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# Long-Term Safety, Outcome, and Clinical Effects of Subcutaneous and Intravenous Treprostinil Treatment in Patients with Severe Chronic Pulmonary Arterial Hypertension

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**Keywords**
Pulmonary arterial hypertension · Prostacyclin · Treprostinil · Treatment

**Abstract**
***Background:*** Current guidelines recommend treatment with parenteral prostacyclin analogs in patients with severe pulmonary arterial hypertension (PAH), who have insufficient response to treatment. Real-life data are sought to help physicians in treatment decisions and clinical care of patients. ***Objective:*** This study analyzed safety, clinical effects, and long-term outcomes of subcutaneous (sc) and/or intravenous (iv) treprostinil via different pump systems in consecutive patients with PAH. ***Methods:*** Thirty-seven patients with severe progressive PAH despite dual combination therapy (20 female, mean age: 52.3 ± 15 years, mean pulmonary vascular resistance: 12.1 ± 5.1 WU) were initiated with add-on treprostinil sc and were routinely clinically assessed. Changes in clinical parameters, adverse events, and outcome were analyzed retrospectively. ***Results:*** In 24 of 37 patients, treprostinil administration was continued iv via implantation of LENUS Pro® pump after 3 ± 1.3 months, 6 patients continued with sc therapy, and 7 discontinued treatment. After 3, 6, 9, and 12 months of treprostinil treatment, patients showed a significant improvement in mean 6-min walk distance and tricuspid annular plane systolic excursion compared to baseline. In 8 of the 24 patients, iv pumps required surgical revision. During a mean follow-up of 2.82 ± 1.95 years, 12 patients died, four received lung transplantation. Transplant-free survival after 1, 2, and 3 years was 85.7%, 69.2%, and 65.3%, respectively. ***Conclusion:*** sc treprostinil as add-on to double combination treatment significantly improved exercise capacity and right heart function. In most patients, treprostinil could be continued via more tolerable iv administration approach (LENUS Pro® pump), showing reasonable overall survival with respect to the severity of PAH.
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## Introduction

Pulmonary arterial hypertension (PAH) is characterized as a disease of the small pulmonary arteries leading to an increase in pulmonary vascular resistance (PVR) and ultimately right heart failure [1]. The symptoms of PAH are nonspecific and mainly related to progressive right ventricular (RV) dysfunction as consequence of progressive pulmonary vasculopathy [2].

The synthetic prostacyclin epoprostenol was the first approved treatment for PAH and improved short-term (12 weeks) survival in patients with severe disease in a small randomized, open-label, controlled trial [3]. Since then, various prostacyclin analogs (PCA) with different routes of administration have been shown to significantly improve right heart function, quality of life, exercise capacity, and World Health Organization functional class (WHO FC) in PAH patients [4]. Parenteral treprostinil, with either subcutaneous (sc) or intravenous (iv) administration, was shown to be effective for improving symptoms and outcomes [5, 6].

In the first double-blind, placebo-controlled, multicenter trial, treatment with sc treprostinil improved exercise capacity, symptoms, and hemodynamics in patients with PAH in a dose-dependent manner [7]. The safety profile of the drug in the 4-year open-label extension phase of the study showed no additional adverse events (AEs) associated with the drug, while survival significantly improved in the sc treprostinil group [8]. Another multicenter, randomized, double-blind, placebo-controlled trial compared the efficacy of continuous iv treprostinil to placebo in WHO group 1 PAH patients residing in the Indian subcontinent showing a significant increase in 6-min walk distance (6MWD) and improved NYHA class under iv treprostinil treatment [9].

The new 2022 PH guidelines recommend that in patients with idiopathic/heritable/drug associated PAH who present at high risk of death, initial combination therapy with a phosphodiesterase-5-inhibitor (PDE5i), an endothelin receptor antagonist (ERA), and an iv/sc PCA should be considered. Furthermore, in patients with PAH who present at intermediate-high or high risk of death while receiving ERA/PDE5i therapy, the addition of iv/sc PCAs should be considered (IIa C) [2].

This recommendation is however based on few randomized, controlled trials which assessed only short-term treatment effects (after 3 months) or were underdosed [7–9]. Moreover, in these previous studies, only therapy-naive patients were considered for investigating the effects of parenteral PCA. Hence, data from long-term studies on sc and iv treprostinil treatment with a reasonable and effective dose in insufficiently pretreated patients are lacking. Besides, investigation and standardization of usage, titration, and monitoring of treprostinil treatment with different pump systems for each administration form are needed to maximize safety and drug efficacy in PAH patients [10, 11].

The aim of this study was therefore to investigate the long-term safety, outcome (e.g., survival), and clinical effects of sc and iv treprostinil treatment in patients with severe PAH as escalation treatment. Besides, evaluation and standardization of treatment regimen including up-titration and monitoring of treprostinil administration with different pump systems for sc and iv administration were the focus of this study.

## Methods

*Study Population and Design*

We retrospectively analyzed data from adult PAH patients of our center who had been started on sc treprostinil due to clinical worsening despite double oral combination therapy. Excluded from this analysis were PAH patients with comorbidities such as significant respiratory disease or left heart disease and patients who received iv treprostinil as part of the initial treatment of newly diagnosed PAH (upfront triple combination therapy). Clinical data were obtained from medical charts including noninvasive methods and hemodynamics from right heart catheterization (RHC). Assessments of clinical data were performed at the beginning of the observation period (baseline) and at approximately 3-month intervals after starting the treatment (follow-ups) to evaluate long-term clinical course. AEs were recorded with type and date of AE. In our cohort, therapy with parenteral treprostinil was initiated using a sc administration approach allowing rapid up-titration of the drug and enabling assessment of clinical efficacy and tolerability of parenteral treprostinil before pump implantation for iv treprostinil treatment.

After reaching a reasonable, effective, and tolerable dose of the drug, patients were offered to continue iv treprostinil treatment via an implanted pump system. In most cases, sc treprostinil was switched to iv application requiring implantation of a special pump system. In some patients, who tolerated sc treatment well, had the wish to continue sc treatment and showed sufficient drug response by reaching and maintaining a low to intermediate risk profile, continuation of sc treprostinil treatment was offered.

*Treatment and Dosing*

Routine measurements were performed before initiating sc treatment with treprostinil sodium in the hospital at a starting dose of 2 ng/kg/min with dose increments of 1–2 ng/kg/min approximately every 12 h according to tolerability. The individual length of the hospital stay was not only dependent on the tolerability of the medication but also on the learning ability concerning the unassisted sc administration of treprostinil using a micro-infusion pump (Crono 5; Canè Medical Technology), coupled with either the Cleo (Smiths Medical) or Quickset (Medtronic) infusion set. Ideally, medication was up-titrated in an outpatient setting at

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least once a week by dose increments of 2 ng/kg/min aiming for a dose of at least 30 ng/kg/min before further evaluation of treatment during a routine clinical visit after approximately 3 months.

*Pump Implantation and Refill Procedures for LENUS Pro® Pump*

The LENUS Pro® fully implantable pump (Tricumed Medizintechnik GmbH, Kiel, Germany) was implanted after 90 ± 40 days of sc treprostinil treatment in order to switch to iv treprostinil treatment. Further escalation of treprostinil dose toward a maximally tolerable dose 3 months after initiation of iv treatment was performed during refill procedures.

