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Long-Term Treatment With Subcutaneous Treprostinil in Patients With Severe Inoperable Chronic Thromboembolic Pulmonary Hypertension in the Multimodal Therapy Era (Data From CTREPH Study Open Label Extension)

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ABSTRACT

The aim of the open label extension (OLE) of CTREPH study was to characterize multimodal treatment in patients with severe inoperable CTEPH, to describe long-term subcutaneous (SC) treprostinil safety and tolerability, and to evaluate change in functional class and exercise capacity over 24 months since completion of the blinded phase of CTREPH. The target population in the OLE consisted of patients who completed 24 weeks of blinded treatment with either high-dose treprostinil of around 30 ng/kg/min (former high-dose group), or low-dose treprostinil of around 3 ng/kg/min (former low-dose group) in the CTREPH study. From the start of OLE, treprostinil dose and any additional therapy were chosen according to the standard of care and physician's discretion. Out of 47 enrolled patients, 20 patients received other PH drugs during OLE and 17 patients underwent at least 1 BPA session. Number of treprostinil-related AEs was substantially higher in the former low-dose group in comparison to the former high-dose group. Related AEs were also more frequent during the first 6 months of the preceding blinded trial than over 24 months of OLE, especially infusion site pain and all local infusion site reactions. No new safety signal was detected. Evaluated clinical outcomes show sustained benefit from long-term treprostinil treatment. Long-term SC treprostinil is a safe and effective component of multimodal treatment for patients with severe CTEPH. Patients who tolerate treprostinil after initiation are likely to continue tolerating it over time, with the clinical benefit maintained over 24 months.

1 | Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by symptomatic persistent obstruction of the pulmonary arteries due to organized thrombi and a secondary microvasculopathy, resulting in progressive pulmonary hypertension and right heart failure if left untreated. CTEPH develops in 2%–4% of patients who survive acute pulmonary embolism [1, 2]. Pulmonary endarterectomy (PEA) is the first-choice treatment [2–7], but up to 50% of patients are considered inoperable and up to 25% develop persistent/recurrent pulmonary hypertension after PEA [8]. Patients with inoperable CTPEH and with residual PH after PEA represent a target for balloon pulmonary angioplasty (BPA) and medical therapies. Approved medications for inoperable CTEPH are riociguat, an oral guanylate cyclase stimulator approved by EMA in March 2014, treprostinil, a subcutaneous (SC) prostacyclin analog approved by EMA in April 2020 and selexipag exclusively in Japan since 2021.

Authorization of treprostinil by EMA was based on the results of CTREPH study which compared high-dose SC treprostinil (target dose around 30 ng/kg/min) with low-dose SC treprostinil (target dose around 3 ng/kg/min) subcutaneously for 24 weeks showing significant improvement of exercise capacity [9]. It is important to note that BPA was introduced after the initiation of the CTREPH study and has significantly changed the current practice of treating inoperable and residual CTEPH. However, only limited evidence on the efficacy and safety of multimodal therapy in patients with severe CTEPH has been obtained to date.

Here, we present data from open label extension (OLE) of CTREPH study collected over 24 months in which SC treprostinil dosing and the performance of BPA were left to physician's discretion in accordance with standard of care. The aim of this report is to characterize multimodal treatment in patients with severe CTEPH, to describe long-term SC treprostinil safety and tolerability, and to evaluate change in New York Heart Association (NYHA) functional class and exercise capacity over 24 months since the completion of the blinded phase of CTREPH.

2 | Methods

2.1 | Study Design

Participation in OLE was offered to patients who completed Stage 2 of the double-blind Phase III CTREPH study. CTREPH study enrolled patients with severe CTEPH, classified as nonoperable, or with persistent or recurrent PH after PEA, who were randomized (1:1) to high-dose SC treprostinil (target dose around 30 ng/kg/min) or low-dose SC treprostinil (target dose around 3 ng/kg/min) for 24 weeks [9]. Eligibility criteria included World Health Organization (WHO) functional Class III or IV and a 6-min walk distance (6MWD) of 150–400 m. Inoperable disease status was based on the decision of multidisciplinary team before inclusion into the study.

The dose of SC treprostinil in the OLE was not prespecified. Patients were allowed to receive any additional therapy for CTEPH as deemed appropriate. The primary objective of CTREPH OLE was to provide a treatment option for patients after completion of the CTREPH study until the availability of SC treprostinil in routine practice, but also to assess the long-term efficacy and safety of SC treprostinil. The OLE was conducted from October 28, 2013 (first patient first visit) to April 9, 2021 (last patient last visit) in four centers: two sites in Austria, one site in the Czech Republic, and one site in Poland.

2.2 | Ethics

OLE was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The ethics committee at each participating site approved the OLE study protocol and all documents provided to patients before the initiation of patient enrollment. All patients signed separate informed consent for participation in OLE as per applicable legislation.

