Subcutaneous treprostinil for the treatment of severe non-operable chronic thromboembolic pulmonary hypertension (CTREPH): a double-blind, phase 3, randomised controlled trial

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Summary

Background **Treprostinil, a prostacyclin analogue, is effective for the treatment of pulmonary arterial hypertension. However, information is scarce regarding treprostinil for treatment of chronic thromboembolic pulmonary hypertension (CTEPH). The aim of this study was to examine the efficacy and safety of subcutaneous treprostinil in this setting.**

Methods **In this 24-week, randomised, double-blind controlled trial, we enrolled patients with CTEPH, classified as non-operable, or with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy, in six European expert centres in Austria, Czech Republic, Germany, and Poland. Patients in WHO functional class III or IV with a 6-min walk distance of 150–400 m were randomly assigned at a 1:1 allocation ratio to continuous high-dose subcutaneous treprostinil (target dose around 30 ng/kg per min at week 12) or low-dose subcutaneous treprostinil (target dose around 3 ng/kg per min at week 12). The primary endpoint was the change from baseline in 6-min walk distance at week 24. All patients who received at least one dose of the study drug were included in the intention-to-treat efficacy and safety analyses based on assessment of adverse events. The trial was registered at ClinicalTrialsRegister.eu EudraCT number 2008-006441-10 and ClinicalTrials.gov, number NCT01416636.**

Findings **From March 9, 2009, to June 9, 2016, 105 patients were enrolled with 53 (50%) patients randomly assigned to high-dose and 52 (50%) patients to low-dose subcutaneous treprostinil. At week 24, marginal mean 6-min walk distance improved by 44·98 m (95% CI 27·52 to 62·45) in the high-dose group, and by 4·29 m (95% CI –13·34 to 21·92) in the low-dose group (treatment effect 40·69 m, 95% CI 15·86 to 65·53, p=0·0016). 12 serious adverse events were reported in ten (19%) of 52 patients from the low-dose group and 16 serious adverse events were reported in nine (17%) of 53 patients from the high-dose group. The most common treatment-related adverse events in both groups were infusion site pain and other infusion site reactions.**

Interpretation **Treatment with subcutaneous treprostinil was safe, and improved exercise capacity in patients with severe CTEPH. Subcutaneous treprostinil provides a parenteral treatment option for patients of WHO functional class III or IV and those who do not tolerate other therapies or need combination treatment.**

Funding **SciPharm Sàrl.**

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is characterised by the obstruction of major pulmonary arteries with organised thrombi resulting in increased pulmonary vascular resistance and right-sided heart failure. Although CTEPH affects all age groups, most cases occur in older people (≥60 years). CTEPH is a long-term complication of pulmonary embolism[1] with a cumulative incidence in Europe of 0·5–4·1% after symptomatic pulmonary embolism.[2–4] Pulmonary endarterectomy is the treatment of choice with a remarkable functional recovery of patients and low mortality at 30 days of less than 5%.[5] However, across European countries, between 12·0% and 60·9% of patients are classified as non-operable.[6] This variation is because of the variability of operability definitions between centres. In addition, 16·7% of European patients are diagnosed with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy,[6] thus illustrating an unmet need for alternative treatments. Classic pulmonary arteriopathy has been described in CTEPH lung biopsies,[7] serving as a justification for the use of drugs approved for pulmonary arterial hypertension.[8–10] In contrast to the successes of pulmonary endarterectomy,[5] specific pharmacological treatments for CTEPH were not licensed by authorities until 2014 because of lack of efficacy in randomised controlled trials (RCTs).[11,12] Balloon pulmonary angioplasty is arising as a promising treatment option for CTEPH[13–15] and RCTs of medical treatments in

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Research in context

Evidence before this study

Pulmonary endarterectomy is the treatment of choice for patients with CTEPH. However, approximately 50% of patients are not able to undergo pulmonary endarterectomy in Europe, and a fifth are diagnosed with persistent or recurrent pulmonary hypertension after pulmonary endarterectomy. Classic pulmonary arteriopathy has been described in CTEPH lung biopsies, justifying the use of pulmonary hypertension-specific medications. When the CTREPH trial was initiated, no drug was approved for the treatment of CTEPH, and balloon pulmonary angioplasty was not established. Off-label treatments were not possible in many European countries. Riociguat, a soluble guanylate cyclase stimulator was the first substance approved for non-operable and persistent or recurrent CTEPH in WHO functional class II and III on the basis of the CHEST-1 trial reporting significant efficacy and safety. In 2017, MERIT-1, a 16-week phase 2 trial with macitentan, a dual-endothelin receptor antagonist, reported a significant improvement in pulmonary vascular resistance. We surveyed the literature by searching PubMed for clinical trials published in any language during the past five decades (from Jan 1, 1968, to Feb 1, 2018), investigating medicinal treatments for CTEPH. By combining the search terms "inoperable", and "chronic thromboembolic pulmonary hypertension" with "randomized clinical trial", we found only four trials. A substantial unmet need exists for long-term data from randomised studies investigating pulmonary hypertension-specific treatments in patients with severe non-operable CTEPH.

Added value of this study

The CTREPH trial is the first randomised controlled trial of subcutaneous treprostinil for non-operable CTEPH or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy. Despite severe disease, the well-known side-effect profile of subcutaneous treprostinil, and the low-dose comparator, significant changes in 6-min walk distance, haemodynamics, and WHO functional class were observed in CTREPH. Subcutaneous treprostinil is the only effective prostacyclin for severe CTEPH as it circumvents the need for intravenous lines that could be sources of thromboembolism. Furthermore, the study is unique for the use of a low-dose comparator. Up to week 12, improvements of 6-min walk distance were similar in both treatment groups.

Implications of all the available evidence

The results of the CTREPH trial shows that long-term subcutaneous treprostinil is safe and effective, leading to dose-dependent improvements of 6-min walk distance, haemodynamics, WHO functional class, and N-terminal prohormone of brain natriuretic peptide amounts in patients with severe non-operable CTEPH. Subcutaneous treprostinil provides a parenteral treatment option for patients who are WHO functional class IV and for patients who do not tolerate riociguat or need combination treatment.