The implantation of the LENUS Pro® pump was performed under general anesthesia. All patients were monitored in the intensive care unit after surgery. Treprostinil solution was injected into a drug reservoir within the pump which was sealed by a silicone septum, and gas-driven titanium bellows generated a constant flow from the reservoir (40 mL) regulated by a chip capillary [12]. Pump refills were performed under aseptic conditions using special needles in our center. Intervals between percutaneous refills were usually 14–33 days depending on the flow rate of the pump. The dose was adjusted at each refill by injecting solutions with specific concentrations of treprostinil into the pump's drug reservoir, based on the flow rate and clinical requirement to escalate or reduce the drug dose. Flow rates were monitored regularly at refills due to potential inter-pump variability. In this context, the calculation of the flow rate was performed via residual drug volume in milliliters and time interval between refills.

*Statistical Methods*

Analyses were performed with the support of a statistician (NB). Data are given as mean values ± standard deviations and 95% confidence intervals of the mean. Frequencies are given as *n* and respective percent. Changes in clinical data between baseline and follow-up were analyzed by paired student's *t* tests. Changes were analyzed for sc treatment, iv treatment, and overall treprostinil treatment irrespective of the type of medication administered. AEs were defined according to international criteria and listed according to their occurrence (during sc or iv treatment) and outcome (revision or explantation of pump, discontinuation of treatment).

Survival was analyzed as overall survival and transplant-free survival by Kaplan-Meier analysis. Start of treprostinil treatment was set as baseline for survival analysis. Death was defined as death due to any cause.

The date of treprostinil initiation was used as the index date for determining survival, which was calculated using Kaplan-Meier estimates. Date of death or transplantation was used to determine transplant-free survival.

Responder status of treprostinil treatment was determined by parameters showing treatment response and respective classification according to ESC/ERS risk stratification. Risk group at baseline and changes from baseline to 3 months of follow-up in the respective parameters were analyzed by Cox regression analysis with stepwise forward selection (likelihood ratio) regarding their meaning for survival.

All analyses were performed using IBM SPSS 25 (SPSS Statistics V25, IBM Corporation, Somers, NY, USA). Different risk stratification models including REVEAL 2.1, COMPERA, and the French approach, were applied to the data [13–15].

For the French and COMPERA approaches, the three most widely used, practicable, and routinely implemented noninvasive parameters for risk stratification of the 2015 ESC/ERS treatment guidelines including 6MWD, WHO FC, and serum levels of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) were used [16]. Using the French noninvasive approach, parameters in the green risk zone were counted for each patient [15]. The COMPERA approach was defined as average risk group at baseline out of the three named parameters. In addition, risk stratification by number of improved parameters at first follow-up was performed. Due to the exploratory nature of the study, all *p* values were considered descriptive.

**Table 1.** Baseline characteristics of the patients

| | |
|---|---|
| Patients, *n* | 37 |
| Gender [male/female] | 17/20 |
| Age, years | 52.3±15 |
| Height, cm | 170±8 |
| Weight, kg | 77±17 |
| WHO functional class, *n* (%) baseline | |
| II | 7 (19) |
| III | 25 (67) |
| IV | 5 (13) |
| Diagnosis, *n* (%) | |
| IPAH | 23 (62.2) |
| HPAH | 5 (13.5) |
| CHD-APAH | 6 (16.2) |
| CTD-APAH | 3 (8.1) |
| Right heart catherization | |
| Mean pulmonary arterial pressure, mm Hg | 62.4±13.5 |
| Pulmonary vascular resistance [dyn × sec × $cm^{-5}$] | 969.4±406.2 |
| Pulmonary vascular resistance, WU | 12.1±5.1 |
| Mean central venous pressure, mm Hg | 11.6±4.7 |
| Mean pulmonary arterial oxygen saturation, % | 60±9.6 |
| Pulmonary arterial wedge pressure, mm Hg | 11.3±4.2 |
| Cardiac index [l × min × $m^{-2}$] | 2.38±0.58 |
| PAH-targeted medication, *n* (%) | |
| Endothelin receptor antagonists | |
| Bosentan | 4 (10.8) |
| Ambrisentan | 13 (35.1) |
| Macitentan | 19 (51.3) |
| PDE5i/sGC-stimulator, *n* (%) | |
| Sildenafil | 26 (70.2) |
| Tadalafil | 5 (13.9) |
| sGC riociguat | 5 (11.1) |

Values are given as mean ± SD or *n* (%), respectively. sGC, soluble guanylate cyclase; WHO, World Health Organization; IPAH, idiopathic pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; APAH, associated pulmonary arterial hypertension; CHD, congenital heart disease; CTD, connective tissue disease.

## Results

*Study Population*

From 2015 to 2019, a total of 37 patients (20 female, mean age 52 ± 15 years, 23 [62%] idiopathic PAH, 5 [14%] heritable PAH, 3 [8%] connective tissue disease-associated

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PAH [CTD-APAH], 6 [16%] PAH associated with congenital heart disease [CHD-APAH]) who were on different combination treatments with PAH-targeted drugs including PDE5i or soluble guanylate cyclase-stimulator (sGC) and ERA, were enrolled into the study. Patients were severely affected at baseline with mean pulmonary arterial pressure (mPAP) of 62.4 ± 13.5 mm Hg, and mean pulmonary vascular resistance (PVR) of 12.1 ± 5.1 WU. Seven patients (19%) were in WHO FC II, 25 patients (67%) in WHO FC III, and 5 (13%) in WHO FC IV (Table 1).

*Treprostinil Dose Titration*

In 37 patients with insufficient response or deterioration under oral PH medication, sc treprostinil treatment was initiated. sc treatment with treprostinil was initiated as inpatient treatment and was escalated individually according to tolerability, reaching a mean dose of 7.4 ± 8.6 ng/kg/min within a short period of time before discharge from the hospital as previously reported [6]. Further up-titration was conducted in an outpatient setting, and a mean dose of 38 ± 18.3 ng/kg/min of sc treprostinil was reached after approximately 3 months.

After a mean of 90 ± 40 days of sc treprostinil, a LENUS Pro® pump for iv administration was implanted in 24 out of 37 patients (64.9%). The subsequent switch to iv treatment allowed for further dose escalation toward a maximum tolerable dose of 52.94 ± 17.38 ng/kg/min on average within another 3 months.

*Safety and Tolerability of sc Treprostinil Treatment*

In six out of the 37 patients (16.2%), no iv pump implantation was performed as sc treatment was well tolerated and patients wished to stay on sc administration (Fig. 1). In the remaining seven out of 37 patients (18.9%), treprostinil treatment was discontinued and no iv pump implantation was performed due to the following reasons: death ($n$ = 2), unmasking of pulmonary veno-occlusive disease (PVOD) ($n$ = 1), non-sufficient response to treatment in the view of both physician and patient ($n$ = 2), or severe pain ($n$ = 2) (Fig. 1). Death was not related to the treatment: 1 patient with PAH associated with congenital heart disease died from perioperative complications during lung transplantation, the second patient died suffering from end-stage cancer. Two patients who discontinued the sc treatment due to severe pain refused implantation of medical devices such as iv pump systems (Fig. 1).