2.3 | Statistical Methodology

Descriptive statistics were performed using the full analysis set. Number of available values, mean, standard deviation (SD), and 95% confidence intervals (95% CI) of mean were presented for continuous variables. Categorical variables were summarized with frequencies (n) and percentages (%). Adverse events (AEs) were tabulated by system organ class (SOC) and individual preferred term within each SOC and dose group (former high-/low-dose group) presenting the number and percentage of patients who experienced at least a single AE. Definitions of an AE, treatment-related AE, and a serious adverse event (SAE) follow International Conference on Harmonization (ICH) Guideline E2A as introduced in 1994. For NYHA functional class and 6MWD, change from randomization visit of the core CTREPH study, that is, 6 months before baseline in OLE, was calculated to evaluate clinical outcome of the long-term SC treprostinil treatment.

Missing data were not imputed. The statistical analysis was performed using the SAS statistical software package (Statistical Analysis System, Version 9.4).

3 | Results

3.1 | Patient Disposition

In total, 47 patients were included in OLE, 22 patients from former high-dose group and 25 patients from the former low-dose group, and 27 patients completed the visit at Month 24, 13 patients from the former low-dose group and 14 from the former high-dose group. Figure 1 summarizes reasons for withdrawal of patients before Month 24. Of note, all four deaths reported in the OLE were caused by the deterioration of the underlying disease. Furthermore, all AEs resulting in the treatment discontinuation were related to SC treprostinil and

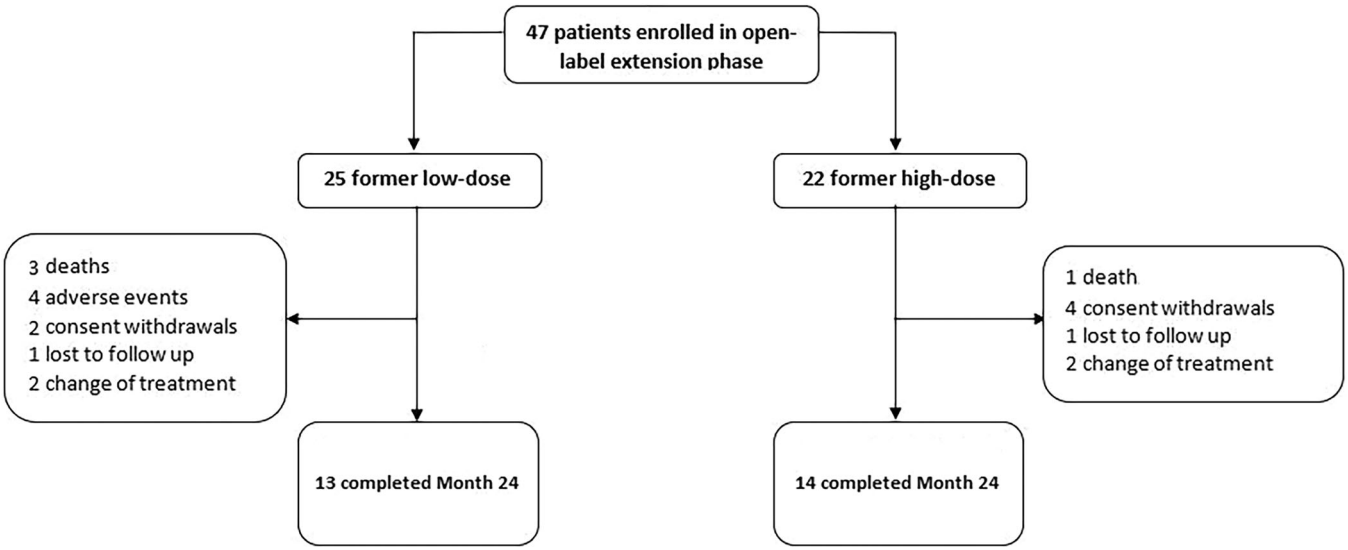

FIGURE 1 | Disposition of patients during 24 months of OLE.

reported from the former low-dose group only: two infusion site reactions and one infusion site pain (all nonserious) as well as one headache (serious).

The median duration of participation/SC treprostinil treatment in OLE was 730 days (24 months) in both subgroups. Mean (SD) duration of participation/SC treprostinil treatment was 536.5 (246.3) days in the former low-dose group and 557.7 (247.5) days in the former high-dose group.

3.2 | Baseline Characteristics

Baseline characteristics of the study population at the time of the enrollment into OLE are summarized in Table 1.

3.3 | Dose of SC Treprostinil During 24 Months of OLE

Table 2 summarizes administered SC treprostinil doses per 6-month intervals during OLE in patients with available data from both subgroups. While SC treprostinil mean dose (ng/kg/min) increased slightly in the former high-dose group (30.51 at baseline vs. 37.35 at Month 24), the dose increase was more substantial in the former low-dose group (4.42 at baseline vs. 28.56 at Month 24). It is important to note that the target dose of SC treprostinil at the time of enrollment to OLE was ~30 ng/kg/min in the high-dose group and around 3 ng/kg/min in the low-dose group as required by the CTREPH protocol. Overall, exposure to SC treprostinil remained lower in the former low-dose group during 24 months of OLE than in patients from the former high-dose group.

