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Results of an Expert Consensus Survey on the Treatment of Pulmonary Arterial Hypertension with Oral Prostacyclin Pathway Agents

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Results of an Expert Consensus Survey on the Treatment of Pulmonary Arterial Hypertension with Oral Prostacyclin Pathway Agents

Running head: Expert Survey on Pulmonary Arterial Hypertension

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Adaani Frost has received honoraria and travel expenses for Actelion-sponsored lectures and expert advice litigation related to PH therapies; has received honoraria for consultation and study endpoint adjudication for United Therapeutics; consults for PhaseBio; and performs data safety monitoring for Complexa.

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Abbreviations list:

6MWD, 6-minute walk distance

ACCP, American College of Chest Physicians

BNP, brain natriuretic peptide

CTD, connective tissue disease

ERA, endothelin receptor antagonist

ERS, European Respiratory Society

ESC, European Society of Cardiology

FC, functional class

IP, prostaglandin I2

IPAH+, idiopathic, heritable, and drug- or toxin-induced PAH

mPAP, mean pulmonary arterial pressure

NT-proBNP, *N*-terminal prohormone of BNP

PAH, pulmonary arterial hypertension

PDE5i, phosphodiesterase type 5 inhibitor

PPA, prostacyclin pathway agents

PVR, pulmonary vascular resistance

RAP, right atrial pressure

RV, right ventricular

UCLA, University of California, Los Angeles

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WHO, World Health Organization

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ABSTRACT

Background: Treatment of pulmonary arterial hypertension (PAH) has evolved substantially over the past two decades and varies according to etiology, functional class (FC), hemodynamic parameters, and other clinical factors. Current guidelines do not provide definitive recommendations regarding the use of oral prostacyclin pathway agents (PPAs) in PAH. To provide guidance on the use of these agents, an expert panel was convened to develop consensus statements for the initiation of oral PPAs in adults with PAH.

Methods: A systematic literature search was conducted using MEDLINE. The established RAND/University of California Los Angeles Appropriateness Method, which incorporates the Delphi method and the nominal group technique, was utilized to create consensus statements. Idiopathic, heritable, repaired congenital heart defect, and drug- or toxin-induced PAH was considered as one etiological grouping (IPAH+). The process was focused on the use of oral treprostinil or selexipag in patients with IPAH+ or connective tissue disease-associated PAH and FC II or III symptoms receiving background dual endothelin receptor antagonist/phosphodiesterase type 5 inhibitor therapy.

Results: The panel developed 14 consensus statements regarding the appropriate use of oral PPAs in the target population. The panel identified 13 clinical scenarios in which selexipag may be considered as a treatment option.

Conclusion: The paucity of clinical evidence overall, and particularly from randomized trials in this setting creates a gap in knowledge. These consensus statements are intended to aid clinicians in navigating treatment options and utilizing oral PPAs in the most appropriate manner in patients with PAH.

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INTRODUCTION

Currently approved therapies for pulmonary arterial hypertension (PAH) consist of endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE5i), a soluble guanylate cyclase stimulator, and oral, inhaled, and parenteral prostacyclin pathway agents (PPAs). Three oral PPAs, treprostinil and beraprost (prostacyclin analogs), and selexipag (a selective IP receptor agonist), have been developed for the treatment of PAH. Use of beraprost is currently restricted to select Asian countries and oral treprostinil is not widely available outside North America.

For adult patients with PAH and functional class (FC) II or III symptoms, guidelines recommend initial combination therapy with an ERA and PDE5i.[1,2] If a patient's risk status is intermediate while receiving combination therapy, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines and the 6th World Symposium on Pulmonary Hypertension proceedings recommend escalation to triple therapy by adding an oral or parenteral PPA.[2,3] However, discordance exists between ESC/ERS guidelines and the American College of Chest Physicians (ACCP) guidelines. Because the primary endpoint in the phase 3 oral PPA trials differed, the ACCP chose to base their guidance on 6-minute walk distance (6MWD) since it was a common endpoint among the trials. Based on these data the ACCP was not able to make a definitive recommendation on when to add selexipag and found no evidence to support the addition of oral treprostinil to ERA and/or PDE5i therapy.[2]

Five randomized trials of oral treprostinil or selexipag have been published.[4–8] Two phase 3, placebo-controlled clinical trials (FREEDOM-C and FREEDOM-C2) evaluated oral treprostinil in adults with primarily FC II (23%) or FC III (74%) symptoms receiving combination therapy with an ERA and/or a PDE5i.[5,7] In contrast to the phase 3 study of oral treprostinil monotherapy in which patients treated with oral treprostinil vs placebo demonstrated a statistically significant improvement in 6MWD,[6] no statistically significant improvement in the primary endpoint, 6MWD,

was observed in the combination therapy trials.[5,7] In a phase 2 trial comparing the addition of selexipag vs placebo in adults receiving combination therapy with an ERA and/or a PDE5i, selexipag-treated patients had a statistically significant decrease in mean pulmonary vascular resistance, the primary endpoint of the study.[4] One phase 3 randomized, placebo-controlled clinical trial (GRIPHON) evaluated selexipag in adults with primarily FC II (46%) or FC III (53%) symptoms receiving background therapy with an ERA and/or PDE5i or no background therapy.[8] The primary endpoint was a composite of death or a complication related to PAH, which included disease progression or worsening of PAH that resulted in hospitalization, initiation of parenteral PPA therapy or long-term oxygen therapy, or the need for balloon atrial septostomy or lung transplantation. In the overall patient population, selexipag statistically significantly reduced the risk of a primary endpoint event. In subgroup analysis, the treatment effect was consistent among subgroups regardless of background therapy

The gaps in data with oral PPAs in patients with FC II or III symptoms who are receiving ERA plus PDE5i coupled with a lack of definitive guidance on their use in published treatment guidelines creates uncertainty for clinicians regarding the role of oral PPAs in managing these patients. Additionally, complicated real-world scenarios arise that are not well addressed in the setting of a controlled clinical trial. Thus, we sought to use a well-described scientific methodology to develop expert consensus opinion statements on when to initiate the oral PPAs treprostinil and selexipag in common clinical scenarios in adults with PAH and World Health Organization (WHO) FC II or III symptoms.