During sc treprostinil treatment, abscess formation occurred in 3 patients, local skin infection and skin necrosis in 1 patient, respectively. Early switch to iv treprostinil was performed in 2 patients due to severe local pain at the site of sc injection (Fig. 1).

*Safety and Tolerability of iv Treatment via LENUS Pro® Pump*

Four out of 24 pumps required surgical revision after 1.5 ± 1 months (one due to adjustment of catheter length, one due to vertebral rotation of the pump with unreachable refill membrane and impossible refill, one due to catheter occlusion, and one with rupture of catheter); four further pumps had to be explanted after 11 ± 12 months (due to infection of catheter pocket, $n$ = 2; pump dysfunction, $n$ = 1; dislocation of catheter and impracticable catheter change due to venous thrombosis, $n$ = 1). Three out of these 4 patients were reinitiated with treprostinil treatment and received subsequent sc treprostinil treatment. An increased flow rate leading to an empty pump and consecutive rebound phenomenon of pulmonary hemodynamics occurred in 1 patient. One further patient experienced catheter occlusion, leading to rebound with impairment of pulmonary hemodynamics. Further AEs were abdominal wall hematoma ($n$ = 1), pneumothorax ($n$ = 1), and seroma ($n$ = 1), which were successfully treated (Fig. 1).

*Clinical Course of PAH Patients during Treprostinil Treatment*

At initiation of treprostinil sc treatment (baseline), echocardiographic features in all 37 subjects indicated severe impairment of right heart function and hemodynamics, with a mean right atrial (RA) area of 26.4 ± 9.3 $cm^2$, mean RV area of 31.0 ± 8.3 $cm^2$, systolic pulmonary arterial pressure (sPAP) of 74.5 ± 20.5 mm Hg, and mean tricuspid annular plane systolic excursion (TAPSE) of 16.3 ± 4.5 mm (Table 2). Mean NT-proBNP levels were elevated at 2,988 ± 4,677 pg/mL, and mean 6MWD was 347 ± 106 m (Table 2). Under add-on therapy with parenteral treprostinil, patients showed a significant increase in 6MWD (Fig. 2a; Table 2) and TAPSE (Fig. 2b; Table 2) after 3, 6, 9, and 12 months compared to baseline. The RV area (Fig. 2c; Table 2) significantly decreased at 3 and 6 months after baseline, and also tended to be lower after 9 months and 12 months. TAPSE/sPAP ratio significantly improved after 3, 6, 9, and 12 months of treprostinil treatment (Table 2; Fig. 2d). The RA area also tended to be lower at 3, 6, 9, and 12 months after baseline, with a statistically significant difference being found only at the 3-month follow-up. SPAP and NT-proBNP also tended to improve from baseline toward the 12-month follow-up, but only the measurements after 12 months were significantly different from baseline (Table 2).

When looking at the course of subjects with sc treprostinil, the abovementioned clinical parameters also improved during therapy. Improvements of

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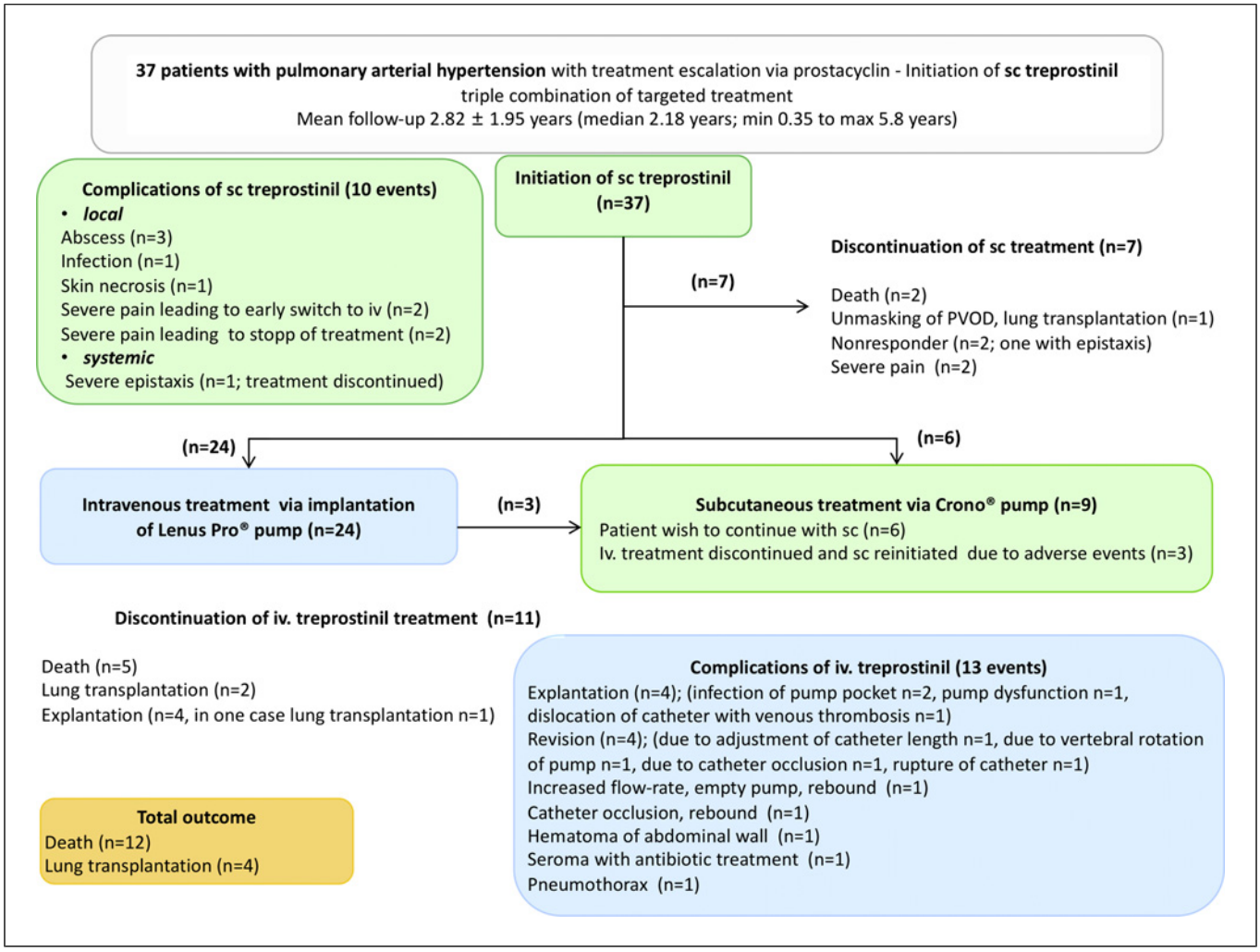


**Fig. 1.** Study flow chart. The figure depicts the course of the patients including adverse events (AEs). In total, 37 patients received treprostinil treatment, and 24 of these patients received an implantable pump system. During follow-up, 12 patients died, and 4 received lung transplantation.

most clinical parameters (6MWD, RA area, TAPSE) were observed mainly at the 3- and 6-month follow-up, while RV area was significantly improved after 3, 9, and 12 months compared to baseline. TAPSE/sPAP ratio significantly improved after 3, 6, and 12 months of sc treprostinil treatment. NT-proBNP was significantly different from baseline only after 12 months. The improvement of sPAP in sc treprostinil patients was not significantly different at the respective follow-ups. After switching to iv treprostinil, echocardiographic parameters, 6MWD, and NT-proBNP remained largely stable during the following 12 months observation period, except for sPAP at 9 months after onset of iv administration (Table 2).