CTEPH=chronic thromboembolic pulmonary hypertension.

combination with balloon pulmonary angioplasty are in preparation.

The CHEST-1 trial[16] was the first trial reporting significant efficacy and safety of riociguat, a soluble guanylate cyclase stimulator in patients with CTEPH over 16 weeks. MERIT-1,[17] a 16-week, phase 2 trial with macitentan, a dual-endothelin receptor antagonist, reported statistically significant improvement of pulmonary vascular resistance. Still, randomised, long-term data investigating drugs approved for pulmonary arterial hypertension in patients with severe non-operable CTEPH are absent.

Treprostinil is a stable prostacyclin analogue with a half-life of 4·6 h,[18] permitting subcutaneous administration. Treprostinil has acute haemodynamic effects similar to epoprostenol, with vasodilation and inhibition of platelet aggregation.[19] Despite only moderate effects in one RCT,[20] excellent efficacy, safety, and tolerability of subcutaneous treprostinil have been reported in patients with pulmonary arterial hypertension.[20,21] One uncontrolled study has also suggested the treatment is efficacious, safe and tolerated in CTEPH.[22,23] Our main objective was to establish the effect of subcutaneous treprostinil on 6-min walk distance after 24 weeks in patients with severe non-operable CTEPH or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy.

See Online for appendix

Methods

Study design and participants

CTREPH was a 24-week, double-blind, randomised controlled phase 3 trial to investigate the efficacy and tolerability of subcutaneous treprostinil in patients with severe, non-operable CTEPH. The study compared high-dose subcutaneous treprostinil (target dose around 30 ng/kg per min) with low-dose subcutaneous treprostinil (target dose around 3 ng/kg per min) to avoid use of a placebo in very ill patients and to allow complete double-blinding for a drug that causes local infusion site reactions. Target doses were determined based on published literature.[20,24,25] According to the only published RCT with subcutaenous treprostinil,[20] a dose of 3 ng/kg per min was to be expected to lead to less clinical improvement than the 30 ng/kg per min dose.

CTREPH was done in six European expert centres (in Austria, Czech Republic, Germany, and Poland) for pulmonary hypertension and approved by respective ethics committees and national competent authorities (appendix). Patients with confirmed non-operable CTEPH or persistent pulmonary hypertension after pulmonary endarterectomy were screened and randomly assigned.

Patients were eligible if they had a confirmed diagnosis of CTEPH (mean resting pulmonary artery pressure

≥25 mm Hg, pulmonary vascular resistance >300 dyn·s·cm^{-5}, at least 3 months of effective anticoagulation, and imaging results supporting diagnosis) that was classified as severe on the basis of an unencouraged 6-min walk distance of between 150 and 400 m and WHO functional class III or IV. Diagnosis had to be confirmed by at least two imaging methods: ventilation perfusion scanning, pulmonary angiography, spiral CT, or magnetic resonance angiography. In addition, patients had to be classified as non-operable by experienced pulmonary endarterectomy surgeons and the principal investigator. Non-operability criteria were distal disease, persistent or recurrent pulmonary hypertension following pulmonary endarterectomy, or other reasons precluding pulmonary endarterectomy, including patient refusal.[26] The main reasons for excluding patients from enrolment were: (1) the patient having another form of pulmonary arterial hypertension, a total lung capacity of less than 70% predicted, or a FEV_1/forced vital capacity of less than 50%. Any drug approved for pulmonary arterial hypertension other than the study medication had to be given at a stable dose for at least 1 month before inclusion in the study and remain unchanged throughout the study. Balloon pulmonary angioplasty was not offered to patients before and during the study period. At present, the role of balloon pulmonary angioplasty for the treatment of CTEPH is still being evaluated.[27]

All patients provided written informed consent according to the Declaration of Helsinki. Detailed information about the population and the study design of CTREPH is available in the appendix. Important changes to methods and outcomes after trial commencement are reported in the appendix. The study was completed and data were obtained according to Good Clinical Practice guidelines and the protocol is available in the appendix.

Randomisation and masking

A predefined randomisation scheme with random block lengths was used to assign patients either to high-dose subcutaneous treprostinil (target dose around 30 ng/kg per min at week 12) or low-dose subcutaneous treprostinil (target dose around 3 ng/kg per min at week 12) at a 1:1 allocation ratio. After random assignment, patients who were masked received the study drug in an ascending order. Medication packages were numbered consecutively and new patients were randomised by assigning the lowest available number of the masked study medication to the patient. To facilitate complete masking of patients and clinical staff involved in the trial, patients with similar bodyweight had identical dosing schedules, regardless of randomisation group (appendix). The study drug was administered continuously through an ambulatory infusion pump. Dose adjustments were done by patients every second to fourth day during the up-titration phase according to the predefined dosing schedule (appendix). Beyond week 12, doses were kept constant in both groups until study completion at week 24. Investigators involved in the trial enrolled the participants. The dosing plan and detailed information about randomisation and masking procedures are provided in the appendix.

Procedures

The study drug was administered by continuous subcutaneous infusion via commercial infusion pumps (CADD-MS3; Smiths Medical MD, Minneapolis, MN, USA). All patients were trained to independently use the pump and were advised to adapt the infusion rate and refill the pump's cartridge according to predefined infusion rate settings. Patients received continuous support according to their individual needs and the study team regularly monitored procedures and drug accountability to check the correct amount had been used. Patient diaries were collected and reviewed at each study visit.

Visits, including clinical assessments, were done at weeks 6, 12, 18, and 24. Clinical outcome measures, and blood tests were assessed at weeks 12 and 24. If possible, a termination visit was done if a patient discontinued therapy or was withdrawn from the study before week 24.