Expert consensus statements cannot replace assessment and clinical decision-making by a qualified healthcare practitioner for an individual patient. These statements are intended to guide clinicians in common scenarios and do not address all possible clinical situations, nor do these statements account for additional individual patient factors not specifically stated, such as various comorbidities, patient preference, the ability of a patient to manage or adhere to a

treatment, or the patient's ability to pay for treatment. Additionally, the consensus statements presented within are not intended for use as criteria for third-party payor reimbursement of specific drugs or treatments for groups or individuals with PAH of any etiology.

METHODS

The consensus process is outlined in Figure 1. The panel utilized the established RAND/University of California Los Angeles (UCLA) Appropriateness Method,[9] which incorporates the Delphi method and the nominal group technique, to create consensus statements. This method was developed to reach consensus among participants, particularly in situations in which evidence is lacking to support decision-making. The process was directed by a moderator skilled in the RAND/UCLA Appropriateness Method. All authors served as panel members and were chosen by a small group of PAH experts who selected members with a goal of representing a variety of geographic regions and clinical expertise both in patients with PAH and in the use of oral PPAs. Data were analyzed independently by Humanitas, Inc. (Silver Spring, Maryland).

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A systematic literature search was conducted using MEDLINE via PubMed utilizing the search terms (“pulmonary arterial hypertension” OR “pulmonary hypertension”) AND (prostacyclin[tw] OR prostanoid[tw] OR PGI2[tw]). The search was limited to English language, adult patients (≥18 years of age), Group 1 PH (ie, PAH), human clinical studies, and a 10-year time frame from October 1, 2008, through October 1, 2018. Relevant articles containing clinical information and review articles were retained. The search was augmented with drug prescribing information for PPAs (epoprostenol injection; treprostinil tablets, inhalation, and injection; iloprost inhalation; and selexipag tablets), key articles identified in reference lists outside the search time window, and pivotal trials for oral treprostinil and selexipag (additional details are provided in the Supplement).

Based on the literature search, and informed by expert opinion and an initial pre-survey of the panelists, the first author and the moderator decided that questions would be posed about oral treprostinil and selexipag separately, that idiopathic, heritable, repaired congenital heart defect, and drug- or toxin-induced PAH would be considered as one etiological grouping (IPAH+), that the process would focus on the use of oral treprostinil or selexipag in patients on background dual ERA/PDE5i therapy with FC II or III symptoms, and that the process would exclude oral PPA monotherapy, upfront double combination therapy with an oral PPA and another agent, and use of an oral PPA in patients with FC IV PAH, consistent with current evidence and clinical practice. Panelists ranked, in descending order of importance, the clinical factors that they typically use to make routine treatment decisions regarding the initiation of oral PPAs. The initial list of clinical factors was drawn from clinical trial endpoints and multiparameter risk assessment algorithms. Based on these results, the following clinical factors were considered in this order of importance (within each FC): hemodynamics, PAH-associated hospitalization within the prior 6 months, right ventricular (RV) function, serum brain natriuretic peptide (BNP)/*N*-terminal prohormone of BNP (NT-proBNP) levels, and 6MWD. Although PAH-associated hospitalization

was ranked higher than hemodynamics in the survey, the first author and the moderator opted to construct the survey so that the panel would consider hemodynamics first, reasoning that these data are more likely to be available to the clinician at the time of decision-making and because hemodynamics have historically been the most critical factor in decision making. Clinical factors evaluated but excluded from further ranking were right atrial area, stroke volume index, age, sex, cardiopulmonary exercise testing, diffusing capacity of the lungs for carbon monoxide, blood pressure, heart rate, clinically significant renal insufficiency, syncope, and right ventricular failure (the last two are indicative of FC IV, where evidence supports the use of parenteral prostacyclin therapy[2,3]).

Panelists were presented with a series of clinical scenarios created by the first author and the moderator for a patient in one of three etiological groups (IPAH+, connective tissue disease [CTD]-associated PAH, and portopulmonary hypertension), with FC II or III symptoms, and with mostly low-, intermediate-, or high-risk hemodynamic parameters (based on 2 of the 3 following variables meeting the risk category level: right atrial pressure (RAP), mixed venous oxygen saturation, and cardiac index [Table 1]). Panelists were then asked questions sequentially about the appropriateness of selexipag or oral treprostinil in patients with a specific clinical scenario regarding clinical factors in the following order: (1) hospitalization due to PAH in the last 6 months (Y/N); (2) RV function (normal, mild dysfunction, moderate/severe dysfunction based on echocardiogram or magnetic resonance imaging); (3) BNP/NT-proBNP levels (normal or abnormal); and (4) 6MWD (>440 m or ≤440 m) (Figure S1). Consistent with the RAND/UCLA method, cost was not considered in the decision-making model.