*Survival Analysis*

During a mean follow-up period of 2.82 ± 1.95 years, 12 patients died (2 patients died after quitting the sc treatment after treatment initiation, five under iv treprostinil, and 5 patients under sc treprostinil during the study period). Four patients received lung transplantation (one had developed PVOD). Survival rates after 1, 2, and 3 years were 85.7%, 77.9%, and 73.6%. Transplant-free survival after 1 year was 85.7%, after 2 years 69.2%, and after 3 years 65.3% (Fig. 3).

Risk stratification by the COMPERA approach significantly predicted survival of the study cohort at baseline ($p$ = 0.003) and showed a trend for first ($p$ = 0.093) and second follow-up ($p$ = 0.059, data not shown). When



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**Table 2.** Effects of treprostinil treatment on clinical parameters

| Parameter | Baseline (*N* = 37) | | 3 months Δ to baseline (*N* = 29) | | | 6 months Δ to baseline (*N* = 24) | | | 9 months Δ to baseline (*N* = 21) | | | 12 months Δ to baseline (*N* = 20) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | mean±SD | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) |
| Changes of clinical parameters during treprostinil treatment (sc and iv) | | | | | | | | | | | | | | |
| Dose, ng/kg/min | 36 | 7.4±8.6 | 29 | 32.2±20.8 | (24.3–40.1)* | 24 | 37.0±18.3 | (29.3–44.7)* | 16 | 38.4±15.7 | (30.1–46.8)* | 20 | 41.1±15.4 | (34.0–48.3)* |
| 6MWD, m | 32 | 347±106 | 21 | 52.1±87.6 | (−91.9 to −12.1) | 14 | 84.5±109.7 | (147.8–21.2) | 12 | 48.4±59.0 | (85.9– 11.0) | 16 | 82.3±88.7 | (129.6-–35.1) |
| RA area, $cm^2$ | 36 | 26.4±9.3 | 26 | −4.0±7.3 | (−7.0 to −1.1)* | 24 | −3.4±8.2 | (−6.9 to 0.1) | 15 | −3.9±9.3 | (−9.0 to 1.3) | 20 | −3.5±9.9 | (−8.1-to 1.1) |
| RV area, $cm^2$ | 36 | 31.0±8.3 | 26 | −3.6±5.1 | (−5.7 to −1.6)* | 24 | −3.3±7.5 | (−6.5 to −0.2)* | 15 | −3.6±6.8 | (−7.4 to 0.2) | 20 | −4.4±9.7 | (−8.9 to 0.1) |
| sPAP, mm Hg | 36 | 74.5±20.5 | 26 | −7.7±22.1 | (−16.6 to 1.3) | 24 | −6.3±21.1 | (−15.2 to 2.7) | 15 | −5.7±28.1 | (−21.2 to 9.9) | 20 | −12.3±21.8 | (−22.5 to −2.0)* |
| TAPSE, mm | 35 | 16.3±4.5 | 25 | 2.3±4.0 | (0.7–4.0)* | 22 | 3.9±5.5 | (1.4–6.3)* | 15 | 3.7±5.3 | (0.7–6.6)* | 19 | 4.7±7.5 | (1.1–8.4)* |
| TAPSE/sPAP, mm/mm Hg | 35 | 0.24±0.09 | 25 | −0.44±0.92 | (−0.81 to 0.06)* | 22 | −0.59±0.85 | (−0.97 to −0.21)* | 14 | −0.64±1.01 | (−1.23-to −0.06)* | 19 | −0.84±0.96 | (−1.31 to- −0.38)* |
| NT-proBNP, pg/mL | 36 | 2,988±4,677 | 28 | −1,355±5,159 | (−3,356 to 645) | 21 | −1,496±6,144 | (−4,292 to 1,301) | 21 | −61.4±4,477 | (−2,099 to 1,976) | 20 | −2,694±5,206 | (−5,130 to −257)* |
| | Baseline (*N* = 37) | | 3 months Δ to baseline (*N* = 27) | | | 6 months Δ to baseline (*N* = 17) | | | 9 months Δ to baseline (*N* = 5) | | | 12 months Δ to baseline (*N* = 7) | | |
| | *n* | mean±SD | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) |
| Changes of clinical parameters during sc treprostinil treatment | | | | | | | | | | | | | | |
| Dose, ng/kg/min | 36 | 7.4±8.6 | 27 | 30.0±19.9 | (22.2–37.9)* | 16 | 28.9±13.6 | (21.6–36.2)* | 5 | 37.0±9.6 | (25.1– 48.9)* | 7 | 44.3±19.6 | (26.2–62.4)* |
| 6MWD, m | 32 | 347±106 | 20 | 50.3±89.5 | (8.5-–92.0)* | 10 | 87.4±110.2 | (8.6– 166.2)* | 3 | 37.0±30.3 | (−38.3 to 112.3) | 6 | 60.0±78.0 | (−21.9 to 141.9) |
| RA area, $cm^2$ | 36 | 26.4±9.3 | 24 | −4.8±6.9 | (−7.6 to −1.9)* | 16 | −5.8±8.5 | (−10.3 to −1.2)* | 5 | −3.2±5.2 | (−9.6 to 3.2) | 7 | −4.1±8.7 | (−12.2 to 3.9) |
| RV area, $cm^2$ | 36 | 31.0±8.3 | 24 | −4.1±5.0 | (−6.2 to-−2.0)* | 16 | −4.4±8.6 | (−9.0 to 0.2) | 5 | −7.2±2.9 | (−10.7 to −3.6)* | 7 | −8.9±9.6 | (−17.7 to −0.03)* |
| sPAP, mm Hg | 36 | 74.5±20.5 | 24 | −7.9±23.0 | (−17.6 to 1.8) | 16 | −9.7±19.2 | (−19.9 to 0.5) | 5 | −3.0±32.5 | (−43.4 to 37.4) | 7 | −14.0±23.0 | (−35.3 to 7.3) |
| TAPSE, mm | 36 | 16.3±4.5 | 23 | 2.7±3.8 | (1.1– 4.3)* | 14 | 5.0±6.0 | (1.5–8.5)* | 5 | 4.0±6.4 | (−4.0 to 12.0) | 7 | 3.1±5.8 | (−2.2 to 8.5) |
| TAPSE/sPAP, mm/mm Hg | 35 | 0.24±0.09 | 23 | 0.07±0.11 | (0.03–0.12)* | 14 | 0.14±0.17 | (0.04–0.23)* | 5 | 0.10±0.19 | (−0.13 to 0.33) | 7 | 0.12±0.11 | (0.02–0.22)* |
| NT-proBNP, pg/mL | 36 | 2,988±4,677 | 26 | −1,695±5,087 | (−3,749 to 360) | 13 | −2,337±7,715 | (−7,000 to 2,325) | 5 | −1,634±3,681 | (−6205 to 2936) | 7 | −3,326±2,604 | (−5735 to −918)* |
| | Baseline (*N* = 24) | | 3 months Δ to baseline (*N* = 17) | | | 6 months Δ to baseline (*N* = 18) | | | 9 months Δ to baseline (*N* = 10) | | | 12 months Δ to baseline (*N* = 12) | | |
| | *n* | mean±SD | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) | *n* | mean±SD | (95% CI) |
| Changes of clinical parameters during iv treprostinil treatment | | | | | | | | | | | | | | |
| Dose, ng/kg/min | 23 | 42.8±16.7 | 16 | 8.5±11.5 | (2.4–14.6)* | 18 | 10.1±11.3 | (4.5–15.7)* | 10 | 10.2±10.0 | (3.1–17.3) | 12 | 16.7±10.4 | (10.2–23.3)* |
| 6MWD, m | 18 | 410.0±16.72 | 9 | 10.0±44.8 | (−24.5 to 44.5) | 11 | 3.3±49.3 | (−29.9 to 36.4) | 4 | 14.8±33.9 | (−39.2 to 68.7) | 6 | 20.7±32.5 | (−13.5 to 54.8) |
| RA area, $cm^2$ | 21 | 22.9±8.5 | 15 | 1.5±3.6 | (−0.6 to 3.5) | 15 | 0.8±5.1 | (−2.0 to 3.6) | 8 | −0.9±6.0 | (−5.9 to 4.1) | 11 | 3.1±7.2 | (−1.7-to 7.9) |
| RV area, $cm^2$ | 21 | 26.0±6.7 | 15 | 1.7±5.9 | (−1.6 to 4.9) | 15 | 1.3±4.4 | (−1.2 to 3.7) | 8 | 1.0±4.3 | (−2.6 to 4.6) | 11 | 2.2±8.2 | (−3.3 to 7.7) |
| sPAP, mm Hg | 21 | 65.6±20.50 | 15 | 1.3±20.3 | (−9.9 to 12.6) | 15 | 1.4±18.2 | (−8.3 to 11.0) | 8 | 7.1±8.0 | (0.4–13.9)* | 11 | 1.9±22.9 | (−13.5 to 17.3) |
| TAPSE, mm | 21 | 19.2±4.71 | 15 | 1.1±4.9 | (−1.7 to 3.8) | 15 | 1.5±5.6 | (−1.5 to 4.6) | 8 | 0.0±5.2 | (−4.4 to 4.4) | 11 | 1.6±6.2 | (−2.6 to 5.7) |
| TAPSE/sPAP, mm/mm Hg | 21 | 0.33±0.15 | 15 | 0.02±0.15 | (−0.06 to 0.11) | 15 | 0.03±0.14 | (−0.05 to 0.11) | 8 | −0.03±0.09 | (−0.11 to 0.05) | 11 | 0.01±0.17 | (−0.10 to 0.12) |
| NT-proBNP, pg/mL | 18 | 1910±3834 | 14 | −365±1087 | (−993- to 263) | 14 | 730±1911 | (−734 to 1833) | 6 | 34±122 | (−95 to 162) | 9 | 312±857 | (−347 to 971) |

