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RESEARCH ARTICLE

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INSPIRE: Safety and tolerability of inhaled Yutrepia (treprostinil) in pulmonary arterial hypertension (PAH)

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Abstract

The INSPIRE trial was a Phase 3, open-label, multicenter trial (LTI-301) that enrolled patients with pulmonary arterial hypertension (PAH) ≥ 18 years of age who transitioned to Yutrepia from nebulized treprostinil (Transition) or added Yutrepia to prostacyclin naïve patients on ≤2 nonprostacyclin oral therapies. The objectives of the trial were to evaluate the safety and tolerability of Yutrepia (dry-powder formulation of treprostinil) in patients with PAH. The primary safety measures were the incidence of adverse events (AEs) and serious AEs. Exploratory efficacy measures were also assessed during the trial. Transition patients initiated Yutrepia at a dose comparable to their nebulized treprostinil dose while prostacyclin naïve patients received 26.5-mcg QID; up-titration in 26.5-mcg increments was permitted for both groups. A total of 121 patients were enrolled, of which 29 patients discontinued from the trial, with the most common reason being AEs. Eighty percent of the Transition group and 96% of the prostacyclin naïve group titrated to a dose ≥79.5 mcg QID at Day 360, respectively, with one patient achieving a dose of 212-mcg QID. The most common AEs were cough, headache, upper respiratory tract infection, dyspnea, dizziness, throat irritation, diarrhea, chest discomfort, fatigue, and nasopharyngitis. Most of these events were considered treatment-related though mild to moderate in severity and expected for prostacyclin therapy administered by inhalation. In an evaluation of exploratory efficacy measures, patients remained stable or improved over the 1 year of treatment. Yutrepia was found to be a convenient, safe, and well-tolerated inhaled prostacyclin treatment option for PAH patients.

KEYWORDS
combination therapy, dry-powder inhaler, prostacyclin, pulmonary arterial hypertension, treprostinil

INTRODUCTION

Prostacyclin therapy has long been considered a mainstay for the treatment of mid- and late-stage PAH by virtue of its vasodilatory, antiproliferative, antithrombotic, and anti-inflammatory effects.[1–3] Currently, approved prostacyclins can be delivered by the intravenous,[4,5] subcutaneous,[4] inhaled,[6,7] or oral[8] routes. However, many patients fail to receive optimal prostacyclin therapy to help them achieve and maintain low-risk status.[9–11] Only 34.1% of patients enrolled in the REVEAL Registry™ received a prostacyclin analog,[12] and only 56% of patients with a PAH-related death were treated with intravenous prostacyclin before death.[9]

Clinical challenges associated with up-titration, side effects, and the risks associated with different routes of administration are factors that limit the use of prostacyclin therapy.[13–18] The inhaled route offers an advantage of direct delivery into the airways and nearby tissues and cells thereby increasing local drug concentrations and minimizing systemic toxicity.[19–22] However, inhaled prostacyclins are subject to dosing errors due to variations in breathing patterns, have up-titration ceilings that may limit efficacy, and require frequent administration using multiple breaths delivered by cumbersome devices, all of which impose a significant burden on patients and may contribute to treatment nonadherence or discontinuation.[23]

Yutrepia is a novel, inhaled, dry-powder formulation of treprostinil designed using the proprietary PRINT® technology that enables the development of drug particles that are precise and uniform in size (1.5 microns), shape (trefoil), and composition (Supporting Information: Figure S1). Particles are engineered to achieve optimal aerosolization and deposition in the lungs. Yutrepia is dosed four times daily (QID), delivering treprostinil doses in 2 breaths per capsule via a convenient, dry-powder inhaler, the Plastiape RS00 Model 8 device (Supporting Information: Figure S2). A Phase 1 trial (LTI-102) demonstrated that 79.5 mcg dose of Yutrepia resulted in similar systemic exposure to treprostinil as seen with nine breaths of treprostinil inhalation solution.[24] The absorption of Yutrepia is rapid, with a median Tmax of 0.18 to 0.31 h across all dose levels studied (LTI-101). Treprostinil plasma concentrations dropped below the limit of quantification in cohorts with doses up to 75 mcg by 3.5 h postdose, and by 6 h postdose in higher dose cohorts (up to 150 mcg).[25]

The present Phase 3 trial (Investigation of the Safety and Pharmacology of Dry Powder Inhalation of Treprostinil [INSPIRE], LTI-301) was performed in consultation with the Federal Drug Administration to evaluate the safety and tolerability of Yutrepia in PAH patients who were transitioned from a stable dose of nebulized treprostinil or were receiving no more than two approved background oral PAH therapies. Patients enrolled in the INSPIRE trial were allowed to roll over into an open-label safety extension trial at varying times, (LTI-302) between 8 and 18 months after enrolling into the LTI-301 trial. This publication reports outcomes through the end of the INSPIRE Phase 3 study with a mean treatment duration of approximately 1 year.