Outcomes

The primary efficacy endpoint was the change in 6-min walk distance from baseline to week 24. Secondary efficacy endpoints were the change from baseline to week 12 in 6-min walk distance as well as changes from baseline to week 24 in WHO functional class, Borg Dyspnoea Score, heart rate and oxygen saturation during the 6-min walk test, quality of life with the Minnesota Living with Heart Failure Questionnaire, and clinical worsening. Clinical worsening was defined as a decrease of 6-min walk distance of more than 20% from baseline due to CTEPH, decrease of WHO or New York Heart Association functional class, and hospitalisation with the requirement for additional CTEPH specific treatment, or death due to worsening CTEPH. Exploratory endpoints were changes in haemodynamic variables (ie, mean resting pulmonary artery pressure, cardiac output, cardiac index, mean right atrial pressure, and pulmonary vascular resistance), the changes in signs and symptoms, and changes in N-terminal pro-brain natriuretic peptide concentrations after 24 weeks. Safety endpoints were the occurrence of treatment emergent adverse events, treatment emergent serious adverse events, and adverse events leading to discontinuation of the study.

Moreover, vital signs, electrocardiogram results, and laboratory variables were documented throughout the study. Safety monitoring was done by establishing the causal relation between each serious adverse event and the study medication by the investigators, the sponsor, and pharmacovigilance team. Furthermore, the safety profile stated in the investigator´s brochure was evaluated at least once a year and updated if necessary.

Statistical analysis

A sample size of 46 patients per group was estimated to detect a difference in mean 6-min walk distance of 50 m (effect size 0·6) at 80% power (when applying the two-sided *t* test for the 6-min walk distance at the two-sided significance level of 0·05 and for calculation with the normal approximation in ADDPLAN, release 4). The null hypothesis was defined as change from baseline of 6-min walk distance after 24 weeks in patients on high-dose subcutaneous treprostinil to be less than or equal to the change from baseline in 6-min walk distance for patients on low-dose subcutaneous treprostinil.

	High-dose subcutaneous treprostinil (n=53)	Low-dose subcutaneous treprostinil (n=52)	Total (n=105)
Age (years)	68 (11·2)	61 (14·6)	64 (13·4)
Distribution (years)			
≥60	40 (75%)	32 (62%)	72 (69%)
<60	13 (25%)	20 (38%)	33 (31%)
Sex			
Female	19 (36%)	30 (58%)	49 (47%)
Male	34 (64%)	22 (42%)	56 (53%)
Weight (kg)	76·9 (15)	80·4 (17)	78·7 (16)
Medical history			
Pulmonary embolism	29 (55%)	27 (52%)	56 (53%)
Deep venous thrombosis	15 (28%)	10 (19%)	25 (24%)
Pulmonary endarterectomy	3 (6%)	5 (10%)	8 (8%)
Concomitant medications			
Anticoagulation	52 (98%)	52 (100%)	104 (99%)
Sildenafil	6 (11%)	8 (15%)	14 (13%)
Bosentan	6 (11%)	5 (10%)	11 (10%)
Riociguat	2 (4%)	2 (4%)	4 (4%)
Bosentan, sildenafil in combination	0 (0%)	2 (4%)	2 (2%)
Riociguat, macitentan in combination	1 (2%)	0 (0%)	1 (1%)
WHO functional class			
II	3 (6%)	3 (6%)	6 (6%)
III	47 (89%)	44 (85%)	91 (86%)
IV	3 (6%)	5 (10%)	8 (8%)
6-min walk distance (m)	307·7 (68·8)	299·13 (85·7)	303·4 (77·4)
Borg Dyspnoea Score	4·8 (2·1)	5·2 (2·3)	5·0 (2·2)
N-terminal prohormone of brain natriuretic peptide (pg/mL)	2301 (2624·4)	2040·3 (1650·6)	2169·3 (2180·1)
Haemodynamics			
Heart rate (beats/min)	77·7 (12·9)	79·8 (9·8)	78·8 (11·5)
Blood pressure systolic (mm Hg)	123·9 (16·6)	120·9 (16·8)	122·4 (16·7)
Mean right atrial pressure (mm Hg)	9·7 (6·0)	10·3 (5·6)	10 (5·8)
Mean pulmonary artery pressure (mm Hg)	49·9 (12·4)	49·8 (10·8)	49·9 (11·6)
Cardiac output (L/min)	4·3 (1·3)	4·4 (1·4)	4·3 (1·3)
Cardiac index (L/min per m^2)	2·3 (0·7)	2·3 (0·6)	2·3 (0·7)
Pulmonary vascular resistance (dyn·s·cm^{-5})	845·1 (385·5)	809·0 (296·7)	827·2 (343·2)

Data are mean (SD) or n (%). The Borg Dyspnoea Score ranges from 0 to 10, with 0 representing no dyspnoea and 10 maximal dyspnoea.

Table 1: **Baseline clinical characteristics and haemodynamics**

Because CTEPH is a rare disease and therefore sample size calculations are difficult, an adaptive study design was chosen and an interim analysis was done when approximately 50% of data had been collected. Considering repeated significance testing, an α spending function of O'Brien-Fleming type was used. The bound for stopping for success after the interim analysis was 2·797 with an α of 0·0052 (0·0026 one-sided). The bound for success at end-analysis was 1·977 with α=0·048 (0·024 one-sided), allowing to control the overall α level to less than 0·050 (0·025 one-sided). To derive a stage-wise p value, the same parametric statistical model was used for both analyses (ANCOVA). For the final statistical test of the primary endpoint, the one-sided, stage-wise p values ($p^{(1)}$ for stage I and $p^{(2)}$ for stage II) were combined with use of the inverse normal function[28] with equal weights:

$$Z^{*(2)} = \sqrt{1/2}\,\Phi^{-1}\{1-p^{(1)}\} + \sqrt{1/2}\,\Phi^{-1}\{1-p^{(2)}\}$$

In the final analysis, the one-sided null hypothesis for the primary endpoint could be rejected if the combination test statistics $Z^{*(2)}$ exceeded the O'Brien-Fleming bound of 1·977.

The first and second stage data were pooled and analysed with the same ANCOVA model as for the stage-wise analyses. The primary analysis was done in the intention-to-treat and per-protocol populations. To ensure full intention-to-treat analysis of the primary endpoint, missing values were imputed with use of the last observation carried forward approach in which the last value available for each patient is used. The last observation method is justified by a low rate of missing data (nine of 105 patients, <10%) and a similar rate of missing data in both treatment groups (four of 52 patients in the low-dose group *vs* five of 53 patients in the high-dose group). Furthermore, a per-protocol analysis and a sensitivity analysis with a worst observation carried forward imputation rule supported the results (appendix pp 12–13).