3.4 | Additional CTEPH Treatments

During OLE, patients were allowed to use multimodal treatment on top of SC treprostinil as per physician's discretion. Summary of additional treatment is provided in Table 3.

In total, 17 patients underwent BPA during 24 months of OLE, of which 8 patients belonged to the former high-dose group and 9 patients to the former low-dose group.

In addition to SC treprostinil, 15 (5 from the former high-dose group and 10 patients from the former low-dose group) of 47 enrolled patients were pretreated with PH-specific medication at OLE Baseline (details are provided in Table 2). Specifically, 13 patients already received dual combination (treprostinil and sildenafil or riociguat or bosentan) and 2 patients received triple combination (treprostinil with bosentan and sildenafil or with macitentan and riociguat) at the time of enrollment in OLE. During 24 months of OLE, both riociguat and sildenafil were used by 4 patients (2 from the former high-dose group and 2 from the former low-dose group). Five patients (three from the former high-dose group and two from the former low-dose group) initiated riociguat during their participation in OLE and one patient from the former low-dose group initiated riociguat in addition to bosentan. Two patients (both from the former low-dose group) were switched from sildenafil to riociguat. Sildenafil was discontinued during OLE in two patients (both from the former low-dose group). Additional macitentan plus riociguat were continuously used by one patient (one from the former high-dose group) and additional bosentan plus sildenafil were continuously used by one patient from the former low-dose group until withdrawal from OLE. Overall during 24 months of OLE, no change of therapy was observed in 10 patients (8 with dual and 2 with triple combination), 6 patients initiated additional treatment (all riociguat, 5 as dual and 1 as triple combination), 2 patients discontinued additional sildenafil in dual combination and 2 patients switched sildenafil to riociguat in dual combination.

With respect to combination of BPA and additional medical CTEPH treatment, there were 7 patients (5 from the former high-dose group and 2 from the former low-dose group) who were pretreated with additional PH medications at the time of BPA in OLE: 4 patients (3 from the former high-dose

TABLE 1 | Baseline characteristics of the population enrolled in the OLE.

Parameter	Former high-dose group ($n = 22$)	Former low-dose group ($n = 25$)	Total ($n = 47$)
Age distribution	68 (9.3)	62 (11.8)	65 (11.1)
≥ 60 years	16 (72.7%)	15 (60.0%)	31 (66.0%)
< 60 years	6 (27.3%)	10 (40.0%)	16 (34.0%)
Sex			
Female	9 (40.9%)	13 (52.0%)	22 (46.8%)
Male	13 (59.1%)	12 (48.0%)	25 (53.2%)
Weight (kg)	75.5 (17.09)	80.7 (15.64)	78.3 (16.52)
Hemodynamics			
mPAP (mmHg)	46.0 (9.7)	47.6 (8.7)	46.9 (9.2)
PVR (dyn s cm^{-5})	664.4 (302.6)	851.0 (352.7)	763.7 (343.1)
NT-proBNP (pg/mL)	1582.0 (1419.8)	2157.9 (1806.4)	1888.4 (1661.8)
Concomitant medications			
Anticoagulation	22 (100.0%)	25 (100.0%)	47 (100.0%)
Sildenafil	2 (9.1%)	6 (24.0%)	8 (17.0%)
Bosentan	0 (0.0%)	1 (4.0%)	1 (2.1%)
Riociguat	2 (9.1%)	2 (8.0%)	4 (8.5%)
Bosentan and sildenafil in combination	0 (0.0%)	1 (4.0%)	1 (2.1%)
Riociguat and macitentan in combination	1 (4.5%)	0 (0.0%)	1 (2.1%)
WHO functional class			
I	1 (4.5%)	0 (0.0%)	1 (2.1%)
II	9 (40.9%)	3 (12.0%)	12 (25.5%)
III	11 (50.0%)	19 (76.0%)	30 (63.8%)
IV	1 (4.8%)	3 (12.0%)	4 (8.7%)
6-min walk distance (m)	355.3 (78.67)	310.9 (102.97)	331.7 (95.02)

Note: Data are mean (standard deviation) or number of patients (%).
Abbreviations: NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAMP, pulmonary artery mean pressure; PVR, pulmonary vascular resistance.

TABLE 2 | SC treprostinil dose (ng/kg/min) per 6-month intervals during OLE.