METHODS

Study design

The INSPIRE study was a Phase 3, open-label, multicenter trial (https://clinicaltrials.gov/ct2/show/NCT03399604; NCT03399604) conducted to support the New Drug Application submission for Yutrepia under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The study protocol was approved by the institutional review board or ethics committee at each participating site. Liquidia Technologies performed data collection, management, and analysis according to a prespecified statistical analysis plan. Additional details about the study design can be found in the Supporting Information.

Study eligibility

Eligible patients were ≥18 years of age, World Health Organization (WHO) Group 1 PAH classified and receiving stable doses for ≥3 months of nebulized treprostinil (Transition) or two or fewer nonprostacyclin oral therapies (Prostacyclin naïve). Additional inclusion criteria were New York Heart Association (NYHA) Functional Class (FC) II–IV, 6-min walk distance (6MWD) ≥ 150 m, forced expiratory volume in 1 s (FEV_1) ≥ 60%, and FEV_1/forced vital capacity ratio ≥60%. Key exclusion criteria were WHO Groups 2–5 pulmonary hypertension or Group 1 porto-pulmonary hypertension or PAH associated with schistosomiasis; current treatment with an oral or intravenous prostacyclin analog or agonist; hemodynamically significant left-sided heart disease; and recent initiation of a new PAH therapy. All patients provided written informed consent. For full Inclusion and Exclusion Criteria, please see Supporting Information.

Study procedures

Patients in both groups were trained on the proper use of the RS00 Model 8 dry-powder inhaler device (Plastiape

S.p.A.) and received their first dose of Yutrepia at the baseline visit. The initial dose for Transition patients was comparable to their prescribed dose of nebulized treprostinil; 85% of patients had been prescribed nine or more breaths of nebulized treprostinil (Supporting Information: Table S1). Prostacyclin naïve patients initiated Yutrepia at 26.5 mcg QID. Up-titration in 26.5-mcg weekly increments to a maximum of 212 mcg QID in both groups was allowed.

Scheduled visits occurred at screening, baseline (Day 1), Week 2, Month 1, Month 2, Month 4, Month 8, and Month 12. Adverse events (AEs) and serious adverse events (SAEs) were recorded throughout the treatment period, with continued assessment every 4 months beginning at Month 6 until study termination. Among patients who discontinued study participation, follow-up visits occurred 4 months following the last dose of Yutrepia or until all AEs resolved or stabilized.

Outcome measures

The primary safety measures evaluated the incidence of AEs and SAEs during the trial. Additional safety measures evaluated included the incidence of drug/device-related AEs, clinical laboratory results, physical exam findings, and vital signs. Exploratory efficacy measures assessed during the trial included changes from baseline in 6MWD, NYHA FC, N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, and risk assessment based on 6MWD, FC, and NT-proBNP.[26] An additional exploratory endpoint for Transition only was patient-reported satisfaction with the Yutrepia inhaler device compared to the nebulized treprostinil inhalation system.

Statistical analysis

A target of 130 patients was planned to be enrolled to ensure that at least 100 patients completed 2 months of therapy for assessment of safety endpoints. The primary safety measure analysis summarized the frequency, severity, and relatedness of all AEs and SAEs. The study was not designed or powered to evaluate a specific efficacy-related hypothesis. Change from baseline in 6MWD, NYHA FC, NT-proBNP, MLHFQ total and dimension scores, and PAH risk score was summarized for each group at visits where these tests were performed. Satisfaction with the Yutrepia device was also summarized.

RESULTS

Patients

Of the 146 patients screened, 121 were enrolled, including 55 in the Transition group and 66 in the prostacyclin naïve group (Supporting Information: Figure S3). The most common reasons for screen failures were due to stopping of enrollment due to achieving enrollment goal, not meeting PFT criteria, or use of unallowed PAH medication. The Month 12 visit was completed by 69 patients (29 Transition and 40 prostacyclin naïve) with another 25 patients reaching 12 months in the open-label extension trial LTI-302 (whose data are not included in the INSPIRE trial analyses). Twenty-nine patients discontinued from the trial (9 Transition and 20 prostacyclin naïve) with the most common reason being AEs (13 patients). This discontinuation rate of 24% is favorable, considering discontinuation rates of another inhaled treprostinil study (41%) and of inhaled iloprost (43%).[27,28]

Most patients were female, white, and non-Hispanic with a mean age of 54.2 years (Table 1). Approximately, two-thirds of the patients were in NYHA FC II with the rest in NYHA FC III. A higher percentage of patients in the prostacyclin naïve group was NYHA FC III (43.9%) compared with 21.8% of patients in the Transition group. The mean duration of disease was 4.6 years for prostacyclin naïve and 7.2 years for the Transition. Most patients were receiving background PAH medications with a majority of patients in the Transition and prostacyclin naïve groups receiving a combination of endothelin receptor antagonist and phosphodiesterase 5 inhibitor or soluble guanylate cyclase agonists (Table 1).