When data were not normally distributed (assessed with the Shapiro-Wilk test) or the homogeneity of variances (homoscedasticity) could not be assumed (assessed with the Levene test), additional non-parametric testing with the Wilcoxon-Mann-Whitney *U* test was done.

In accordance with phase 3 trial design, hypothesis testing was only done for the primary endpoint to avoid multiplicity testing. Secondary and exploratory efficacy variables were presented only for the intention-to-treat population of the pooled data with use of descriptive methods. Further statistical tests and calculation of p values on secondary and exploratory efficacy variables were done only for the purpose of exploratory research. Detailed information on the sample size calculation and statistical analyses of primary, secondary, and exploratory endpoints are in the appendix. Data are shown as mean (SD). For all statistical analyses, SAS

(version 9.2 or later) or SPSS (version 23.0), or both, were used.

The trial was registered at ClinicalTrialsRegister.eu EudraCT number 2008-006441-10 and ClinicalTrials.gov, number NCT01416636.

Role of the funding source

SciPharm Sàrl took over sponsorship of this study, which previously had academic funding, after the finalisation of the interim analysis because no further funding was available. Repackaged commercial treprostinil provided by United Therapeutics (Silver Spring, MD, USA) was used during the academic stage 1, then SciPharm Sàrl provided Good Manufacturing Practice treprostinil solution developed in accordance with the licensed product in stage two. The formulation and active drug are equivalent to the reference product, and have received marketing authorisation in Austria for the treatment of pulmonary arterial hypertension on July 20, 2018. SciPharm Sàrl participated actively in study management and organisation, provided logistical support during the trial in terms of site management, and did monitoring in all study sites. The lead academic investigators (RS-K and IML) had full access to all the data in the study, wrote the manuscript, and are responsible for the accuracy and completeness of the data and analysis. Although employees of the sponsor assisted in preparation and review of the manuscript, the authors exclusively retained the final decision on the content. Further information about sponsorship and clinical trial material can be found in the appendix.

Results

From March 9, 2009, to June 9, 2016, 138 patients with non-operable CTEPH or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy were assessed for eligibility in six European pulmonary hypertension expert centres. 33 patients did not qualify for enrolment. 105 patients (mean age 64 years, 47% women) were enrolled (table 1). 53 (50%) of 105 patients were assigned to high-dose subcutaneous treprostinil and 52 (50%) of 105 to low-dose subcutaneous treprostinil. 14 patients discontinued the study before week 24 (figure 1). The last patient completed the study on Nov 24, 2016. 32 (30·5%) of 105 patients were on non-parenteral, non-prostanoid-specific background treatments.

At week 12, patients on high-dose subcutaneous treprostinil had reached a mean dose of 29·15 ng/kg per min (SD 4·95) and patients on low-dose subcutaneous treprostinil had reached a mean dose of 3·04 ng/kg per min (SD 0·21; figure 2).

For the primary endpoints, the interim analysis,[23] including data for 28 patients on high-dose subcutaneous treprostinil and 26 patients on low-dose subcutaneous treprostinil, resulted in a p value of 0·0670 (0·0340 one sided), above the O'Brien-Fleming adjusted first stage significance level of 0·0052 (0·0026 one-sided). Therefore, the study was continued. The original sample size was confirmed considering conditional and predictive power arguments,[28,29] whereby both approaches yielded values around 80% with the initially planned sample sizes. Therefore, no sample size reassessment was done.

A p value of 0·0094 (0·0047 one-sided) was obtained from the ANCOVA model for analysing the second stage of the study, including data for 25 additional patients on high-dose subcutaneous treprostinil and 26 additional patients on low-dose subcutaneous treprostinil.

The computed combined $Z^{*(2)}$ value of 3·13 was significantly greater than 1·977, which had been prespecified as the critical bound for end-analysis.

Analysis of pooled data from 105 patients showed that during the 24-week treatment period, marginal mean 6-min walk distance improved by 44·98 m (95% CI 27·52 to 62·45) in the high-dose group, compared with 4·29 m (95% CI –13·34 to 21·92) in the low-dose group (treatment effect 40·69 m, 95% CI 15·86 to 65·53, p=0·0016).