For Delphi round 1 (Delphi 1), 1620 case scenarios were presented with an equal number for treprostinil and selexipag, respectively. Panelists assigned a score of 1 to 9 for each scenario, with scores of 1 to 3 indicating that the oral PPA therapy is inappropriate for that patient scenario with risks outweighing benefits, 4 to 6 indicating the risk/benefit ratio is uncertain and

decisions are made on an individual basis, and 7 to 10 indicating the therapy is appropriate and benefits clearly outweigh the risks. If a respondent assigned a score of 1 to 3 for a scenario, the software cut off further downstream questions and a score of 2 (ie, mean and median of 1 to 3) was imputed for that individual participant. Mean, median, mode, and response distribution according to bottom, middle, and top third of the scale (1 to 3, 4 to 6, and 7 to 9) were calculated. For a case scenario to be included for re-assessment in Delphi 2, a threshold median score of >3 had to be met. Case scenarios with a median score ≤3 were interpreted as a consensus against the appropriateness of the oral PPA in that case. A total of 677 case scenarios passed Delphi 1. For included case scenarios, data for individual respondents were gathered in a summary along with their individual score for each scenario, the median score, and the frequency distribution. This summary was sent to the panelists with the Delphi 2 survey. Panelists had the opportunity to retain their original response or to change their response after seeing the group median and score distribution for each question. In Delphi 2, the threshold for preliminary consensus agreement for appropriateness of the oral PPA in a case scenario was a median score ≥7 with ≤33% of respondents scoring the appropriateness as 1 to 3. Items with a median score <7 were designated as case scenarios lacking consensus agreement (and therefore rejected). Items with median score ≥7 and with >33% scored 1 to 3 were discussed at the face-to-face meeting, during which nominal group technique was used to obtain group consensus on each of the draft consensus statements developed based on Delphi 2. Each consensus statement was discussed and voted upon silently using a computerized audience response system and the same scale (1 to 9, with 1 indicating “not appropriate”). Panelists agreed to not designate the strength of evidence for the consensus statements given the paucity of clinical and/or trial evidence for the clinical scenarios analyzed. The RAND/UCLA method is designed to gain consensus in situations with insufficient evidence, such as clinical scenarios not well represented in clinical trials.

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RESULTS

A total of 677 case scenarios passed Delphi 1, and 458 were accepted in Delphi 2. During discussion, the panel determined that the final clinical factor rankings were most appropriate for patients with IPAH+ and CTD-associated PAH and drafted 14 consensus statements (Table 2) Consensus statements for use of oral PPAs in portopulmonary hypertension were not developed as treatment goals were ambiguous: symptom improvement versus achievement of transplant-acceptable hemodynamic thresholds.

The median score for the use of oral treprostinil did not meet the predetermined threshold for a recommendation in favor of its use in any clinical scenario evaluated (median scores all <7). Oral treprostinil data were analyzed according to panel members' location (US vs non-US) to examine the possibility that the lack of oral treprostinil availability in non-US locations may have affected the appropriateness determination. However, all scenarios that entered Delphi 2 were rejected in both US and non-US panelist subgroups. Median scores for all scenarios ranged from 3 to 6.5 among US panelists and from 1.5 to 2.5 among non-US panelists. Therefore, the resulting panel consensus statements are limited to the use of clinical situations in which oral selexipag is considered appropriate.

IPAH+ and Low- or Intermediate-Risk Hemodynamics

Among patients with IPAH+ and low- or intermediate-risk hemodynamic parameters who are receiving dual oral ERA/PDE5i therapy, the panel determined that selexipag may be considered as additional therapy for patients with the following clinical scenarios (Figure 2).

Functional Class II

The panel determined that in patients with IPAH+ and FC II symptoms, selexipag may be considered in patients with low-risk hemodynamics, if the patient has *not* been hospitalized for PAH in the last 6 months but has moderate-to-severe RV dysfunction, irrespective of their

BNP/NT-proBNP levels, or 6MWD. The panelists discussed that severe RV dysfunction may represent a poor prognostic factor[10–13] and determined that RV dysfunction in this patient population warrants additional therapy with selexipag.

In patients with IPAH+ and FC II symptoms, selexipag may be considered in patients with low-risk hemodynamics, if the patient *has* been hospitalized for PAH in the last 6 months, irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD. The panelists discussed that patients in clinical practice who fit this scenario may be younger or those with drug- or toxin-induced PAH whose noncompliance with diuretics have led to hospitalization. The panel agreed that hospitalization for worsening PAH represents a poor prognostic factor,[14] and the patient may require additional medication.

In patients with IPAH+ and FC II symptoms, selexipag may be considered in patients with intermediate-risk hemodynamics, irrespective of hospitalization for PAH in the last 6 months, RV function, BNP/NT-proBNP levels, or 6MWD.

Functional Class III

The panel determined that in patients with IPAH+ and FC III symptoms, selexipag may be considered in patients with low-risk hemodynamics irrespective of hospitalization for PAH in the last 6 months, RV function, BNP/NT-proBNP levels, or 6MWD.

In patients with IPAH+ and FC III symptoms, selexipag may be considered in patients with intermediate-risk hemodynamics who have *not* been hospitalized for PAH in the last 6 months, and irrespective of RV function, BNP/NT-proBNP levels, or 6MWD.

In patients with IPAH+ and FC III symptoms, selexipag may be considered in patients with intermediate-risk hemodynamics who *have* been hospitalized for PAH in the last 6 months, and with normal or mildly impaired RV function, irrespective of BNP/NT-proBNP levels, or 6MWD.

The panelists discussed that this subgroup of hospitalized patients may be appropriate candidates for oral rather than parenteral therapy.