Exposure

The initial Yutrepia treprostinil dose for the Transition group was based on the nebulized treprostinil dose before study enrollment and ranged from 26.5 to 106 mcg QID. The starting dose was 26.5 mcg QID for patients in the prostacyclin naïve group. Dose increases were permitted in 26.5-mcg increments weekly to symptom relief in both cohorts. A total of 43 (78%) Transition group patients up-titrated from their starting dose. At Day 60, 78% of the Transition group achieved a dose ≥79.5 mcg QID and 71% of patients in the prostacyclin naïve group up titrated to ≥79.5 mcg QID. For those patients on study at Day 360 this dose, this was achieved by 80% of the Transition group and 96% of the prostacyclin naïve group. The distribution of doses in the Transition and prostacyclin naïve groups is shown in Figure 1.

TABLE 1 Baseline demographic and clinical characteristics: Safety population[a]

	Transitions ($n = 55$)	Prostacyclin naïve ($n = 66$)	Overall ($N = 121$)
Sex, *n* (%)			
Female	47 (85.5)	52 (78.8)	99 (81.8)
Male	8 (14.5)	14 (21.2)	22 (18.2)
Race, *n* (%)			
American Indian or Alaska Native	1 (1.8)	2 (3.0)	3 (2.5)
Asian	3 (5.5)	3 (4.5)	6 (5.0)
Black	11 (20.0)	4 (6.1)	15 (12.4)
White	40 (72.7)	56 (84.8)	96 (79.3)
Other	0 (0.0)	1 (1.5)	1 (0.8)
Ethnicity, *n* (%)			
Hispanic	10 (18.2)	10 (15.2)	20 (16.5)
Non-Hispanic	45 (81.8)	56 (84.8)	101 (83.5)
Age (years)			
Mean (SD)	53.3 (14.1)	55.0 (14.6)	54.2 (14.3)
BMI (kg/m^2)			
Mean (SD)	29.5 (7.5)	29.3 (7.8)	29.4 (7.6)
NYHA Functional Class, *n* (%)			
II	43 (78.2)	37 (56.1)	80 (66.1)
III	12 (21.8)	29 (43.9)	41 (33.9)
PAH duration (years)			
Mean (SD)	7.2 (5.1)	4.6 (5.1)	5.8 (5.2)
Median	5.7	2.2	4.4
Oral PAH Therapy at screening, *n* (%)			
None	5 (9.1)	0	5 (4.1)
One (ERA, PDE-5i, or sGC)	13 (23.6)	17 (25.8)	30 (24.8)
Two (ERA + PDE-5i, or sGC)	37 (67.3)	49 (74.2)	86 (71.1)

Abbreviations: BMI, body mass index; ERA, endothelin receptor antagonist; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE5i, phosphodiesterase 5 inhibitor; PGI2, prostacyclin; SD, standard deviation; sGC, soluble guanylate cyclase.

[a]The safety population included all patients who received at least 1 dose of Yutrepia.

Safety endpoints

Overall, 99.2% of patients experienced at least 1 AE, and 79.3% experienced at least 1 AE related to treatment (Table 2). Most patients reported mild ($n = 34$; 28.1%) or moderate ($n = 58$; 47.9%) AEs, with 28 (23.1%) patients having experienced severe AEs. A higher percentage of prostacyclin naïve than Transition patients experienced a treatment-related AE (84.8% vs. 72.7%), and an AE that was considered moderate or severe (81.8% vs. 58.1%). Fifteen (12.4%) patients experienced AEs that resulted in the withdrawal of Yutrepia or discontinuation from the study, with 11 (9.1%) of these patient events considered related to treatment. Overall, 21 (17.4%) patients experienced SAEs. Twenty-eight SAEs resulted in hospitalization due to accidents, comorbidities, and viral infections (e.g., COVID-19). None of the SAEs were considered treatment-related by the medical monitor. No SAEs lead to death in this study.

