the accuracy and integrity of the publication. All authors are responsible for the integrity of the manuscript, had access to the data, and controlled the decision to publish.

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Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki (1964 and later amendments). The research was classified as market research, and institutional review board approval was not required.

Consent

All participants provided written informed consent and were compensated for their time in the focus groups.

Conflicts of Interest

Jean M. Elwing has served as a speaker/consultant and has received fees and honoraria from United Therapeutics, Aerovate, Gossamer Bio, Liquidia, Merck, Janssen/Actelion/Johnson & Johnson, and Roivant; her institution has received research grants/funding from United Therapeutics, Gossamer Bio, Bayer, Acceleron/Merck, Altavant, Aerovate, Pharmosa/Liquidia, Janssen/Actelion/Johnson & Johnson, Lung LLC, and Roivant. Stacey Barta and Tim Smith are members of Johnson & Johnson's Pulmonary Hypertension Patient Engagement Research Council and were compensated financially for their time in the focus groups but were not compensated for authorship. Wesley Peters is an

employee of CorEvitas LLC, part of ThermoFisher Scientific LLC, which derives its profits from interactions with pharmaceutical sponsors. David Lopez, Marinella Sandros, and Gabriela Gomez Rendon are employees of Actelion Pharmaceuticals US Inc., a Johnson & Johnson Company. Akshay Muralidhar has served on advisory boards with Johnson & Johnson.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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