CTD-Associated PAH and Low- or Intermediate-Risk Hemodynamics

Among patients with CTD-associated PAH and low- or intermediate-risk hemodynamic parameters who are receiving dual oral ERA/PDE5i therapy, the panel determined that selexipag may be considered as additional therapy for patients with specific clinical scenarios (Figure 3).

Functional Class II

The panel agreed that in patients with CTD-associated PAH and FC II symptoms, selexipag may be considered for patients with low-risk hemodynamics who have *not* been hospitalized for PAH in the last 6 months but have any degree of RV dysfunction and abnormal BNP/NT-proBNP levels, irrespective of 6MWD.

In patients with CTD-associated PAH and FC II symptoms, selexipag may be considered for patients with low-risk hemodynamics who *have* been hospitalized for PAH in the last 6 months, irrespective of RV dysfunction, BNP/NT-proBNP levels, or 6MWD. Panelists noted that some patients in this category may benefit from parenteral therapy, specifically those with moderate-to-severe RV dysfunction and 6MWD ≤440 m. However, patients with CTD-associated PAH may have difficulty managing parenteral therapy due to the necessity of manipulating pumps and a higher incidence of adverse events compared to patients with IPAH+[15]; selexipag offers an alternative therapy in such situations.

In patients with CTD-associated PAH and FC II symptoms, selexipag may be considered in patients with intermediate-risk hemodynamics, irrespective of hospitalization for PAH in the last 6 months, RV function, BNP/NT-proBNP levels, or 6MWD.

Functional Class III

The panel determined that in patients with CTD-associated PAH and FC III symptoms, selexipag may be considered in patients with low-risk hemodynamics, who have *not* been hospitalized for PAH in the last 6 months, and RV function is abnormal, BNP/NT-proBNP levels are abnormal, or 6MWD is ≤440 m.

In patients with CTD-associated PAH and FC III symptoms, selexipag may be considered in patients with low-risk hemodynamics who *have* been hospitalized for PAH in the last 6 months, irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD.

In patients with CTD-associated PAH and FC III symptoms, selexipag may be considered in patients with intermediate-risk hemodynamics, who have *not* been hospitalized for PAH in the last 6 months, and irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD.

In patients with CTD-associated PAH and FC III symptoms, selexipag may be considered in patients with intermediate-risk hemodynamics who *have* been hospitalized for PAH in the last 6 months, and with normal or mildly impaired RV function, irrespective of BNP/NT-proBNP levels or 6MWD. Consistent with patients of IPAH+ etiology, the panelists concluded that this lower-risk subgroup of hospitalized patients may be appropriate candidates for oral rather than parenteral therapy.

IPAH+ or CTD-Associated PAH and High-Risk Hemodynamics

The panel determined that in patients with IPAH+ or CTD-associated PAH, who are on dual oral therapies and who have high-risk hemodynamics, intravenous or subcutaneous prostacyclin is the treatment of choice. Exceptions may occur in which selexipag may be considered in patients who decline or are unable to use parenteral therapy; each patient must be evaluated individually with consideration for patient preference, comorbidities, and other pertinent patient-related factors.

DISCUSSION

The current expert panel consensus survey represents the first comprehensive set of consensus statements focused on the use of oral PPAs in patients with PAH developed through established, formal methodology for consensus-building. These consensus statements were limited to individuals receiving background dual oral therapy with ERA and PDE5i in alignment with current standard of care.[1–3] At the time of the literature analysis, data did not support the use of an oral PPA as a component of upfront double combination therapy.

Consistent with treatment guidelines,[1–3] the addition of oral PPAs were not recommended for patients with FC IV PAH or high-risk hemodynamics, with parenteral prostacyclin being the treatment of choice for these patients. The addition of selexipag was recommended for patients with FC II IPAH+ and intermediate-risk hemodynamics, in patients with FC III IPAH+ and low-risk hemodynamics, and in patients with FCII CTD-associated PAH and intermediate-risk hemodynamics, irrespective of any other clinical factor, underlining the importance the panel placed on hemodynamic data. Recent hospitalization was also a critical factor for the panel. It was the sole precipitating factor for adding selexipag in patients with FC II IPAH+ or FC II CTD-associated PAH and low-risk hemodynamics, and lack of recent hospitalization was the sole precipitating factor for adding selexipag in patients with FC III IPAH+ or FC III CTD-associated PAH and intermediate-risk hemodynamics. Notably, 6MWD was not a determining factor in recommendations for IPAH+ or CTD-associated PAH and BNP levels were not considered a key factor in IPAH+.

Some differences emerged in recommendations between treatment of patients with IPAH+ and CTD-associated PAH despite identical clinical scenario queries: (1) For patients with FC II symptoms, low-risk hemodynamics, and no hospitalization in the last 6 months for PAH, experts determined that selexipag could be considered for patients with IPAH+ if they had moderate-to-severe RV dysfunction, but for patients with CTD-associated PAH if they had any degree of RV

dysfunction and abnormal BNP/NT-proBNP levels. (2) For patients with FC III symptoms and low-risk hemodynamics, experts determined that selexipag could be considered for patients with IPAH+ irrespective of hospitalization in the last 6 months for PAH and other features, whereas for CTD-associated PAH, patients with no hospitalization in the last 6 months for PAH should have either abnormal RV function, abnormal BNP/NT-proBNP levels, or 6MWD ≤440 m. A possible explanation for the lower threshold for use in patients with FC II symptoms may be that because of the poorer prognosis associated with scleroderma-associated PAH,[16,17] the panelists perceived a need for more intensive therapy. However the threshold for addition of selexipag appears to be more nuanced in CTD-PAH vs IPAH+ patients with FC III symptoms and low-risk hemodynamics. Selexipag use is recommended for IPAH+ patients in this scenario regardless of hospitalization; however, in CTD-patients, it is recommended if they had been hospitalized or, if that were not the case, if they had another abnormal variable. This scenario suggests a higher threshold for use in CTD-PAH patients such that another abnormality in a PAH-related variable (in addition to FC III status) is required since there could be an alternate cause of FC III status, such as deconditioning or musculoskeletal limitations, in these patients. A separate consideration among patients with CTD-associated PAH is the frequent presence of gastrointestinal symptoms, which may affect treatment choice since oral PPAs are known to be associated with gastrointestinal side effects.[4-8] Panelists were not queried about their reasons for voting on scenarios, so explanations for these differences are purely speculative.