The most common AEs considered to be related to Yutrepia and reported in ≥10% of patients are shown in Table 3. With few exceptions, AEs were mild or moderate in severity in both patient groups. Four patients experienced a severe treatment-related AE during the

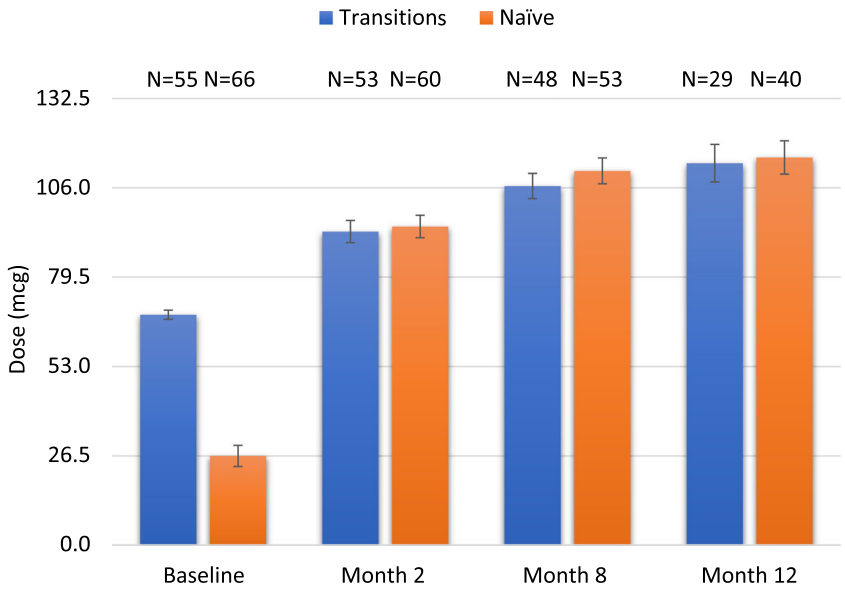

FIGURE 1 Mean Yutrepia dose. All patients in the Transition group initiated Yutrepia at a dose comparable to their nebulized treprostinil dose. All patients in the prostacyclin naïve group initiated Yutrepia at 26.5 mcg QID. Naïve, prostacyclin naïve.

TABLE 2 Overall summary of TEAEs[a]: Safety population[b]

	Transitions ($n = 55$)	Prostacyclin Naïve ($n = 66$)	Overall ($N = 121$)
TEAE, *n* (%)			
Any	54 (98.2)	66 (100)	120 (99.2)
Any treatment-related	40 (72.7)	56 (84.8)	96 (79.3)
Any resulting in study drug withdrawal or study discontinuation	4 (7.3)	11 (16.7)	15 (12.4)
Treatment-related resulting in study drug withdrawal or study discontinuation	3 (5.5)	8 (12.1)	11 (9.1)
Any TEAE by maximum severity, *n* (%)			
Mild	22 (40.0)	12 (18.2)	34 (28.1)
Moderate	24 (43.6)	34 (51.5)	58 (48.0)
Severe	8 (14.5)	20 (30.3)	28 (23.1)
Treatment-related TEAE by maximum severity, *n* (%)			
Mild	30 (54.5)	28 (42.4)	58 (47.9)
Moderate	9 (16.4)	25 (37.9)	34 (28.1)
Severe	1 (1.8)	3 (4.5)	4 (3.3)
SAE, *n* (%)			
Any	6 (10.9)	15 (22.7)	21 (17.4)
Treatment-related assessed by medical monitor	0 (0.0)	0 (0.0)	0 (0.0)
SAE resulting in death, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Treatment-related TEAEs were those considered as at least possibly related to study drug by the Investigator.

[b]The safety population included all patients who received at least 1 dose of Yutrepia.

TABLE 3 Treatment-Emergent Adverse Events[a] reported for ≥10% of all patients: Safety population

	Transitions ($n = 55$)				Prostacyclin naïve ($n = 66$)				Overall ($N = 121$)			
	No. (%) patients	No. and severity of events			No. (%) patients	No. and severity of events			No. (%) patients	No. and severity of events		
		Mild	Mod	Sev.		Mild	Mod	Sev.		Mild	Mod	Sev.
Cough	23 (41.8)	20	3	0	41 (62.1)	31	10	0	64 (52.9)	51	13	0
Headache	18 (32.7)	14	4	0	23 (34.8)	15	6	2	41 (33.9)	29	10	2
Upper respiratory tract infection	10 (18.2)	9	1	0	18 (27.3)	13	5	0	28 (23.1)	22	6	0
Dyspnea	13 (23.6)	5	7	1	10 (15.2)	5	4	1	23 (19.0)	10	11	2
Dizziness	10 (18.2)	9	1	0	13 (19.7)	11	2	0	23 (19.0)	20	3	0
Throat irritation	8 (14.5)	8	0	0	14 (21.2)	13	1	0	22 (18.2)	21	1	0
Diarrhea	7 (12.7)	5	2	0	15 (22.7)	9	6	0	22 (18.2)	14	8	0
Chest discomfort	11 (20.0)	9	2	0	7 (10.6)	6	1	0	18 (14.9)	15	3	0
Fatigue	4 (7.3)	1	2	1	10 (15.2)	7	2	1	14 (11.6)	8	4	2
Nasopharyngitis	6 (10.9)	5	1	0	6 (9.1)	5	1	0	12 (9.9)	10	2	0
Nausea	6 (10.9)	4	1	1	6 (9.1)	4	1	1	12 (9.9)	8	2	2

Abbreviations: Mod, moderate; no, number; sev, severe; TEAE, treatment-emergent adverse event.