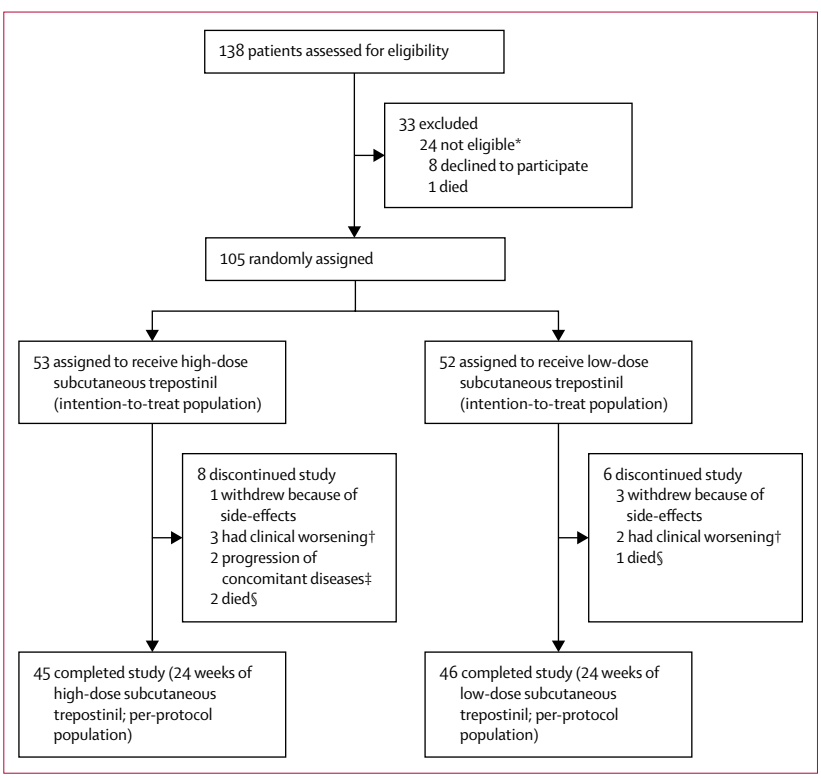

Figure 1: **Trial profile**

*Of 24 patients ineligible for enrolment, 15 underwent pulmonary endarterectomy, three had a 6-min walk distance of more than 400 m, two had other forms of pulmonary hypertension, two were unable to walk, one had atrial flutter, and one had no anticoagulation. †In the high-dose group, two patients were unmasked, and the dose of subcutaneous treprostinil was up-titrated, and one patient was upscaled to combination therapy; in the low-dose group one patient underwent lung transplantation, and one was unmasked, and the dose of subcutaneous treprostinil was up-titrated. ‡In the high-dose group, one participant had progression of polycythaemia vera and developed aortic stenosis, and one participant was withdrawn because of deterioration of general health. §In the high-dose group, one patient died from pneumonia and right-sided heart failure, and one from isolated right-sided heart failure; in the low-dose group one patient died from acute appendicitis and sepsis.

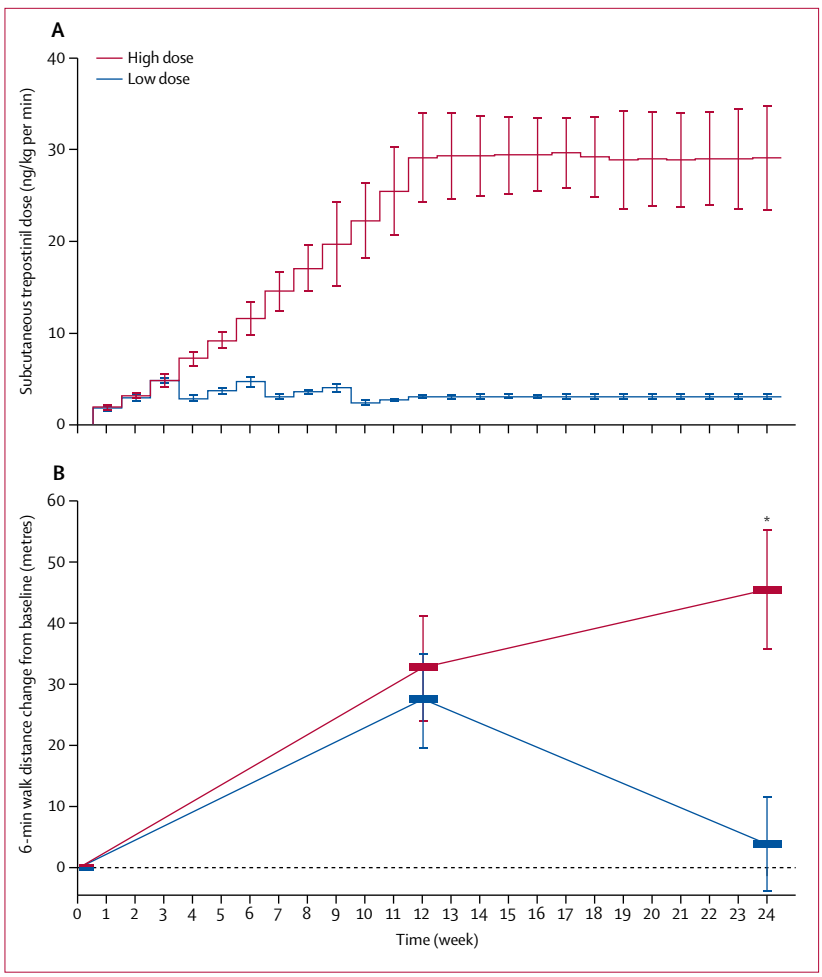

Figure 2: **Dose and 6-min walk distance by week of treatment**
(A) Dose titration of subcutaneous treprostinil: mean and SD of dose titration levels in ng/kg per min, at the end of each treatment week. (B) Changes in 6-min walk distance: mean and SEM changes from baseline in the distance walked in 6 min during the 24-week study are represented by boxplots. *p<0·05.

These results were confirmed by non-parametric testing (p=0·00028, table 2, figure 2). In the high-dose, per-protocol population, marginal means of 6-min walk distance increased by 59·23 m (95% CI 41·80 to 76·60) from baseline, compared with 5·80 m (95% CI –10·80 to 22·50) in the low-dose group (treatment effect 53·40 m, 95% CI 29·20 to 77·60, p<0·0001).

For the secondary outcomes, intention-to-treat analysis showed an improvement of WHO functional class in 27 patients (50·9%) on high-dose subcutaneous treprostinil, versus 9 patients (17·3%) on low-dose subcutaneous treprostinil (p=0·0019, table 2).

Pulmonary vascular resistance decreased by 214·2 (SD 324·3) dyn·s·cm^{-5} from baseline in patients on high-dose subcutaneous treprostinil and increased by 73 (SD 285) dyn·s·cm^{-5} in patients on low-dose subcutaneous treprostinil (table 2, figure 3). Subcutaneous treprostinil was also associated with significant improvement in mean pulmonary artery pressure and cardiac output (table 2).

N-terminal pro-brain natriuretic peptide decreased in high-dose patients by 157·5 (SD 1052·0) pg/mL and increased in low-dose patients by 330·6 (SD 1456·7) pg/mL with a statistically significant percentage change between high-dose and low-dose (p=0·032, table 2).

At 12 weeks, 6-min walk distance had improved from baseline in patients treated with high-dose subcutaneous treprostinil, compared with patients treated with low-dose subcutaneous, but not to a statistically significant degree (table 2).

Seven patients on high-dose subcutaneous treprostinil and 12 patients on low-dose subcutaneous treprostinil had clinical worsening (p=0·21, table 2).

Borg Dyspnoea Score improved in patients receiving high-dose subcutaneous treprostinil by 0·44 (SD 2·21) points and in patients on low-dose subcutaneous treprostinil by 0·13 (SD 2·43), without statistical significance (p=0·31). Heart rate and oxygen saturation were not evaluated because data were only available for patients included after the interim analysis.