Given the availability of a number of different treatment options for PAH, treatment decisions have become more complex. The opinions described should be considered as suggestions, with the caveat that each patient presents a unique set of features that must also be considered. For example, if a patient has not attained treatment goals with the inclusion of an oral PPA, a parenteral PPA will likely be necessary. In addition, there are two inhaled PPAs approved for

the treatment of PAH; they may be an alternative to oral PPAs in patients who have difficulty tolerating them or who prefer an inhaled formulation for other reasons.

Ultimately, these consensus statements were limited to use of oral selexipag, as the panel did not support the use of oral treprostinil for the presented clinical scenarios, consistent with published phase 3 clinical trial data at the time of the meeting.[5,7] Neither FREEDOM-C nor FREEDOM-C2 demonstrated a benefit in the primary endpoint of 6MWD with the addition of oral treprostinil to background ERA and/or PDE5i. Clinical trial data with oral treprostinil in patients on background monotherapy with either ERA or PDE5i have recently been reported (FREEDOM-EV, NCT01560624). When these results are published, they may affect the consensus opinion. However, it should be noted that FREEDOM-EV evaluates the addition of oral treprostinil to monotherapy with an ERA or a PDE5i (ie, double combination therapy). This consensus opinion is built around the addition of an oral PPA to the regimen of combination therapy with an ERA and a PDE5i (ie, triple combination therapy). As such, results of FREEDOM-EV would not have direct bearing on these opinions. Nonetheless, future expert panels should consider these results, along with any additional new data in creating future consensus statements or recommendations.

Patients with portopulmonary hypertension were not considered in the final consensus statements, as the goals for treatment differ from those with IPAH+ or CTD-associated PAH. Whether patients are candidates for transplant is an overarching factor in treatment planning, and that line of questioning was not included in the Delphi process. Panelists agree that future consideration of consensus statements for oral PPA use in this population is warranted.

Based on the panel's rankings, clinical factors were considered within each FC. The panel recognizes the subjectivity of this assessment and inherent disagreement among practicing clinicians in assigning FC to an individual patient.[18] For all patients in whom selexipag was considered appropriate, and particularly in those with more high-risk features within an FC

category, the panelists made the determination with the expectation of timely and consistent patient follow-up to assess efficacy and to adjust treatment if necessary. The panel also acknowledges that the importance of any given clinical factor is patient-specific and that clinicians must use clinical judgement and their knowledge of the individual patient to prioritize clinical factors when making treatment decisions. Data gleaned from this survey highlight the importance of multiparameter risk assessment and its impact on daily clinical decision-making.

A strength of this expert consensus panel survey was the use of the RAND/UCLA method, which is a well-established, reliable, and widely used process for gaining expert consensus in the setting of limited available data. Limitations of the survey include the small quantity of evidence available for evaluation, which was five clinical trials, including two studies of selexipag and three studies of oral treprostinil.[4–8] Expert consensus, based on available clinical trial data at the time the survey was conducted, eliminated oral treprostinil as an appropriate therapy for patients with FC II or III IPAH+ or CTD-associated PAH who were receiving an ERA and PDE5i. As such, the resulting consensus statements are based on clinical experience driven by the two primary studies of selexipag.[4,8]

In summary, this expert panel survey provides clinicians with guidance for the use of oral PPAs in patients with FC II or III IPAH+ and CTD-associated PAH receiving dual oral ERA/PDE5i therapy. The paucity of clinical evidence in this setting creates a gap in knowledge. These expert opinions must be validated with rigorous prospective studies, and this document may serve as a template for future investigations.

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FIGURE LEGENDS

Figure 1. Overview of the consensus methodology. Abbreviations: UCLA, University of California Los Angeles.

Figure 2. Clinical scenarios in which the expert panel determined that oral selexipag may be considered for patients with idiopathic, heritable, drug- or toxin-induced, or repaired congenital heart disease-associated pulmonary arterial hypertension who are receiving dual oral therapy with an ERA and a PDE5i. Numbers indicate corresponding consensus statement. Abbreviations: ERA, endothelin receptor antagonist; HD, hemodynamic parameters; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; RV, right ventricular.

Figure 3. Clinical scenarios in which the expert panel determined that oral selexipag may be considered for patients with connective tissue disease-associated pulmonary arterial hypertension who are receiving dual oral therapy with an ERA and a PDE5i. Numbers indicate corresponding consensus statement. Abbreviations: 6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; ERA, endothelin receptor antagonist; HD, hemodynamic parameters; NT-proBNP, *N*-terminal prohormone BNP; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; RV, right ventricular.