	Former high-dose group ($n = 22$)			Former low-dose group ($n = 25$)		
Timepoint	***n***	**Mean (SD)**	**95% CI**	***n***	**Mean (SD)**	**95% CI**
Baseline	21	30.51 (4.21)	28.59; 32.42	25	4.42 (1.78)	3.68; 5.15
Month 6	17	33.85 (8.61)	29.42; 38.27	21	22.30 (11.46)	17.08; 27.51
Month 12	16	35.55 (8.78)	30.87; 40.23	16	26.94 (8.63)	22.34; 31.54
Month 18	12	37.18 (13.56)	28.57; 45.80	11	30.88 (5.63)	27.09; 34.66
Month 24	14	37.35 (9.99)	31.58; 43.11	12	28.56 (12.42)	20.67; 36.45

Abbreviations: CI, confidence interval; *n*, number of patients with available data; SD, standard deviation.

group and 1 from the former low-dose group) with riociguat, 2 patients (1 from the former high-dose group and 1 from the former low-dose group) with sildenafil and 1 patient from the former high-dose group with macitentan plus riociguat. One more patient from the former high-dose group received additional riociguat after BPA (after 294 days).

3.5 | Long-Term Safety of SC Treprostinil

An overview of reported AEs during 24 months of OLE is provided in Table 4. Overall, there was a substantially higher number of any AEs and treprostinil-related AEs in the former low-dose group than in the former high-dose group (91 vs. 66

TABLE 3 | Number of patients using additional treatments to SC treprostinil.

Timepoint	Baseline		Month 6		Month 12		Month 18		Month 24	
Formed dose subgroup	**H**	**L**	**H**	**L**	**H**	**L**	**H**	**L**	**H**	**L**
Total number of participants	22	25	19	21	16	18	14	16	14	13
Balloon pulmonary angioplasty	—	—	5	7	1	2	1	—	1	—
Riociguat	2	2	3	2	2	3	3	4	4	0.4
Sildenafil	2	6	2	5	2	2	2	—	2	—
Macitentan and riociguat in combination	1	—	1	—	1	—	1	—	1	—
Bosentan and riociguat in combination	—	1[a]	—	1		1	—	1		1
Bosentan and sildenafil in combination	—	1	—	—	—	—	—	—	—	—

Abbreviations: H, former high-dose group; L, former low-dose group.
[a]Bosentan only, riociguat added Day 129.

TABLE 4 | Safety overview.

Summary of reported adverse events	Former high-dose group ($n = 22$) *n* (%) *E*	Former low-dose group ($n = 25$) *n* (%) *E*	Total ($n = 47$) *n* (%) *E*
Any reported AE	20 (90.9%) 66	20 (80.0%) 91	40 (85.1%) 157
Any treprostinil-related AE	7 (31.8%) 15	11 (44.0%) 44	18 (38.3%) 59
Any SAE	11 (50.0%) 20	12 (48.0%) 20	23 (48.9%) 40
Any treprostinil-related SAE	1 (4.5%) 1	2 (8.0%) 3	3 (6.4%) 4
Any AE resulting in discontinuation	—	4 (16.0%) 4	4 (8.5%) 4
Number of any AEs experienced by a patient	***n* (%)**	***n* (%)**	***n* (%)**
0	2 (9.1%)	5 (20.0%)	7 (14.9%)
1	3 (13.6%)	5 (20.0%)	8 (17.0%)
2	5 (22.7%)	7 (28.0%)	12 (25.5%)
3	5 (22.7%)	1 (4.0%)	6 (12.8%)
4	4 (18.2%)	1 (4.0%)	5 (10.6%)
5 and more	3 (13.6%)	6 (24.0%)	9 (19.1%)

Abbreviations: AE, adverse event; *E*, number of events; *n*, number of patients; SAE, serious adverse event.

AEs and 44 vs. 15 AEs, respectively). Number of any SAEs reported over 24 months of OLE was comparable in both groups (20 SAEs each). Out of 40 SAEs reported in OLE, 4 SAEs were related to SC treprostinil, 1 SAE in 1 patient in the former high-dose group (infusion site abscess), and 3 SAEs in 2 patients in the former low-dose group (accidental overdose, headache, and infusion site infection). There was a higher number of patients with multiple AEs (5 and more AEs) in the former low-dose group (24.0%) in comparison to the former high-dose group (13.6%).

The following four related AEs resulted in early discontinuation: two infusion site reactions, one infusion site pain, and one headache. All those events were reported from four patients in the former low-dose group and judged as related to SC treprostinil. Headache was considered to be a SAE, the other three AEs resulting in premature withdrawal were not serious.

Four deaths (one in the former high-dose group and three in the former low-dose group) were reported during the 24 months of OLE. All four deaths were caused by the deterioration of the underlying disease, and none was related to SC treprostinil treatment.

Out of 17 patients who underwent BPA during the OLE, no patient discontinued SC treprostinil treatment or OLE participation in relation to the procedure. Within 1 month after BPA, one patient experienced a subdural hematoma 1 day after BPA which was completely recovered within 12 days and one patient experienced multiple fractures in the context of a fall on Day 29 after BPA which were also recovered in the next 38 days. Both patients were from the former low-dose group and both events were judged to be serious, but not related to SC treprostinil treatment.