In both groups, decreases from baseline in sum scores of quality of life were observed (high-dose –6·4 [SD 22·9] *vs* low-dose –4·6 [19·3]) at week 24, whole population statistics: –5·5 [21·2]; p=0·56). Signs and symptoms were analysed only in a descriptive way and were not statistically different between groups.

39 (74%) of 53 patients on high-dose treatment and 42 (81%) of 52 patients on low-dose treatment had infusion site pain (table 3). Other infusion site reactions occurred in 25 (47%) patients on the high-dose treatment and 24 (46%) patients on the low-dose treatment. One patient in the high-dose group and three patients in the low-dose group discontinued the study before week 24 because of infusion site pain.

Diarrhoea, headache, and pain in extremity were significantly more common in the high-dose than in the low-dose group (table 3).

28 serious adverse events were reported during the study (12 events in ten patients from the low-dose group and 16 events in nine patients from the high-dose group; table 3). Of those, three serious adverse events resulted in death (two due to right-sided heart failure, including one patient who also had pneumonia, in the high-dose group and one due to acute appendicitis with sepsis in the low-dose group) and were classified as not related to the study drug. One serious adverse event due to mild diarrhoea or nausea was classified as possibly related to subcutaneous treprostinil. Six (11%) in the high-dose and six (12%) patients in the low-dose group were hospitalised to receive diuretic treatment.

Discussion

The CTREPH trial is the first RCT of subcutaneous treprostinil for non-operable CTEPH or persistent or recurrent pulmonary hypertension after pulmonary endarterectomy. Riociguat has been market released for non-operable and persistent or recurrent CTEPH in

	High-dose subcutaneous treprostinil			Low-dose subcutaneous treprostinil			p value for difference between high and low dose
	Number of patients	Baseline	Change	Number of patients	Baseline	Change	
Primary endpoint							
6-min walk distance at week 24* (m)	53	307·7 (68·8)	45·4 (71·3)	52	299·1 (85·7)	3·8 (56·2)	0·00028†
Secondary endpoints							
6-min walk distance at week 12* (m)	53	307·7 (68·8)	32·7 (63·5)	52	299·1 (85·7)	27·3 (57·3)	0·27†
WHO functional class‡	51	3 (6%) in class II; 47 (89%) in class III; 3 (6%) in class IV	27 (51%) improved; 22 (42%) unchanged; 2 (4%) worsened	48	3 (6%) in class II; 44 (85%) in class III; 5 (10%) in class IV	9 (17%) improved; 36 (69%) unchanged; 3 (6%) worsened	0·0019§
Clinical worsening	53	..	7 (13%)	52	..	12 (23%)	0·21¶
N-terminal prohormone of brain natriuretic peptide (pg/ml)	46	2301 (2624·4)	−157·5 (1052)	46	2040·3 (1650·6)	330·6 (1456·7)	0·032‖
Borg Dyspnoea Score** mean (SD)	48	4·8 (2·1)	−0·4 (2·2)	48	5·2 (2·3)	−0·1 (2·4)	0·307†
Minnesota Questionnaire Quality of Life,†† mean (SD)	50	42·2 (21·2)	−6·4 (22·9)	46	45·8 (23·2)	−4·6 (19·4)	0·557†
Haemodynamic variables							
Mean right atrial pressure (mm Hg)	48	9·7 (6·0)	0·7 (5·1)	47	10·3 (5·6)	2·9 (6·8)	0·23†
Mean pulmonary artery pressure (mm Hg)	48	49·9 (12·4)	−3·4 (8)	47	49·8 (10·8)	−0·4 (6·9)	0·040†
Cardiac output (L/min)	48	4·3 (1·3)	0·6 (1·5)	47	4·4 (1·4)	−0·2 (1·1)	<0·0001†
Cardiac index (L/min per m^2)	48	2·3 (0·7)	0·4 (0·9)	47	2·3 (0·6)	−0·2 (0·5)	<0·0001†
Pulmonary vascular resistance (dyn·s·cm^{-5})	48	845·1 (385·5)	−214·2 (324·3)	47	809 (296·7)	73·0 (285)	<0·0001†

Data are mean (SD) or n (%). To convert NT-proBNP to ng/L, multiply values by 1; to convert mm Hg to kPa, multiply values by 0·133; to convert cardiac output to mL/min, multiply values by 1000; to convert cardiac index to mL/min per m^2, multiply values by 1000. *Missing data were imputed with the last observation carried forward approach; for five patients in the high-dose group and four patients in low-dose group at week 24; for four patients in high-dose group and five patients in the low-dose group at week 12. †p values are results of Wilcoxon Mann-Whitney U-test. ‡No WHO functional class data for two patients in the high-dose group and four patients in the low-dose group at week 24. §p value is results of the χ^2 test. ¶p value is results of Fisher's exact test. ‖p value is result of Wilcoxon Mann-Whitney U test with the individual percentage change. **Borg Dyspnoea Score ranges from 0 to 10, with 0 representing no dyspnoea and 10 maximal dyspnoea. ††The Minnesota Living with Heart Failure Questionnaire includes 21 items to be scored between 0 representing no and 5 very much. The change in individual sum score was evaluated.

Table 2: **Study endpoints**

patients in WHO functional class II and III.[16] Still, treatment of patients with severe CTEPH is an unmet need because not all patients tolerate riociguat and few long-term data are available. Despite a severely diseased study population (6-min walk distance less than 400 m, WHO functional class III or IV, and pulmonary vascular resistance above 800 dyn·s·cm^{-5}), the well known adverse event profile of subcutaneous treprostinil, and the low-dose comparator, significant changes in 6-min walk distance at week 24, some haemodynamics, and WHO functional class were observed in the study. 6-min walk distance had a mean improvement of 45·4 m in the high-dose intention-to-treat population and by 60·3 m in the high-dose per-protocol population at week 24.