Executive summary

Current guidelines do not provide clear recommendations regarding the use of oral prostacyclin pathway agents (PPAs) in patients with pulmonary arterial hypertension (PAH). To provide guidance on the use of these agents, an expert panel was convened to develop consensus statements for initiation of oral PPAs in adults with PAH. A systematic literature search was conducted using MEDLINE. The established RAND/University of California Los Angeles Appropriateness Method, which incorporates the Delphi method and the nominal group technique, was utilized to create consensus statements. Idiopathic, heritable, repaired congenital heart defect, and drug- or toxin-induced PAH was considered as one etiological grouping (IPAH+). The process was focused on the use of oral treprostinil or selexipag in patients with IPAH+ or connective tissue disease-associated PAH and FC II or FC III symptoms receiving background dual endothelin receptor antagonist/phosphodiesterase type 5 inhibitor therapy. The panel developed the following 14 consensus statements regarding the appropriate use of the oral PPA, selexipag, in patients with IPAH+ or connective tissue disease-associated PAH.

Expert Consensus Statements	
Patients with IPAH+ and low- or intermediate-risk hemodynamic parameters	
Selexipag may be considered for patients with IPAH+ who are receiving dual oral therapy with an ERA and PDE5i and who meet any of the following clinical scenario criteria:	
FC II	
1	FC II symptoms and low-risk hemodynamic parameters, and who have *not* been hospitalized for PAH in the last 6 months, but have moderate-to-severe RV dysfunction, irrespective of their BNP/NT-proBNP levels, or 6MWD
2	FC II symptoms and low-risk hemodynamic parameters, and who *have* been hospitalized for PAH in the last 6 months, irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
3	FC II symptoms and intermediate-risk hemodynamic parameters, irrespective of hospitalization for PAH in the last 6 months, their RV function, BNP/NT-proBNP levels, or 6MWD
FC III	
4	FC III symptoms and low-risk hemodynamic parameters irrespective of hospitalization for PAH in the last 6 months, their RV function, BNP/NT-proBNP levels, or 6MWD
5	FC III symptoms and intermediate-risk hemodynamic parameters, who have *not* been hospitalized for PAH in the last 6 months, and irrespective of their RV

	function, BNP/NT-proBNP levels, or 6MWD
6	FC III symptoms and intermediate-risk hemodynamic parameters who *have* been hospitalized for PAH in the last 6 months, and with normal or mildly impaired RV function, irrespective of BNP/NT-proBNP levels, or 6MWD
Patients with CTD-associated PAH and low- or intermediate-risk hemodynamic parameters	
Selexipag may be considered for patients with CTD-associated PAH and one of the following clinical scenarios:	
FC II	
7	FC II symptoms and low-risk hemodynamic parameters, and who have *not* been hospitalized for PAH in the last 6 months, but have any degree of RV dysfunction and abnormal BNP/NT-proBNP levels, irrespective of 6MWD
8	FC II symptoms and low-risk hemodynamic parameters, and who *have* been hospitalized for PAH in the last 6 months irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
9	FC II symptoms and intermediate-risk hemodynamic parameters, irrespective of hospitalization for PAH in the last 6 months, their RV function, BNP/NT-proBNP levels, or 6MWD
FC III	
10	FC III symptoms and low-risk hemodynamic parameters, and who have *not* been hospitalized for PAH in the last 6 months, and RV function is abnormal, BNP/NT-proBNP levels are abnormal, or 6MWD is ≤440 m
11	FC III symptoms and low-risk hemodynamic parameters, and who *have* been hospitalized for PAH in the last 6 months, irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
12	FC III symptoms and intermediate-risk hemodynamic parameters, who have *not* been hospitalized for PAH in the last 6 months, and irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
13	FC III symptoms and intermediate-risk hemodynamic parameters who *have* been hospitalized for PAH in the last 6 months, and with normal or mildly impaired RV function, irrespective of BNP/NT-proBNP levels, or 6MWD
Patients with IPAH+ or CTD-associated PAH and high-risk hemodynamic parameters	
14	In patients with idiopathic, heritable, drug- or toxin-induced, repaired congenital heart disease-associated PAH or connective tissue disease-associated PAH who are on dual oral ERA/PDE5i therapy and who have high-risk hemodynamic parameters, intravenous or subcutaneous prostacyclin is the treatment of choice.

Abbreviations: 6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FC, World Health Organization functional class; IPAH+, idiopathic, heritable, drug- or toxin-induced, or repaired congenital heart disease-associated PAH; NT-proBNP, *N*-terminal prohormone BNP; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; RV, right ventricular

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TABLES

Table 1. Hemodynamic Values Comprising Low, Intermediate, and High Risk Groups

	Low	Intermediate	High
Right Atrial Pressure	<8 mmHg	8–14 mmHg	>14 mmHg
Cardiac Index	≥2.5 L/min/m^2	2.0 –2.4 L/min/m^2	<2.0 L/min/m^2
Mixed Venous Oxygen Saturation	>65%	60–65%	<60%

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Table 2. Expert Consensus Statements