*Denotes confidence intervals which do not include "0." Data are presented as mean±SD. Δ, differences; Dose, treprostinil dose; 6MWD, 6-min walk distance; RA area, right atrium area; RV area, right ventricular area; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; SD, standard deviation.

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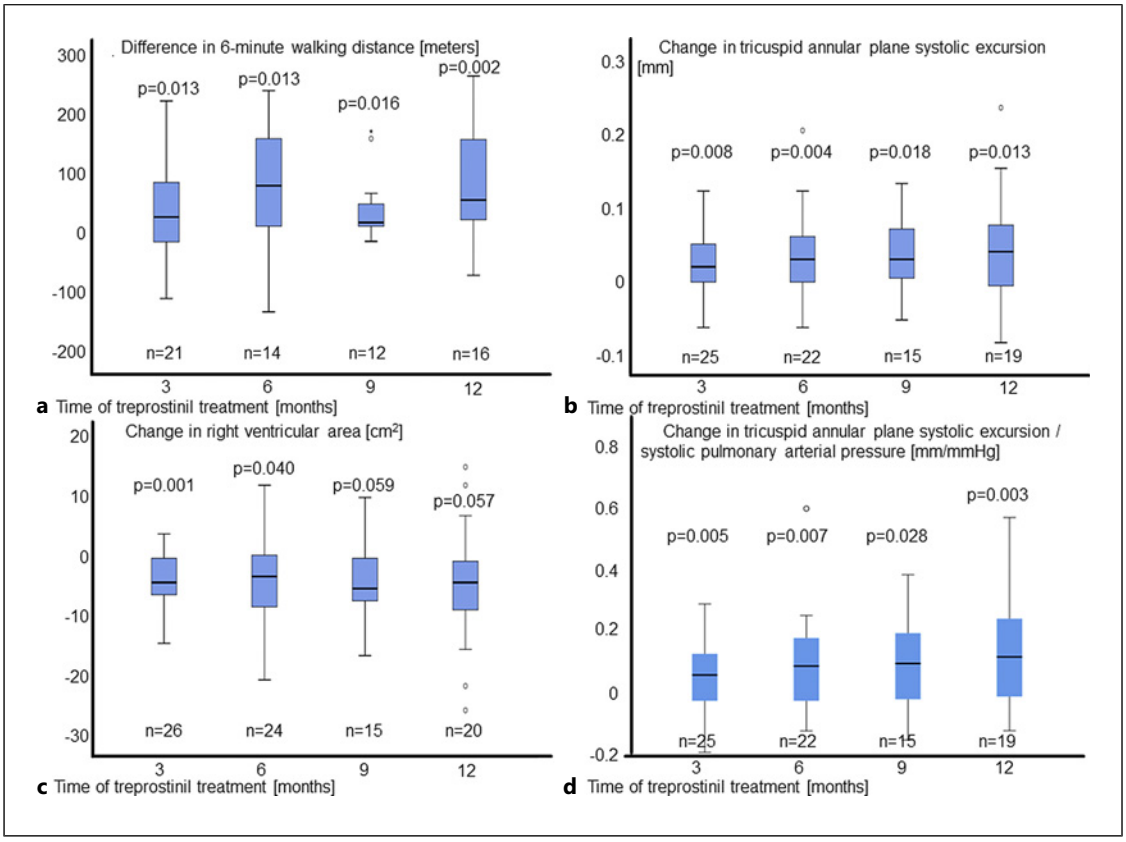


**Fig. 2.** Changes of clinical parameters during treprostinil treatment. **a** 6MWD. Patients showed a significant increase in 6MWD after 3, 6, 9, and 12 months of treprostinil (including sc and iv) treatment compared to baseline. **b** TAPSE. Right heart function, assessed by tricuspid annular plane systolic excursion (TAPSE) showed persistent improvement after 3, 6, 9, and 12 months of treprostinil (including sc and iv) treatment compared to baseline. **c** Right ventricular area. Right ventricular area significantly decreased after 3 and 6 months compared to baseline, and also tended to be lower after 9 and 12 months under treprostinil treatment (including sc and iv). **d** TAPSE/sPAP. TAPSE/sPAP significantly changed at all timepoints compared to baseline before treprostinil treatment.

using the French approach, risk stratification showed a trend to predict survival for values at first follow-up ($p$ = 0.054) but not for baseline (data not shown). REVEAL 2.1 risk stratification did not predict survival in this patient cohort (data not shown). Patients who improved in risk criteria (2–3) after initiation of treprostinil treatment within 3–9 months of treatment showed a tendency toward improved overall survival compared to patients remaining at high risk (0–1) ($p$ = 0.059; Fig. 4).