Subcutaneous treprostinil for CTEPH circumvents the need for intravenous lines that could be sources of thromboembolism.[23,24] The study is completely unique for the use of a low-dose comparator. Up to week 12, improvements of 6-min walk distance were similar in both treatment groups (32·7 m high-dose *vs* 27·3 m low-dose in the intention-to-treat population, table 2 and figure 2), contrasting with the results of the pivotal trial,[21] which had led to a 6-min walk distance improvement of only 3·3 (SD 10·0) m at week 12 with the 5 ng/kg per min or more dose. Since then, expertise of individuals from expert centres regarding all aspects of subcutaneous treprostinil application has substantially improved, and the effects could be due to actual vasodilation, and some

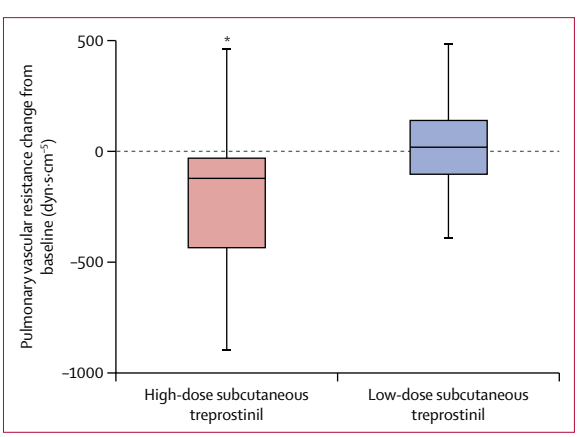

Figure 3: **Change of pulmonary vascular resistance**
*p<0·05.

	High-dose subcutaneous treprostinil (n=53)	Low-dose subcutaneous treprostinil (n=52)
Serious adverse events		
Death*	2 (4%)	1 (2%)
Hospitalisation†	9 (17%)	10 (19%)
Local adverse reactions		
Any event	44 (83%)	46 (88%)
Infusion site pain	39 (74%)	42 (81%)
Infusion site reaction‡	25 (47%)	24 (46%)
Systemic adverse reactions		
Diarrhoea	31 (58%)	13 (25%)
Headache	7 (13%)	4 (8%)
Pain in extremity	9 (17%)	1 (2%)
Nausea or dyspepsia	4 (8%)	2 (4%)
Flushing	4 (8%)	4 (8%)
Pain in jaw	2 (4%)	0 (0%)
Vertigo	1 (2%)	0 (0%)
Skin rash	1 (2%)	2 (4%)
Back pain	0 (0%)	1 (2%)

Data are n (%). *Deaths were due to pneumonia with right heart failure, right ventricular failure, and acute appendicitis with sepsis. †Hospitalisations were due to right heart decompensation, hypokalaemia, diarrhoea, nausea, syncope, progression of aortic valve disease, renal failure, incarcerated hernia, dyspnoea, *Escherichia coli* bacteraemia, sepsis, haematoma, general physical health deterioration, and haemoptysis. ‡Infusion site reaction includes abscess, erythema, haemorrhage, infection, inflammation, irritation, pruritus, rash, and swelling.

Table 3: **Safety data per patient**

placebo effect. As expected, the frequency of local adverse reactions was similar in both treatment groups. Patients were informed before enrolment that they had a realistic chance of having infusion site problems while receiving a dose that was less likely to confer improvements.

Despite controversy over 6-min walk distance as a study endpoint, the measure has been used as a primary outcome measure in many pulmonary arterial hypertension studies,[20] and in the pivotal CHEST study.[16] CTREPH 6-min walk distance changes are beyond the thresholds that were labelled as 6-min walk distance minimally important differences for patients with pulmonary arterial hypertension (33 m or 41·8 m).[30,31] Change of 6-min walk distance from baseline in CTREPH was 45 m in the high-dose group, compared with 39 m in the active group of CHEST,[16] and 35 m as secondary endpoint of MERIT-1.[17]

The need for a low-dose comparator was challenging because of the requirement to choose a comparator dose that was not too low to be harmful but sufficiently high to confer a potential benefit. In controlled trials with a placebo arm, deteriorations of 6-min walk distance were shown in controls.[12,16]

In CTREPH, 6-min walk distance mean improvements of 27·3 m were observed after 12 weeks, and 3·8 m after 24 weeks under low-dose subcutaneous treprostinil. The effect of the low-dose could have several reasons, the most likely being a transient effect of vasodilation that wears off in relation to drug dose, and expertise at expert centres compared with 15 years ago regarding all aspects of subcutaneous treprostinil application. Nevertheless, a significant difference was seen for the CTREPH primary endpoint compared with the comparator.

Secondary endpoint changes support the 6-min walk distance results. For example, changes in pulmonary vascular resistance, one of the most important prognostic indicators of CTEPH,[32,33] were significant in favour of high-dose subcutaneous treprostinil, as were improvements of WHO functional class[32,34] and N-terminal pro-brain natriuretic peptide[35] (table 2). In CTREPH, a low-dose corrected 34% decrease of pulmonary vascular resistance from baseline was observed, compared with a placebo-corrected 31% decrease in CHEST,[16] and a 14·2% decrease from baseline in MERIT-1.[17]

Our study showed small improvements in Borg Dyspnoea Score in both treatment groups. The absence of a statistically significant improvement in the score despite an improvement in exercise capacity has also been observed in other studies with pulmonary arterial hypertension medications.[17,20] In these trials, Borg Dyspnoea Score hardly improved more than a mean 0·5–1·0 points overall.

Non-significant improvements in quality of life measures were observed, regardless of dose. The adverse event profile of subcutaneous treprostinil and the need for an external infusion pump could have negatively affected some aspects of daily life and therefore the analysis of the score sums of the questionnaire.

The safety profile of subcutaneous treprostinil in CTEPH was similar to that in patients with pulmonary arterial hypertension[20] and experience gained from the use of subcutaneous treprostinil during the past decades means that adverse drug reactions are manageable.

The CTREPH trial was initiated at a time when no drug was approved for CTEPH, and balloon pulmonary angioplasty was not yet established. Furthermore, no off-label medication was available in some of the enrolling centres.