Table 5 summarizes treprostinil-related AEs by preferred term in the pivotal CTREPH study over 6-month blinded treatment

TABLE 5 | Comparison of safety results from CTREPH [9] and from 24 months of OLE by number (%) of patients experiencing AEs related to SC treprostinil.

	CTREPH study 6 months in total		OLE 24 months in total	
	High-dose group ($N = 53$)	Low-dose group ($N = 52$)	Former high-dose group ($N = 22$)	Former low-dose group ($N = 25$)
Death	2 (4%)	1 (2%)	1 (4.5%)	3 (12.0%)
Any local reaction	44 (83%)	46 (88%)	6 (27.3%)	8 (32.0%)
Infusion site pain	39 (74%)	42 (81%)	2 (9.1%)	4 (16.0%)
Infusion site reaction[a]	25 (47%)	24 (46%)	5 (22.7%)	5 (20.0%)
Systemic adverse reaction				
Diarrhea	31 (58%)	13 (25%)	2 (9.1%)	3 (12.0%)
Headache	7 (13%)	4 (8%)	0 (0%)	3 (12.0%)
Pain in extremity	9 (17%)	1 (2%)	1 (4.5)	2 (8.0%)
Nausea or dyspepsia	4 (8%)	2 (4%)	0 (0%)	2 (8.0%)
Flushing	4 (8%)	4 (8%)	0 (0%)	0 (0%)
Pain in jaw	2 (4%)	0 (0%)	0 (0%)	1 (4.0%)
Vertigo	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Skin rash	1 (2%)	2 (4%)	0 (0%)	0 (0%)
Back pain	0 (0%)	1 (2%)	0 (0%)	1 (4.0%)

Note: Data are *n* (%).
[a]Infusion site reaction includes abscess, erythema, hemorrhage, infection, inflammation, irritation, pruritus, rash, and swelling.

and in OLE over 24 months. The most frequent side effects of SC treprostinil according to results of CTREPH study are local reactions at the infusion site (83% in the high-dose group and 88% in the low-dose group) which was also observed in the OLE, but less common in both subgroups (27.3% in the former high-dose group and 32.0% in the former low-dose group). Among individual side effects observed in at least three patients, we also observed those less frequently in both subgroups of OLE than in the CTREPH study with the exception of headache that occurred at similar rates (13% in the high-dose group of CTREPH and 12% in the former low-dose group of OLE). Of note, all related AEs in OLE were more frequent in the former low-dose group than in the former high-dose group except infusion site reactions that were reported equally frequent (22.7% in the former high-dose group vs. 20.0% in the former low-dose group).

No new safety signal was recorded in OLE, as all related AEs were expected based on the safety profile of SC treprostinil.

3.6 | Long-Term Effect of SC Treprostinil

Figure 2 shows the change in NYHA functional class from baseline of CTREPH study (6 months before OLE baseline) in categories improved/stable/worsened by 6-month period in OLE. Up to Month 24 in OLE, NYHA class remained stable or improved in the former high-dose group and we observed more improved patients and less worsening patients in the former low-dose group.

Figure 3 shows the mean change in 6MWD from the CTREPH study baseline (6 months before OLE baseline) by a 6-month period in OLE. In the former high-dose group, we observed stable or slow decline in 6MWD up to Month 24 of OLE after significant improvement during 6 months of the CTREPH study. In the former low-dose group, we observed slow improvement in exercise capacity following uptitration of SC treprostinil dose up to 24 months of OLE. Specifically, mean (95% CI) change in 6MWD from the CTREPH study baseline to Months 6, 12, and 24 in OLE was 42.4 m (2.4, 82.5), 48.2 m (7.3, 89.0), and 34.4 m (−9.1, 77.9), respectively, in the former high-dose group and 30.4 m (−6.5, 67.2), 41.5 m (3.5, 79.4), and 50.2 m (9.7, 90.8), respectively, in the former low-dose group.

4 | Discussion

Long-term SC treprostinil therapy administered subcutaneously in accordance with the standard of care was well-tolerated and provided sustained clinical benefit in patients with severe inoperable CTEPH or persistent/recurrent PH after PEA, a life-threatening condition with limited therapeutic alternatives. The target population in the present study consisted of patients who completed 24 weeks of blinded treatment with either high-dose SC treprostinil of around 30 ng/kg/min (former high-dose group) or low-dose SC treprostinil of around 3 ng/kg/min (former low-dose group) in the preceding CTREPH study. From the start of OLE, SC treprostinil dose and any additional therapy were administered according to the standard of care and physician discretion and based on clinical response and tolerance of an individual patient.