After 3 months, 3 patients showed a treatment response or remained stable in both TAPSE/sPAP and NT-proBNP risk categories, while 10 patients showed a worsening in both risk groups. Treatment response in NT-proBNP from baseline to 3 months of follow-up significantly predicted survival ($p$ = 0.001), while treatment response in TAPSE/sPAP was not able to predict survival in this patient cohort ($p$ = 0.216). When analyzing the impact of risk status at baseline and responder status after 3 months of NT-proBNP and TAPSE/sPAP on survival, risk group of TAPSE/sPAP at baseline and NT-proBNP response from baseline to 3 months (change of risk groups) were identified as independent prognostic predictors ($p$ = 0.033). The result remained robust when the analysis was adapted to age. TAPSE/sPAP treatment response after 3 months (risk category) did not significantly predict survival in this patient cohort (data not shown).

## Discussion

This is the first long-term study showing the course of advanced PAH patients with sequential sc and iv treprostinil treatment using different pump systems after clinical deterioration under double oral combination



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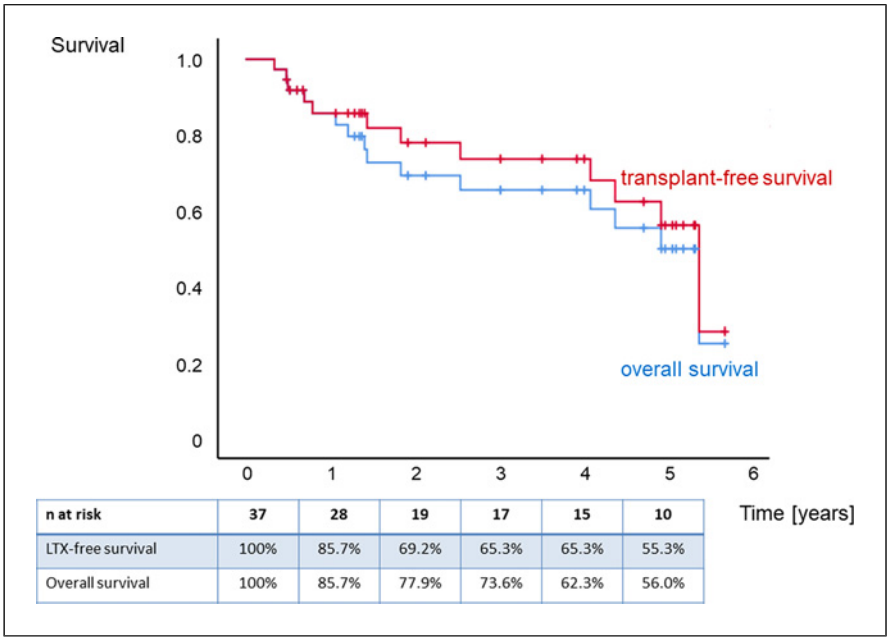


| n at risk | 37 | 28 | 19 | 17 | 15 | 10 |
|---|---|---|---|---|---|---|
| LTX-free survival | 100% | 85.7% | 69.2% | 65.3% | 65.3% | 55.3% |
| Overall survival | 100% | 85.7% | 77.9% | 73.6% | 62.3% | 56.0% |

**Fig. 3.** Survival and transplant-free survival. During the observation period, 12 patients died and four received lung transplantation. Overall survival was 85.7%, 77.9%, and 73.6% after 1, 2, and 3 years.

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therapy. Patients were severely affected at baseline with poor hemodynamics and mainly attributed with WHO FC III or IV. Moreover, most patients in our cohort were actively listed for lung transplantation.

*Forms of Treprostinil Administration*

While initial sc treatment is regarded as a flexible approach for rapid up-titration and evaluation of individual tolerability and efficacy of the drug in daily life (outpatient setting) over an adequate time span [6], continuous central venous administration via implantable pump systems is regarded as the ideal approach to treprostinil delivery in patients on the long term, ensuring constant sufficient bioavailability and improved compliance, especially in patients with severe disease. In this context, iv treatment provides patients with higher ability to perform daily activities while lacking local irritations of sc administration [17].

*Subcutaneous Treprostinil Treatment*

Initiation of treprostinil treatment was based on the sc application approach which successfully allowed identification non-responders and subjects with drug intolerance before undergoing the much more invasive iv approach based on implanted pump systems. Regular adjustments of the application rate of the (easily accessible) external pumps enabled rapid up-titration of sc treprostinil dose.

In this context, nonresponse to treatment was found in only 2 out of 37 patients, and an individual dose of 38 ± 18.3 ng/kg/min was successfully reached in 78% of subjects after only 3 months of sc treprostinil. Interestingly, this is the first study documenting cases of nonresponse to parenteral treprostinil. While achieving and maintaining a low-risk profile on optimized medical therapy is recommended as a treatment goal in patients with PAH [2], the two non-responders not only failed to achieve intermediate-low or low-risk profile under treprostinil treatment but also missed any improvement in the parameters with strongest prognostic value, namely, WHO FC, 6MWD, and NT-proBNP as well as hemodynamics.

By analogy to our study, as already shown in the RAPID trial, rapid up-titration using sc treprostinil administration via external pump systems is highly valuable in evaluating tolerability, safety, and efficacy of this medication in the individual patient [6]. However, distinct side effects were found under sc treprostinil administration with increasing dose, especially local tissue inflammation (8%), severe injection site pain (11%), infection (3%), and skin necrosis (3%). sc abscesses or necrosis requiring special treatment were only observed at sc treprostinil doses exceeding 80 ± 15 ng/kg/min. In agreement with our data, local side effects of sc treprostinil administration were previously reported to represent a possible source of treatment discontinuation or limiting dose increases, thus hampering long-term therapy [6–8, 18–20]. In this context, abrupt discontinuation of treprostinil represents a serious AE, inevitably leading to clinical worsening requiring hospitalization. This was observed in 19% of patients, mainly due to local AEs (10%), similar to previously published results [8, 21].

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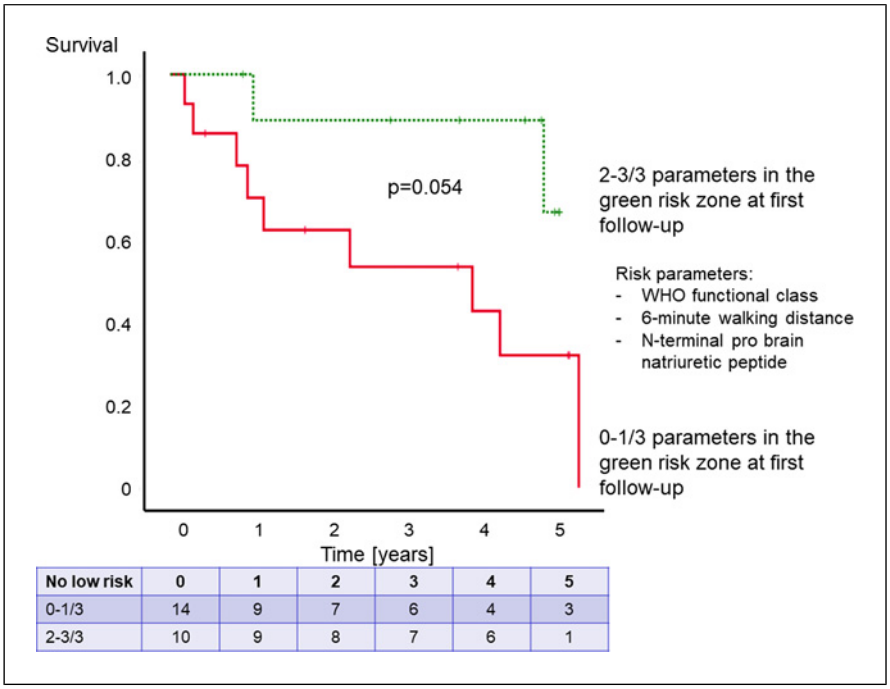


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**Fig. 4.** Overall survival depending on risk stratification. Patients with a higher number of low risk criteria (2–3) after initiation of treprostinil treatment during first follow-up after 3–9 months of treatment showed a tendency toward better survival compared to subjects with fewer low-risk criteria (0–1) ($p$ = 0.054).