Expert Consensus Statements	
Patients with IPAH+ and low- or intermediate-risk hemodynamic parameters	
Selexipag may be considered for patients with IPAH+ who are receiving dual oral therapy with an ERA and PDE5i and who meet any of the following clinical scenario criteria:	
FC II	
1	FC II symptoms and low-risk hemodynamic parameters, and who have *not* been hospitalized for PAH in the last 6 months, but have moderate-to-severe RV dysfunction, irrespective of their BNP/NT-proBNP levels, or 6MWD
2	FC II symptoms and low-risk hemodynamic parameters, and who *have* been hospitalized for PAH in the last 6 months, irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
3	FC II symptoms and intermediate-risk hemodynamic parameters, irrespective of hospitalization for PAH in the last 6 months, their RV function, BNP/NT-proBNP levels, or 6MWD
FC III	
4	FC III symptoms and low-risk hemodynamic parameters irrespective of hospitalization for PAH in the last 6 months, their RV function, BNP/NT-proBNP levels, or 6MWD
5	FC III symptoms and intermediate-risk hemodynamic parameters, who have *not* been hospitalized for PAH in the last 6 months, and irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
6	FC III symptoms and intermediate-risk hemodynamic parameters who *have* been hospitalized for PAH in the last 6 months, and with normal or mildly impaired RV function, irrespective of BNP/NT-proBNP levels, or 6MWD
Patients with CTD-associated PAH and low- or intermediate-risk hemodynamic parameters	
Selexipag may be considered for patients with CTD-associated PAH and one of the following clinical scenarios:	
FC II	
7	FC II symptoms and low-risk hemodynamic parameters, and who have *not* been hospitalized for PAH in the last 6 months, but have any degree of RV dysfunction and abnormal BNP/NT-proBNP levels, irrespective of 6MWD
8	FC II symptoms and low-risk hemodynamic parameters, and who *have* been hospitalized for PAH in the last 6 months irrespective of their RV function,

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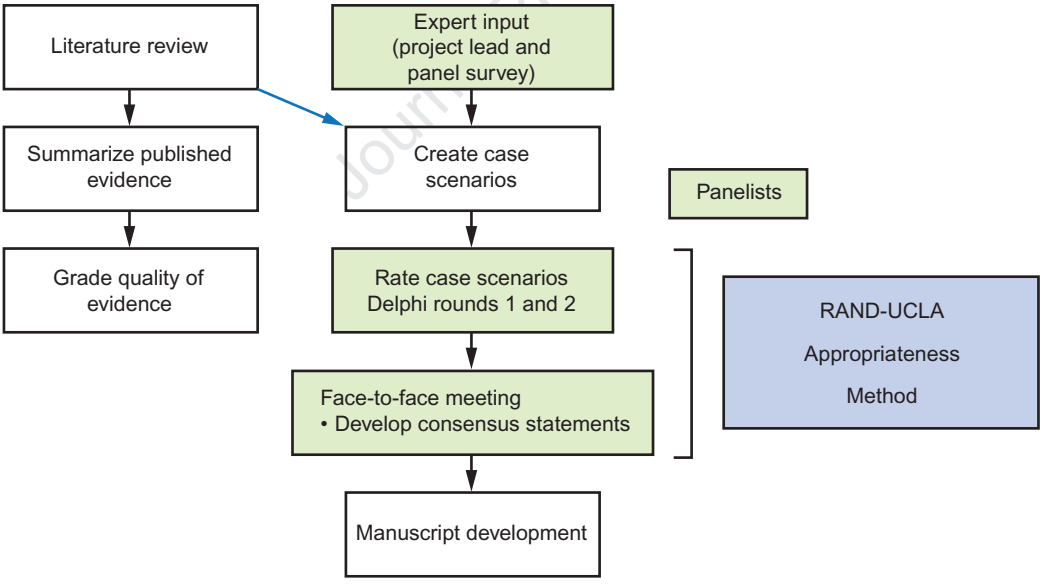
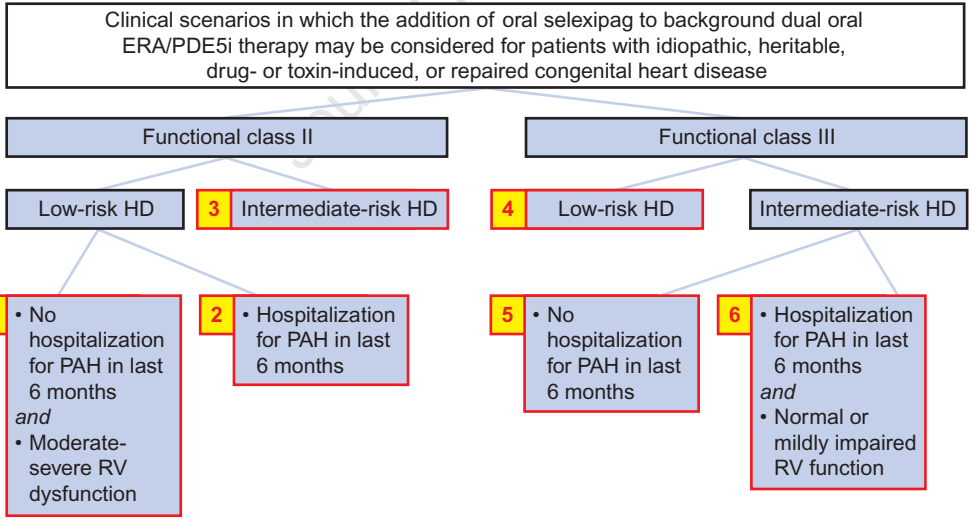
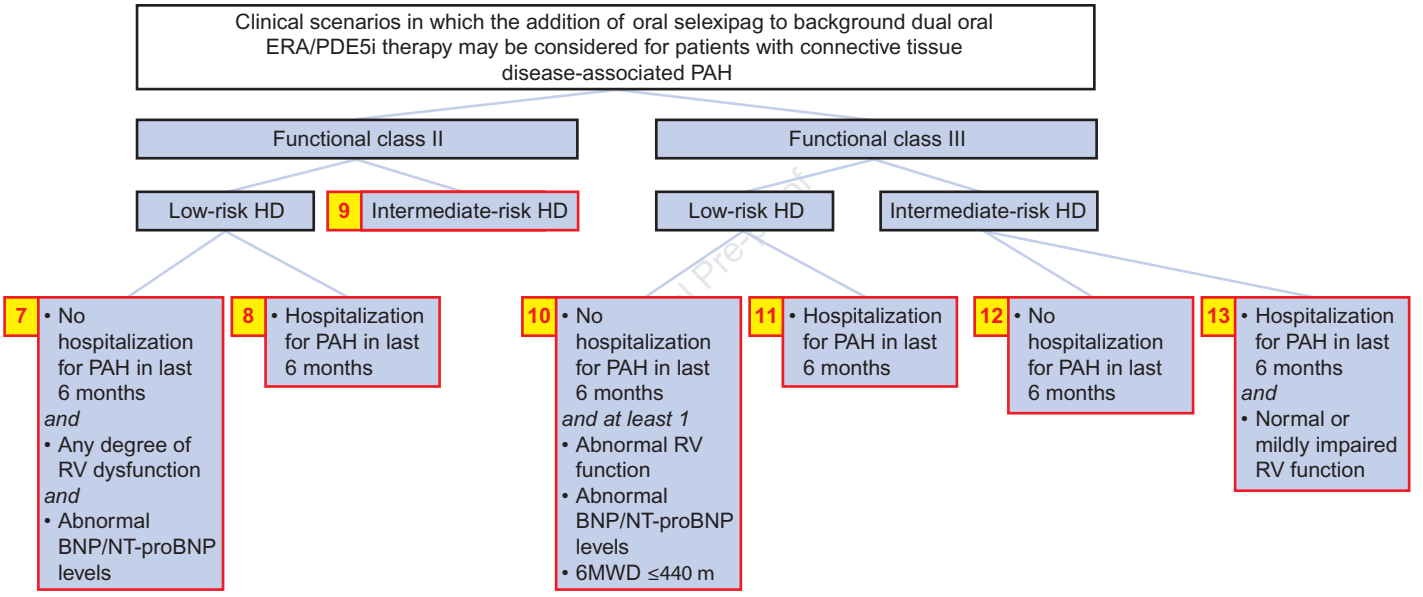
	BNP/NT-proBNP levels, or 6MWD
9	FC II symptoms and intermediate-risk hemodynamic parameters, irrespective of hospitalization for PAH in the last 6 months, their RV function, BNP/NT-proBNP levels, or 6MWD
FC III	
10	FC III symptoms and low-risk hemodynamic parameters, and who have *not* been hospitalized for PAH in the last 6 months, and RV function is abnormal, BNP/NT-proBNP levels are abnormal, or 6MWD is ≤440 m
11	FC III symptoms and low-risk hemodynamic parameters, and who *have* been hospitalized for PAH in the last 6 months, irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
12	FC III symptoms and intermediate-risk hemodynamic parameters, who have *not* been hospitalized for PAH in the last 6 months, and irrespective of their RV function, BNP/NT-proBNP levels, or 6MWD
13	FC III symptoms and intermediate-risk hemodynamic parameters who *have* been hospitalized for PAH in the last 6 months, and with normal or mildly impaired RV function, irrespective of BNP/NT-proBNP levels, or 6MWD
Patients with IPAH+ or CTD-associated PAH and high-risk hemodynamic parameters	
14	In patients with idiopathic, heritable, drug- or toxin-induced, repaired congenital heart disease-associated PAH or connective tissue disease-associated PAH who are on dual oral ERA/PDE5i therapy and who have high-risk hemodynamic parameters, intravenous or subcutaneous prostacyclin is the treatment of choice.