With respect to long-term safety, the number of treprostinil-related AEs as well as AEs resulting in withdrawal during OLE was substantially higher in the former low-dose group than in

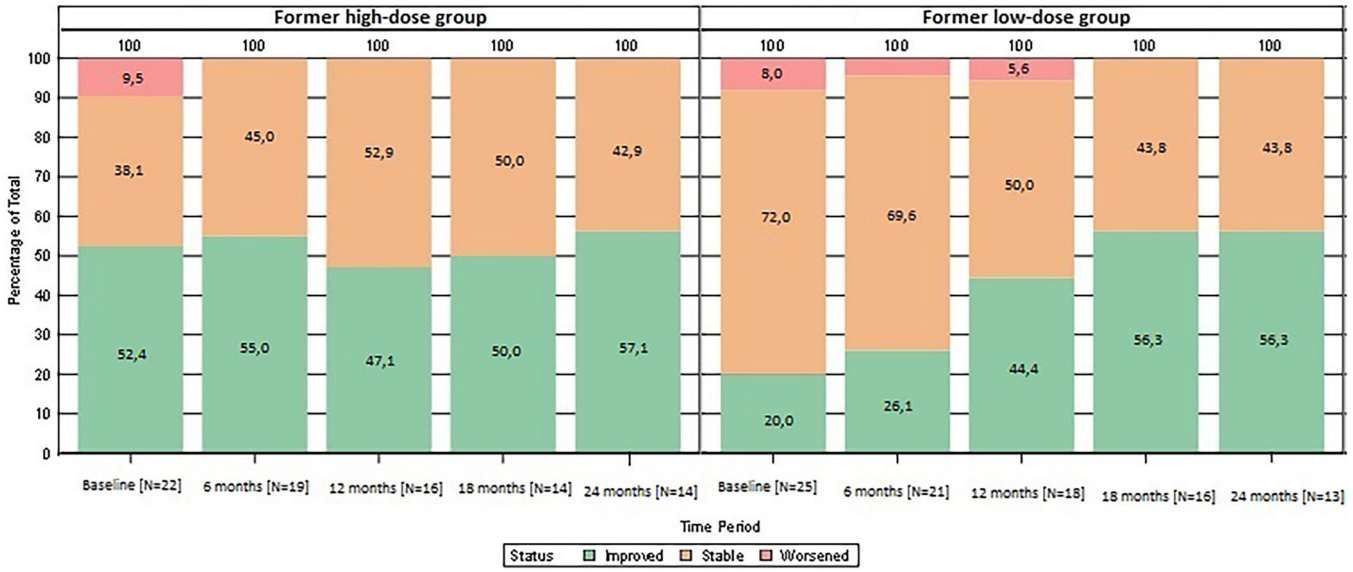

FIGURE 2 | Percentage of patients by change in NYHA functional class from CTREPH study baseline in categories improved/stable/worsened by 6-month period in OLE.

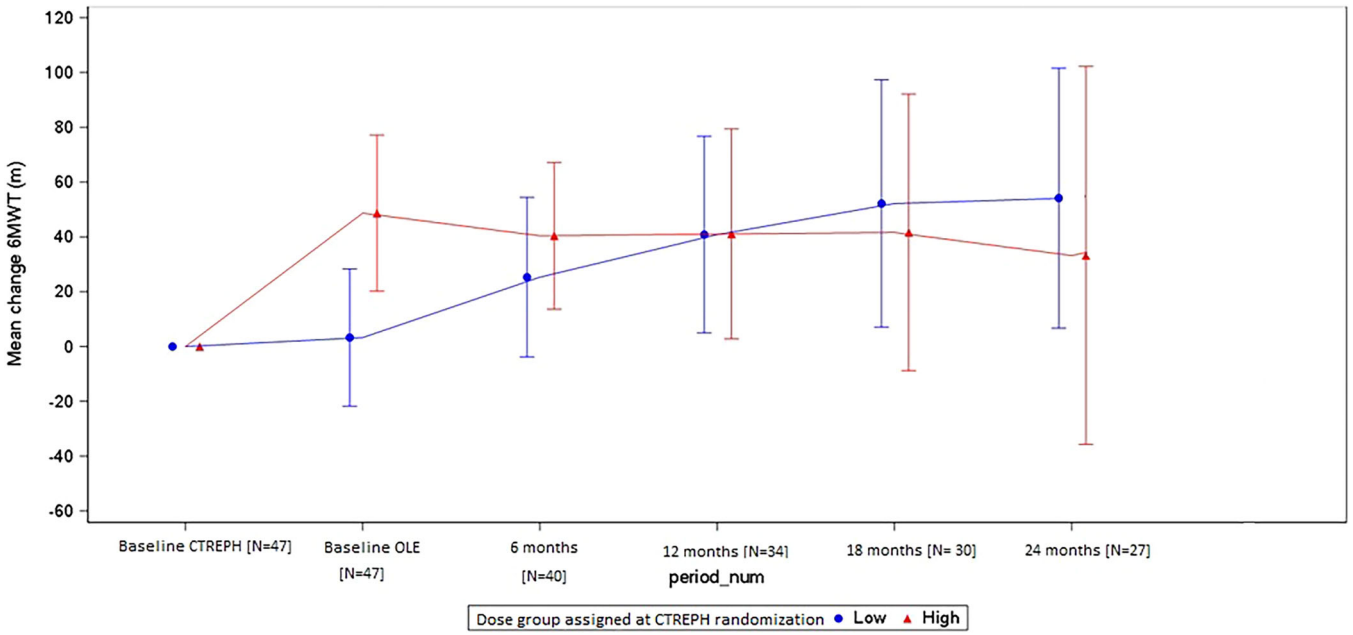

FIGURE 3 | Mean change in 6-min walk distance (6MWD) from baseline of CTREPH study by 6-month period in OLE with 95% confidence interval.