We classified patients as severe on the basis of the inclusion criteria of a 6-min walk distance of 400 m or less, and WHO functional class III or IV. In the IMPRES trial,[36] severe pulmonary arterial hypertension was defined by a 6-min walk distance of 450 m or less, and a pulmonary vascular resistance of more than 800 dyn·s·cm^{-5}; for operable CTEPH, a pulmonary vascular resistance of 1200 dyn·s·cm^{-5} has been associated with in-hospital mortality of more than 10%.[5] Currently, CTREPH can be used as a comparison with BENEFIT,[12] CHEST,[18] and MERIT-1,[17] three randomised, placebo-controlled drug trials targeting non-operable CTEPH. The main differences between CTREPH and these trials include the longer study duration (24 weeks *vs* 16 weeks in the other trials), older mean age of participants

(64 years in CTREPH *vs* 58 years in CHEST, 57 years in MERIT-1, and 63 years in BENEFIT), and sicker patients (mean baseline 6-min walk distance of 303 m in CTREPH *vs* 347 m in CHEST, 353 m in MERIT, and 340 m in BENEFIT). Furthermore, 76% of screened patients were enrolled in the CTREPH trial, compared with only 58% in CHEST, and 43% in MERIT-1. Similar to MERIT-1, background targeted therapy was permitted in our study, but no subgroup analysis was done because of small patient numbers.

In CTREPH, 90 (86%) of patients had local adverse reactions that were manageable except in four (4%) dropouts. For comparison, patients on riociguat had headache (25%), dizziness (23%), and peripheral oedema (16%); and patients on macitentan primarily had peripheral oedema (23%) and decreased haemoglobin concentrations (15%).

Limitations of the study include the small sample size. The CTREPH trial stipulated a maximum dose, however, higher doses and more individualised treprostinil dosing schemes might have been more effective.[21,37] Change in 6-min walk distance might not translate into long-term outcomes in pulmonary arterial hypertension[38,39] and CTEPH. However, previous studies have shown that medical treatments of CTEPH prolong survival.[22] The measure of survival might be less relevant for older people and could be driven by comorbidities.[38] Morbidity-mortality-driven study designs in CTEPH are difficult because of the benign course of CTEPH with less events compared with pulmonary arterial hypertension.[39]

The recruitment period for the trial was 8 years. Enrolment was challenging because of competing trials with oral compounds, the market release of riociguat, and the increased availability of balloon pulmonary angioplasty. Mean recruitment rate per year was 13 patients, and did not change throughout the study, except for in 2012. Between April, 2012, and April, 2013, recruitment of patients was paused for the purpose of the planned interim analysis. Thus, only six patients were enrolled in 2012. Furthermore, limited industry funding was available. Because of the emerging success of balloon pulmonary angioplasty, trials testing pharmacotherapies as an adjunct to mechanical treatments will be greatly needed and highly relevant for payers.

In conclusion, our data show that long-term subcutaneous treprostinil is safe and effective, leading to concentration-dependent improvements of 6-min walk distance, haemodynamics, WHO functional class, and N-terminal pro-brain natriuretic peptide amounts in patients with severe non-operable CTEPH.

Contributors

RS-K and IML had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. IML was responsible for the study concept and design, critical revision of the manuscript for important intellectual content, and study supervision; all authors were responsible for acquisition, analysis, or interpretation of data; RS-K and IML drafted the manuscript.

Declaration of interests

RS-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, outside of the Article. PJ has received fees and grants from Actelion Pharmaceuticals Ltd, AOP Orphan, Bayer HealthCare, Merck Sharp & Dohme, and GlaxoSmithKline. He has served on advisory boards for Actelion Pharmaceuticals Ltd, Bayer HealthCare, and Merck Sharp & Dohme, outside of the Article. GK reports personal fees from AOP Orphan Pharmaceuticals, Merck Sharp & Dohme, and Bayer, outside of the Article; and grants and personal fees from Actelion, AT reports honoraria, consultancy fees, and grants from Actelion Pharmaceuticals, AOP Orphan Pharmaceuticals, Bayer, GlaxoSmithKline, and United Therapeutics, outside of the Article. NS-S has relationships with Actelion, AOP Orphan Pharmaceuticals, Bayer AG, GlaxoSmithKline, Pfizer, and United Therapeutics, and is an investigator in trials involving these companies; relationships include consultancy service, and research grants, outside of the Article. MH reports personal fees (lectures) from Actelion, Bayer Pharma AG, GlaxoSmithKline, Merck Sharp & Dohme, and Optimal Medical Therapies, non-financial support (travel) from Actelion and Optimal Medical Therapies, and is on an advisory board of Actelion, BayerPharma AG, and GlaxoSmithKline, outside of the Article. IS 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. KK reports personal fees from Actelion, AOP Orphan Pharmaceuticals, Merck Sharp & Dohme, and from Boehringer Ingelheim, outside of the Article. MS reports lecture and consultancy fees from Roche, Merck Sharp & Dohme, Pfizer, AstraZeneca, Providence, Tewa, Novartis, GlaxoSmithKline, and Bristol-Myers Squibb, outside of the Article. IML has relationships with Actelion, AOP Orphan Pharmaceuticals, AstraZeneca, Bayer-Schering, Cordis, Daiichi Sankyo, Ferrer, GlaxoSmithKline, Medtronic, SciPharm Sàrl, and Servier, and is an investigator in trials involving these companies; has relationships including consultancy service, research grants, has a membership of scientific advisory boards. All other authors declare no competing interests.

Data sharing

The study protocol is available in the appendix and available to the public immediately following publication. No additional data are available for this Article.

Acknowledgments

This study was sponsored by SciPharm Sàrl. CDMS GmbH, Austria maintained the trial database. Erich Kvas (Hermesoft, Graz, Austria) did the interim analysis. After completion of the trial, a complete copy of the database was transferred to BioConsult GmbH (Breitenfurt, Austria) and Arlenda SA, (Liège, Belgium) where independent statisticians did statistical analyses. The results reported in the manuscript are the results of the analyses done by both companies. Pharmacovigilance reporting and evaluation was done by Assign Data Management and Biostatistics GmbH.We thank the whole study team for making this work possible.

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