[a]The safety population included all patients who received at least 1 dose of Yutrepia.

trial. One patient in the Transition group experienced a decrease in oxygen saturation on Day 36 that was not serious and did not result in study drug discontinuation. One patient in the prostacyclin naïve group experienced vomiting on Day 1, and Yutrepia was discontinued. A second patient in the prostacyclin naïve group developed headache and nausea on Day 1, with the headache resolving after 32 days and nausea continuing for the duration of therapy. A third patient in the prostacyclin naïve group developed oropharyngeal pain on Day 124, which continued for the duration of the therapy. Neither of these two latter events resulted in a change in dose or study discontinuation. There were no device-related AEs in either patient group or changes in clinical labs, vital signs, or physical exam attributed to Yutrepia treatment.

Exploratory endpoints

At baseline, the overall mean 6MWD was 401 m. Notedly, the Transition group did not deteriorate in mean 6MWD. There was a slight increase in the walk distance during the trial in both groups, with larger increases evident in the Transition group compared to the prostacyclin naïve group, especially at the Month 2 time point (Figure 2).

The percentage of patients in FCs I and II improved compared with baseline in both the Transition and prostacyclin naïve groups. This improvement was observed at Month 2 and maintained through Month 12 Figure (S4).

The mean changes from baseline in the NT-proBNP were variable during 12 months in the Transition group with no clear trends over time, whereas there appeared to be a progressive decline in the NT-proBNP in the prostacyclin naïve group during the trial (Figure 3).

Overall, there was a clinically meaningful improvement from baseline to Month 2 and Month 4 in the MLHFQ total score, defined as a >5-point reduction (mean change, −10.2 at Months 2 and 4), with decreases in both emotional and physical dimension scores (Figure 4) and in both the Transition and prostacyclin naïve groups.

A higher percentage of patients had two or more low risk criteria at Months 2, 4, 8, and 12, compared with baseline with a larger change occurring in the prostacyclin naïve group. At Month 2, the percentage of patients with 2 or 3 low-risk criteria increased from 41.6% at baseline to 66.0% in the prostacyclin naïve group versus 61.8% to 63.8% in the Transition group. At Month 12, the percentage of patients meeting 2 or 3 low-risk criteria was 59.0% in the prostacyclin naïve group and 67.8% in the Transition group.

Responses to the patient satisfaction survey at Week 2 indicated that 98.2% of patients in the Transition group preferred or strongly preferred the RS00 Model 8 dry-powder inhaler device compared to their previously used device, the nebulized treprostinil inhalation system (Figure 5). No patients preferred the nebulized treprostinil inhalation system, and one patient reported no preference. This preference was maintained in the survey

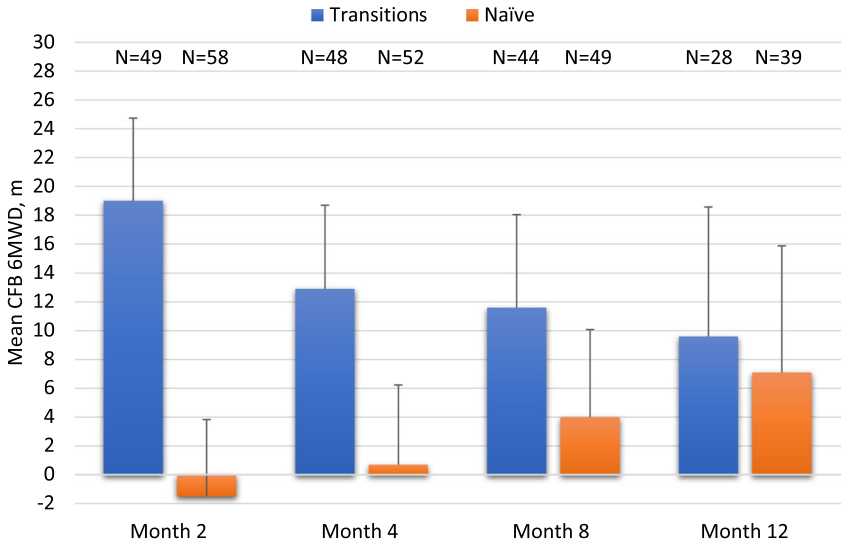

FIGURE 2 Mean change from baseline in 6MWD: Efficacy population*. *The efficacy population included all those who received at least one dose and completed at least one efficacy assessment. 6MWD, 6-min walk distance; CFB, change from baseline; Naïve, prostacyclin naïve.