the former high-dose group suggesting that once patient tolerates their maintenance dose over the first 6 months, SC treprostinil would also be well-tolerated over the subsequent 24 months. In general, related AEs were more common during the first 6 months of the blinded clinical trial than over the 24 months of OLE in both subgroups suggesting sustained tolerability of SC treprostinil. Specifically, the proportion of patients reporting infusion site pain decreased from 74% in the high-dose group and 81% in low-dose group during the blinded phase to 9.1% and 16.0%, respectively, and all local infusion site reactions decreased from 83% and 88% in blinded phase to 27.3% and 32.0%, respectively, in the OLE.

Baseline characteristics of both subgroups at the time of enrollment into OLE were similar, except mean older age and better pulmonary vascular resistance (PVR) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the former high-dose group versus the former low-dose group (68 years vs. 62 years, 664.4 dyn s cm^{-5} vs. 851.0 dyn s cm^{-5}; 1582.0 pg/mL vs. 2157.9 pg/mL, respectively).

According to the treprostinil prescribing information, a starting dose of 1.25 ng/kg/min is recommended, followed by weekly increases after the first 4 weeks to a rate of 2.5 ng/kg/min/week when the mean doses after 12 and 24 months reach 31 ng/kg/min and 33 ng/kg/min, but SC treprostinil dose should always be

adjusted on an individual basis. While SC treprostinil dose in the former high-dose group was stable over OLE, the SC treprostinil dose in former low-dose group remained lower than expected (mean 26.94 ng/kg/min at Month 12 and 28.56 ng/kg/min at Month 24), corresponding to a higher number of AEs in the former low-dose group.

This study also provides important insight in the multimodal treatment of patients with severe CTEPH because the use of additional PH medications on top of SC treprostinil was voluntary as per physician discretion. Overall, 20 patients out of 47 received additional PH medications during OLE.

Clinical efficiency over 24 months of OLE was evaluated as NYHA functional class and 6MWD change from baseline of the preceding blinded phase. The former high-dose group showed stable clinical outcomes and the former low-dose group slow, but steady improvement. In the preceding blinded phase of the CTREPH trial of SC treprostinil high-dose (standard dose of 30 ng/kg/min), improvement in WHO functional class was reported in 50.9% of patients at Month 6 [9]. In the former low-dose group after 6 months from initiating the standard dose in OLE, the improvement in NYHA functional class was reported only in 26.1% patients, but the proportion increased to 44.4% at Month 12 and further to 56.3% at Month 24. Mean 6MWD change over 6 months in the former low-dose group in OLE was lower (30.4 m) in comparison to the CTERPH high-dose group (45.0 m) [9], but it increased to 41.5 m and 50.2 m in Months 12 and 24, respectively. As discussed above, SC treprostinil dose in the former low-dose group increased more slowly than in the high-dose group of the blinded CTREPH study phase. This delay could potentially impact clinical outcome. Nevertheless, the low number of patients with available data and their severe complex conditions do not allow to derive strong efficacy conclusions from OLE.

Simonneau et al. [10] published similar comparison of results in patients receiving riociguat in the blinded phase of the CHEST-1 study and in patients switching from placebo in blinded phase to riociguat in OLE (CHEST-2 study). After transitioning to riociguat treatment, patients achieved improvements in 6MWD and WHO functional class comparable to the former riociguat group, but they did not fully catch up to the former riociguat group by the 1-year cutoff which highlights the importance of initiating the appropriate treatment in the target population as early as possible. CTREPH OLE confirms these observations that adequately dosed SC treprostinil should be started as soon as possible.

Obvious limitations of the OLE study are the low number of patients, the multimodal nature of treatment that were not strictly regulated by the protocol, and the high number of dropouts before Month 24. Also, the primary aim of OLE was to provide access to SC treprostinil until it became available in routine clinical practice, therefore, no efficacy analyses had been planned. Furthermore, new treatment modalities were implemented in the clinical practice during the long recruitment period of OLE, therefore, the study objectives were not focused on evaluation of the effects of multimodal treatment. However, data collected in OLE are providing valuable information about the standard of care for patients with extremely poor prognosis and limited treatment options. The fact that patients in OLE were allowed to receive additional CTEPH therapies as deemed appropriate by their physicians also contributed to optimizing the treatment approach, reflecting real-world conditions where multimodal therapy is common in complex cases like CTEPH.