*Intravenous Treprostinil Treatment*

In consequence, further escalation of treprostinil dose or continuous high-dose treprostinil treatment lacking local complications could only be achieved via iv administration based on implantable pump systems, ensuring optimal bioavailability and high patient compliance in the long term. Hence, it is recommended to immediately switch from sc to iv treprostinil treatment as soon as patients have reached a reasonable effective dose (depending on individual drug tolerability), especially if the required doses are rather high [6]. In contrast to the sc approach, dose escalation in outpatient setting with the available implantable pumps was only possible every 3–5 weeks by changing the concentration of the drug in the pump's reservoir during routine refill procedures. Importantly, most patients (80%) were successfully kept on long-term iv therapy, thus maintaining improved right heart function and exercise capacity over the entire follow-up period.

As expected, only very few patients insisted to or were obliged to continue sc treatment after severe complications related to the iv pump system. By analogy to data from Bourge et al. [22] and Richter et al. [10], a substantial complication rate (54%) was observed in patients with iv treprostinil treatment, mostly issues related to the catheter (dislocation, rupture, occlusion) or pump pocket (infection), which were treated successfully (Fig. 1). Pump-related complications (pump defect, excessive flow rate variability) or periprocedural complications (pneumothorax) were infrequent in our cohort. Ultimately, complication-related discontinuation of iv treatment with explantation of the LENUS Pro® pump was required in only four cases (16%), of which three switched to sc treatment and one underwent lung transplantation. Interestingly, the extent of flow rate variability over the technical lifetime of the LENUS Pro® pump obviously has the potential to cause life-threatening events, as observed in 1 patient who suffered from severe rebound after the pump's reservoir had been emptied before the scheduled refill. In this context, a recent multicenter study showed that in the initial phase, the pump's flow rate was significantly lower than the expected rate (as specified by the manufacturer) and increased slowly but steadily with long-term use, significantly exceeding the expected rate in the end [23]. Hence, frequent assessments of the flow rate and compensatory adjustments of the treprostinil dose are considered mandatory and should be performed by experts. Besides, product information provided by OMT GmbH recommends to exchange the pump after 4 years or after 500 refills (LENUS Pro® instruction for use, Tricumed Medizintechnik GmbH 05/2019). In consequence, fully implantable treprostinil pump systems may need further technical advances.

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Compared to other studies [10, 24], none of our patients died from periprocedural or pump-related complications. Nevertheless, the substantial complication rate resulting from implanted pump systems underlines the need to test drug efficacy in individual patients using the sc administration approach before proceeding to pump implantation.

*Clinical Outcomes*

Under parenteral treprostinil therapy, substantial improvement in clinical parameters such as right heart function and exercise capacity was observed from 3 months after baseline until 12 months of follow-up. Afterward, the clinical condition remained fairly stable, with reasonable transplant-free survival over 3 years (65.3%), despite severe disease. The reasonable overall survival observed in our study is comparable to previously reported outcomes in patients receiving parenteral prostacyclins [13, 25–28]. Transplant-free survival after 3 years (65.3%) was in line with data of Bartolome et al. [21]. In this context, the assessment of prognosis is increasingly important to optimize treatment and thus improve patient survival [16]. As already shown in patients who do not achieve low-risk status during regularly performed follow-up assessments under PAH medication, further treatment escalation should be considered to improve survival [16].

While patients with advanced PAH were subjected to sc and iv treprostinil treatment in the present study, it was already shown that further escalation toward parenteral prostacyclin treatment may also be required in intermediate-risk PAH patients where current PAH treatment is unsuccessful to reach low-risk status [29]. Therefore, initiation of prostacyclin treatment for patients with intermediate risk and its impact on survival should be further investigated in future studies. Due to the extent of complexity, further standardization of procedures concerning the evaluation (of safety, tolerability, efficacy, and eligibility) for parenteral treprostinil treatment, the implantation of the LENUS Pro® pump, periprocedural monitoring, and regular assessments of severely impaired PAH patients are needed. Besides, such treatments should be performed in highly experienced PH centers only, offering all available treatment modalities for the systemic iv and sc application of prostanoids, especially in patients with advanced right heart failure.

In our cohort, treprostinil treatment was associated with an improvement in RV function (TAPSE) and exercise capacity (6MWD). In this context, vasodilative effects of prostanoids are known to play a key role, but little is known about the direct effects of prostanoids on RV contractility. Studies of the acute effects of inhaled iloprost on the right side of the heart in patients with pulmonary hypertension showed significant improvements from baseline in RA function and RV dyssynchrony measured by echocardiography [30], and RV ejection fraction measured by cardiac MRI [31]. Another study indicates an improvement of RV arterial coupling and slight increase in contractility caused by prostanoid administration which leads to acute reduction of afterload [32]. In an animal model, a positive inotropic effect of iloprost on the right ventricle of chronic PAH rats has been shown [33], induced by a dose-dependent increase in cAMP in isolated RV cardiac myocytes. Further studies are necessary to investigate the mechanisms of action of treprostinil treatment on the right ventricle.

Patients showed a significant treatment response in TAPSE/sPAP and NT-proBNP during the course of follow-up. When the ESC/ERS risk stratification thresholds were applied, TAPSE/sPAP at baseline and NT-proBNP treatment response from baseline to 3 months of follow-up presented as independent prognostic parameters, though TAPSE/sPAP also showed improvement after 3 months and was not able to predict survival. These data are in agreement with a previous study highlighting the prognostic relevance of TAPSE/PASP ratio in PAH [34]. Other echocardiographic parameters reflecting RV function in PH patients are currently being evaluated [35]. Future studies with larger sample sizes are needed to determine the optimal parameters of treatment response and their meaning for survival.

*Limitations*

The retrospective nature and the small sample size represent limitations of the present study. However, only few patients receive this treatment option since treatment escalation with iv and sc prostacyclins has mainly been regarded as a rescue therapy in end-stage PAH patients receiving double or triple non-parenteral combination treatment. Besides, randomization of the study using a control group would have been desirable for scientific interpretation, but it would have been highly unethical to withhold treatment from severely affected PAH patients. Data on responder status, determining factors of treatment response as well as impact of treprostinil treatment on quality of life should be focused on in future studies.