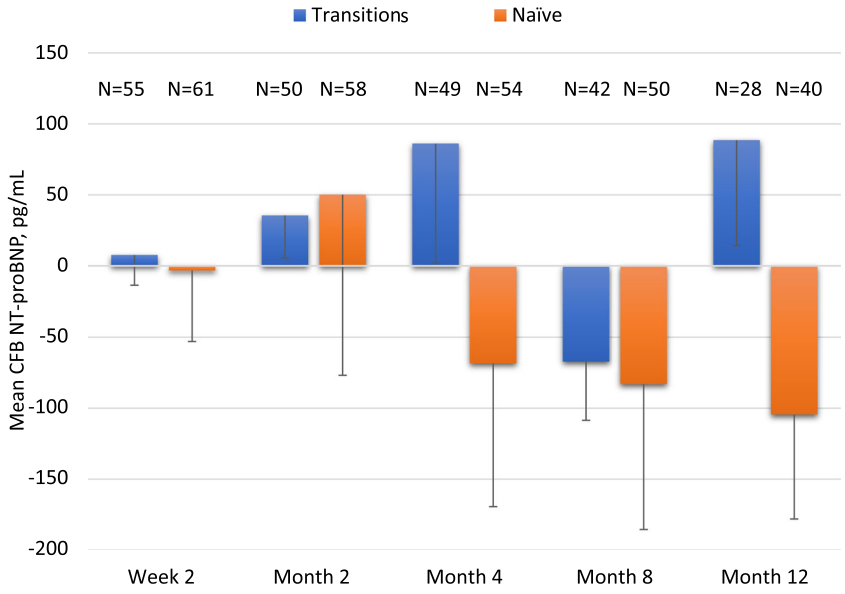

FIGURE 3 Mean change from baseline in NT-proBNP (ng/L): Efficacy population. The efficacy population included all those who received at least one dose and completed at least one efficacy assessment. CFB, change from baseline; Naïve, prostacyclin naïve; NT-proBNP, N-terminal pro-B-type natriuretic peptid.

at Month 4, with all patients preferring or strongly preferring the RS00 device.

DISCUSSION

The present study reports the safety and tolerability of Yutrepia in patients with PAH. Patients receiving stable doses of nebulized treprostinil successfully transitioned to Yutrepia with no significant safety concerns, and the addition of Yutrepia to background oral therapy was also well tolerated. Not surprisingly, the incidence of AEs was less on patients transitioning from nebulized treprostinil relative to those initiating treprostinil therapy. While nearly all patients experienced treatment-related AEs consistent with the known side effects seen with inhaled treprostinil therapy (cough, throat irritation, and oro-pharyngeal pain) as well as the characteristic side effect

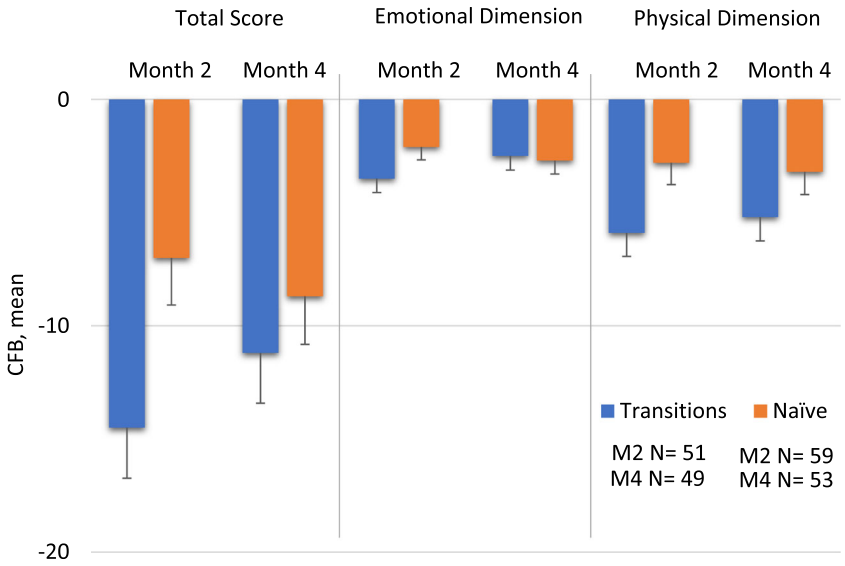

FIGURE 4 Change* from baseline in Minnesota Living with Heart Failure Questionnaire scores: Efficacy population†. *A clinically meaningful improvement from baseline was defined as a 5-point reduction.[35] †The efficacy population included all those who received at least 1 dose and completed at least 1 efficacy assessment. CFB, change from baseline; M, month; Naïve, prostacyclin naïve.