Abbreviations: 6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FC, World Health Organization functional class; IPAH+, idiopathic, heritable, drug- or toxin-induced, or repaired congenital heart disease-associated PAH; NT-proBNP, *N*-terminal prohormone BNP; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase type 5 inhibitor; RV, right ventricular


Literature review
Expert input (project lead and panel survey)
Summarize published evidence
Create case scenarios
Panelists
Grade quality of evidence
Rate case scenarios Delphi rounds 1 and 2
RAND-UCLA Appropriateness Method
Face-to-face meeting
• Develop consensus statements
Manuscript development


Clinical scenarios in which the addition of oral selexipag to background dual oral ERA/PDE5i therapy may be considered for patients with idiopathic, heritable, drug- or toxin-induced, or repaired congenital heart disease
Functional class II
Functional class III
Low-risk HD
3
Intermediate-risk HD
4
Low-risk HD
Intermediate-risk HD
1
• No hospitalization for PAH in last 6 months
and
• Moderate-severe RV dysfunction
2
• Hospitalization for PAH in last 6 months
5
• No hospitalization for PAH in last 6 months
6
• Hospitalization for PAH in last 6 months
and
• Normal or mildly impaired RV function


Clinical scenarios in which the addition of oral selexipag to background dual oral ERA/PDE5i therapy may be considered for patients with connective tissue disease-associated PAH
Functional class II
Functional class III
Low-risk HD
9
Intermediate-risk HD
Low-risk HD
Intermediate-risk HD
7
• No hospitalization for PAH in last 6 months
and
• Any degree of RV dysfunction
and
• Abnormal BNP/NT-proBNP levels
8
• Hospitalization for PAH in last 6 months
10
• No hospitalization for PAH in last 6 months
and at least 1
• Abnormal RV function
• Abnormal BNP/NT-proBNP levels
• 6MWD ≤440 m
11
• Hospitalization for PAH in last 6 months
12
• No hospitalization for PAH in last 6 months
13
• Hospitalization for PAH in last 6 months
and
• Normal or mildly impaired RV function