The OLE results confirm that long-term SC treprostinil is a safe and effective component of multimodal treatment for patients with severe CTEPH. Patients who tolerate SC treprostinil after initiation are likely to continue tolerating it over time, with the clinical benefit maintained over 24 months.

Author Contributions

Pavel Jansa and Irene M. Lang had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Irene M. Lang was responsible for the study concept and design, critical revision of the manuscript for important intellectual content, and study supervision. Pavel Jansa and Irene M. Lang drafted the manuscript. All authors were responsible for acquisition, analysis, or interpretation of data.

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Ethics Statement

The OLE of the CTREPH study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The ethics committee at each participating site approved the study protocol and all documents provided to patients before initiation of patient enrollment.

Consent

All patients signed informed consent as per applicable legislation.

Conflicts of Interest

P.J. has received fees and grants from Janssen Pharmaceutical Companies of Johnson and Johnson, AOP Orphan, Bayer HealthCare, and Merck Sharp & Dohme. He has served on advisory boards for Janssen Pharmaceutical Companies of Johnson and Johnson, Bayer HealthCare, and Merck Sharp & Dohme, outside of the Article. R.S.-K. has relationships with drug companies including Actelion, AOP Orphan Pharmaceuticals, Bayer Schering Pharma, GlaxoSmithKline, and SciPharm Sàrl; is an investigator in trials involving these companies, relationships include consultancy service, and research grants. I.S. has relationships with Actelion, AOP Orphan Pharmaceuticals, Bayer Healthcare, Merck Sharp & Dohme, GlaxoSmithKline, and Pfizer and is an investigator in trials involving these companies, relationships include consultancy service, research grants, and membership of scientific advisory boards, outside of the Article. I.M.L. has relationships with Actelion-Janssen, AOP Orphan Pharmaceuticals, Bayer-Schering, Daiichi Sankyo, Ferrer, SciPharm Sàrl, and MSD, and is an investigator in trials involving these companies; has relationships including consultancy service, research grants, and scientific advisory boards. All other authors declare no competing interests (N.S.-S., G.K., R.S.-M., B.S., and J.L.).

References

1. L. Valerio, A. C. Mavromanoli, S. Barco, FOCUS Investigators, et al., "Chronic Thromboembolic Pulmonary Hypertension and Impairment After Pulmonary Embolism: The FOCUS Study," *European Heart Journal* 43, no. 36 (2022): 3387–3398.

2. H. Gall, M. M. Hoeper, M. J. Richter, W. Cacheris, B. Hinzmann, and E. Mayer, "An Epidemiological Analysis of the Burden of Chronic Thromboembolic Pulmonary Hypertension in the USA, Europe and Japan," *European Respiratory Review* 26, no. 143 (2017): 160121.

3. V. V. McLaughlin, S. L. Archer, D. B. Badesch, et al., "ACCF/AHA Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration With the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association," *Journal of the American College of Cardiology* 53, no. 17 (2009): 1573–1619.

4. H. A. Ghofrani, M. Humbert, D. Langleben, et al., "Riociguat: Mode of Action and Clinical Development in Pulmonary Hypertension," *Chest* 151, no. 2 (2017): 468–480.

5. D. Jenkins, "Pulmonary Endarterectomy: The Potentially Curative Treatment for Patients With Chronic Thromboembolic Pulmonary Hypertension," *European Respiratory Review* 24, no. 136 (2015): 263–271.

6. N. H. Kim, M. Delcroix, D. P. Jenkins, et al., "Chronic Thromboembolic Pulmonary Hypertension," *Journal of the American College of Cardiology* 62, no. Suppl 25 (2013): D92–D99.

7. M. de Perrot, D. Gopalan, D. Jenkins, et al., "Evaluation and Management of Patients With Chronic Thromboembolic Pulmonary Hypertension – Consensus Statement From the ISHLT," *Journal of Heart and Lung Transplantation* 40, no. 11 (2021): 1301–1326.

8. W. C. Hsieh, P. Jansa, W. C. Huang, M. Nižnanský, M. Omara, and J. Lindner, "Residual Pulmonary Hypertension After Pulmonary Endarterectomy: A Meta-Analysis," *Journal of Thoracic and Cardiovascular Surgery* 156, no. 3 (2018): 1275–1287.

9. R. Sadushi-Kolici, P. Jansa, G. Kopec, et al., "Subcutaneous Treprostinil for the Treatment of Severe Non-Operable Chronic Thromboembolic Pulmonary Hypertension (CTREPH): A Double-Blind, Phase 3, Randomised Controlled Trial," *Lancet Respiratory Medicine* 7, no. 3 (2019): 239–248.

10. G. Simonneau, A. M. D'Armini, H. A. Ghofrani, et al., "Riociguat for the Treatment of Chronic Thromboembolic Pulmonary Hypertension: A Long-Term Extension Study (CHEST-2)," *European Respiratory Journal* 45, no. 5 (2015): 1293–1302.