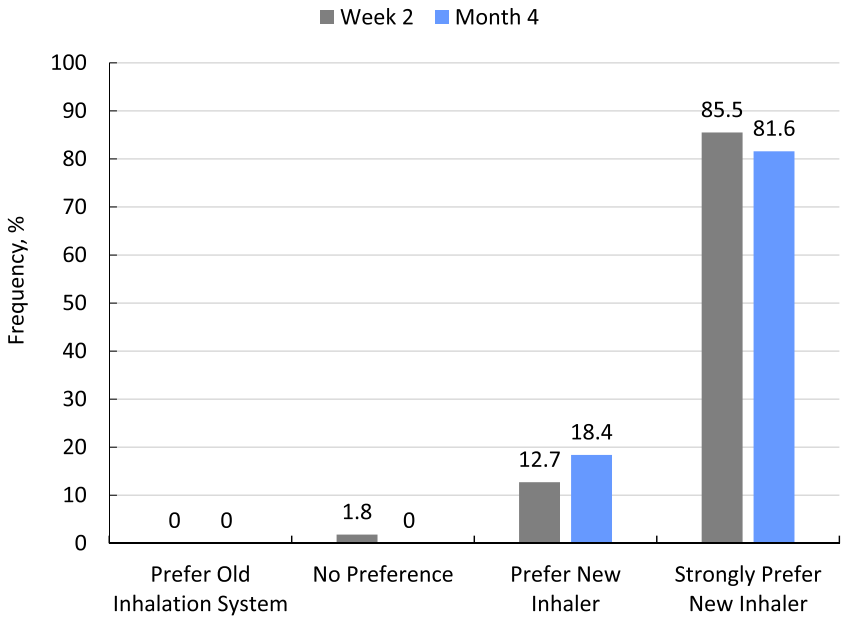

FIGURE 5 Dry-powder inhaler device (RS00 Model 8) satisfaction scores at Week 2 and Month 4: Transition patients

profile of the prostacyclin class, including headache, dizziness, diarrhea, chest discomfort, nausea, dyspnea, and flushing, these were mostly mild to moderate in severity and generally did not hinder patients ability to continue therapy and titrate to higher doses as needed. Overall, 21 patients experienced SAEs with none of the events considered to be treatment-related by the medical monitor. No SAEs led to death in this study. The overall safety profile of Yutrepia was reassuring, with no unexpected safety concerns noted.

Since patients in the INSPIRE trial were allowed to transition to an open-label safety extension trial LTI-302, the number of patients remaining in the trial declined over time. Of the 121 enrolled patients, 69 (29 Transition and 40 prostacyclin naïve) completed Month 12, and another 25 patients reached 12 months during the open label safety extension trial LTI-302. Twenty-nine patients withdrew from the INSPIRE trial. This level of withdrawals from a 1-year trial is not unexpected considering the severity of patients' underlying disease and associated comorbidities.[22,27]

Patients treated with Yutrepia were able to increase their mean inhaled treprostinil doses during the trial. Eighty percent of patients in the Transition group and 96% of those in the prostacyclin naïve group achieved a dose ≥79.5 mcg QID at Day 360, with one patient receiving a dose of 212 μg four times daily. This dose is comparable to approximately 24 breaths of nebulized treprostinil administered four times daily and suggests that Yutrepia may allow patients to be titrated to effective doses more easily than can be accomplished with current options. The clinical benefits of using higher inhaled doses of treprostinil are supported by a real-world effectiveness analysis which found that patients treated with more than nine breaths of treprostinil inhalation solution had a lower incidence of mortality and need for parenteral prostacyclin therapy compared to those treated with nine or less breaths.[29]

Despite the advantages of the inhaled route for delivery of PAH medications, currently approved inhaled prostacyclin therapies have notable limitations such as the need for multiple inhalations and cumbersome inhalation systems that require daily time and maintenance.[20,30,31] These limitations become more pronounced for working individuals or those needing to be away from home. Yutrepia overcomes many of these limitations with an inhaled formulation that delivers an optimal dose in two breaths in a simple, easy-to-use compact dry-powder device that the patient can easily conceal. In the present trial, most patients preferred using Yutrepia versus their prior nebulized treprostinil inhalation system, indicating that a more convenient, less bulky system that requires minimal maintenance is desirable to patients. A more conveniently delivered inhaled therapy such as Yutrepia offers patients and clinicians the benefits of established efficacy of the drug class with a favorable tolerability profile and may lead to long-term treatment adherence. In some patients, a better tolerated inhaled option could be preferable, even when compared with oral medications.[32]

Health-related quality of life is severely impaired in patients with PAH,[33–37] with better quality-of-life outcomes reported for patients administered therapies that improve functional outcomes, such as exercise capacity. While the primary purpose of the INSPIRE trial was to assess the safety of Yutrepia treatment in PAH patients, analysis of the exploratory efficacy endpoints revealed that functional and quality-of-life outcomes were stable or modestly improved over the duration of the trial following initiation of Yutrepia in patients who were naïve to prostacyclin therapy, as well as in those who transitioned from nebulized treprostinil. The apparent improvements in clinical disease are noteworthy considering that most patients were already receiving two oral PAH therapies. The improvements observed in patients' quality of life scores (over 10 points) suggest that clinically meaningful improvements occur when PAH patients are switched to Yutrepia or initiate it as add-on therapy.

Study limitations

These results must be considered within the context of some study design limitations. First, this was an open-label trial, hence definitive conclusions about efficacy cannot be made. Furthermore, the study design did not include a comparison with another inhaled prostacyclin such as nebulized treprostinil or iloprost. However, Yutrepia is being developed under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, which relies on previous research and reports that have established the safety and efficacy of nebulized treprostinil, the selected reference-listed drug, to treat PAH.

While the INSPIRE trials provide approximately 1 year's safety data, data from an ongoing open-label extension study (LTI-302) for patients who participated in the current study and wished to continue treatment with Yutrepia will provide up to 3 years of long-term safety and clinical effectiveness information of Yutrepia in PAH (NCT03992755).[36]

CONCLUSIONS

The favorable safety profile and patient preference ratings as well as the exploratory efficacy analyses suggest that the profile of Yutrepia represents an important advance in inhaled prostacyclin therapy for patients with PAH either in the setting of transitioning from current nebulized prostacyclin therapy or the initiation of therapy. The administration of Yutrepia with an easy-to-use dry-powder inhaler offers clinicians an inhaled PAH therapy that may be preferred by many patients based on its added convenience and potential to facilitate a more active lifestyle.

AUTHOR CONTRIBUTIONS

All authors contributed to the acquisition, analysis, and interpretation of data; reviewed and revised the manuscript; gave final approval for submission; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICTS OF INTEREST

N. S. H.: Liquidia and Aerovate, consulting fees; Altavant, lectures, presentations, speakers bureaus, manuscript writing, and/or educational events; Liquidia, expert testimony; Liquidia, support for attending meetings and/or travel; Merck and United Therapeutics, data safety monitoring board or advisory board. J. P. F.: Liquidia, advisory board. S. S.: ACCP CHEST and United Therapeutics, research grants; Liquidia, steering committee; Gossamer Bio, United Therapeutics, and Bayer, advisor; Bayer, United Therapeutics, and Johnson & Johnson, speaker; Johnson & Johnson, planned patent; Bayer, advisory board; GSK, endpoint adjudication committee. R. L. B.: Bayer, Abbot, United Therapeutics, Abbott, Gossamer Bio, and Acceleron, consulting fees; Society of Heart and Lung Transplantation and the Pulmonary Vascular Disease Institute, leadership and/or fiduciary role. I. R. P.: Janssen, United Therapeutics, PhaseBio, and Tenax, research grants and/or contracts; Altavant, Janssen, United Therapeutics, and Liquidia, consulting fees; Medscape and Med on the Go, lectures, presentations, speakers bureaus, manuscript writing and/or educational events; Bayer, expert testimony; Altavant, Janssen, United Therapeutics, and Liquidia, data safety monitoring or advisory board; ISHLT, leadership or fiduciary role. D. B.: Acceleron, Arena/United Therapeutics, Altavant, Actelion/Janssen/Johnson & Johnson, Ikaria, Reata, Complexa Liquidia, and Merck, research grants; Acceleron, Altavant, Bayer, Merck, and Liquidia, consulting fees; Practice Point Communications, lectures, presentations, speakers bureaus, manuscript writing and/or educational events; Bayer, expert testimony; United Therapeutics, data safety or advisory board; USPHSR (United States Pulmonary Hypertension Scientific Registry), leadership or fiduciary role; Johnson & Johnson, stock or stock options. R. P. F.: NHLBI, research grant; Up to Date, royalties or licenses; Janssen, Liquidia, Shouti, Altavant, Gossamer Bio, Bayer, and Tenax, consulting fees; United Therapeutics, France Foundation, and Janssen, lectures, presentations, speakers bureaus, manuscript writing and/or educational events; Janssen and Liquidia, data safety or advisory board; Tenax, stock or stock options. S. P.: Liquidia, employee, stock or stock options. A. G.: Liquidia, employee, attending meetings and/or travel patents, and stock or stock options. T. M. B.: Bayer, research grant; Liquidia and Bayer, steering committee and consulting fees; NHLBI and MESA, data safety and/or advisory board.

ETHICS STATEMENT

The study protocol was approved by the institutional review board or ethics committee at each participating site.

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SUPPORTING INFORMATION

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

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