## Conclusion

This study presents data on long-term safety, outcome, and clinical effects of sequential sc and iv treprostinil treatment in patients with advanced PAH. Hence, sequential sc and iv

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application regimen help ensure the safety, tolerability, and convenience of long-term prostacyclin therapy and potentially may lead to a broader and earlier use in patients with PAH. Due to the high complexity, parenteral treprostinil treatment in PAH should be reserved for specialized PH centers capable of identifying eligible patients, adequate patient monitoring, minimizing complications, and managing severe complications to improve survival in the long term.


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This study is the doctoral dissertation of Satenik Harutyunova, Heidelberg, Germany.


## Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty of Heidelberg University, Germany, approval number S-569/2016. According to the Ethics Committee of the University of Heidelberg, it was not necessary to obtain explicit, study-specific declarations of consent because of the retrospective character of the study and because most patients had already passed away. Accordingly, data collection was to be restricted to a single center where all of the study patients had been treated, and performed by the treating physician. Data had to be pseudonymized immediately upon collection and anonymized before further scientific evaluation.

## Conflict of Interest Statement

S.H. has received travel fees, consulting fees, speaker fees, and/or honoraria from Janssen, MSD, Bayer, and OMT outside the submitted work. A.M.M. has received personal fees from Bayer outside the submitted work. A.M.M. has received fee for consultation from MSD and Boehringer-Ingelheim (both less than 10.000€) outside the submitted work. C.A.E. has received speaker fees from MSD outside the submitted work. P.X. has received personal fees from MSD and OMT outside the submitted work. B.E. received travel fees, consulting fees, speaker fees, and/or honoraria from Janssen, MSD, Bayer, and OMT outside the submitted work. E.G. has received fees for lectures and/or consultations from Actelion, Bayer/MSD, Ferrer, GSK, Janssen, and OMT. Research grants to his institution have been received from Acceleron, Actelion, Bayer HealthCare, MSD, Bellerophon, Gossamer Bio, GSK, Janssen, Novartis, OMT, Pfizer, REATE, and United Therapeutics. C.N. has no relevant conflicts of interest to declare. All other authors declare that they have no competing interests.


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## Authors Contributions

S.H., B.E., and E.G. designed the study. S.H. collected the data and drafted the manuscript. S.H. and N.B. analyzed and interpreted the data. S.H., N.B., B.E., C.A.E., C.N., A.M.M., P.X., and E.G. have substantially revised the manuscript. The authors have read and approved the final manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

## References


1 Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS): endorsed by: association for European paediatric and congenital cardiology (AEPC), international society for heart and lung transplantation (ISHLT). Eur Heart J. 2016;37(1):67–119.

2 Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.

3 Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296–301.

4 Gomberg-Maitland M, Olschewski H. Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J. 2008;31(4):891–901.

5 Skoro-Sajer N, Gerges C, Balint OH, Kohalmi D, Kaldararova M, Simkova I, et al. Subcutaneous treprostinil in congenital heart disease-related pulmonary arterial hypertension. Heart. 2018;104(14):1195–9.

6 Grunig E, Benjamin N, Lange TJ, Krueger U, Klose H, Neurohr C, et al. Safety, tolerability and clinical effects of a rapid dose titration of subcutaneous treprostinil therapy in pulmonary arterial hypertension: a prospective multi-centre trial. Respiration. 2016;92(6):362–70.

7 Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2002;165(6):800–4.

8 Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;28(6):1195–203.

9 Hiremath J, Thanikachalam S, Parikh K, Shanmugasundaram S, Bangera S, Shapiro L, et al. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. J Heart Lung Transplant. 2010;29(2):137–49.

10 Richter MJ, Harutyunova S, Bollmann T, Classen S, Gall H, Gerhardt Md F, et al. Long-term safety and outcome of intravenous treprostinil via an implanted pump in pulmonary hypertension. J Heart Lung Transplant. 2018;37(10):1235–44.



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11 Ewert R, Richter MJ, Steringer-Mascherbauer R, Grunig E, Lange TJ, Opitz CF, et al. Intravenous treprostinil infusion via a fully implantable pump for pulmonary arterial hypertension. Clin Res Cardiol. 2017;106(10):776–83.
12 Ewert R, Halank M, Bruch L, Ghofrani HA. A case series of patients with severe pulmonary hypertension receiving an implantable pump for intravenous prostanoid therapy. Am J Respir Crit Care Med. 2012;186(11):1196–8.
13 Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017;50(2):1700740.
14 Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-Based risk assessment strategies. Chest. 2019;156(2):323–37.
15 Boucly A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017;50(2):1700889.
16 Galie N, Channick RN, Frantz RP, Grunig E, Jing ZC, Moiseeva O, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J. 2019;53(1):1801889.
17 Shapiro S, Bourge RC, Pozella P, Harris DF, Borg EH, Nelsen AC. Implantable system for treprostinil: a real-world patient experience study. Pulm Circ. 2020;10(2):2045894020907881.
18 Skoro-Sajer N, Lang IM, Harja E, Kneussl MP, Sing WG, Gibbs SJ. A clinical comparison of slow- and rapid-escalation treprostinil dosing regimens in patients with pulmonary hypertension. Clin Pharmacokinet. 2008;47(9):611–8.
19 White RJ, Levin Y, Wessman K, Heininger A, Frutiger K. Subcutaneous treprostinil is well tolerated with infrequent site changes and analgesics. Pulm Circ. 2013;3(3):611–21.
20 O'Connell C, Amar D, Boucly A, Savale L, Jais X, Chaumais MC, et al. Comparative safety and tolerability of prostacyclins in pulmonary hypertension. Drug Saf. 2016;39(4):287–94.
21 Bartolome SD, Sood N, Shah TG, Styrvoky K, Torres F, Chin KM. Mortality in patients with pulmonary arterial hypertension treated with continuous prostanoids. Chest. 2018;154(3):532–40.
22 Bourge RC, Waxman AB, Gomberg-Maitland M, Shapiro SM, Tarver JH 3rd, Zwicke DL, et al. Treprostinil administered to treat pulmonary arterial hypertension using a fully implantable programmable intravascular delivery system: results of the DelIVery for PAH trial. Chest. 2016;150(1):27–34.
23 Richter MJ, Harutyunova S, Bollmann T, Classen S, Fuge J, Gall H, et al. Flow rate variance of a fully implantable pump for the delivery of intravenous treprostinil in pulmonary arterial hypertension. Pulm Circ. 2020;10(1):2045894020910136.
24 Richter MJ, Ewert R, Warnke C, Gall H, Classen S, Grimminger F, et al. Procedural safety of a fully implantable intravenous prostanoid pump for pulmonary hypertension. Clin Res Cardiol. 2017;106(3):174–82.
25 Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med. 1994;121(6):409–15.
26 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation. 2002;106(12):1477–82.
27 Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol. 2002;40(4):780–8.
28 Sadushi-Kolici R, Skoro-Sajer N, Zimmer D, Bonderman D, Schemper M, Klepetko W, et al. Long-term treatment, tolerability, and survival with sub-cutaneous treprostinil for severe pulmonary hypertension. J Heart Lung Transplant. 2012;31(7):735–43.
29 Olsson KM, Richter MJ, Kamp JC, Gall H, Heine A, Ghofrani HA, et al. Intravenous treprostinil as an add-on therapy in patients with pulmonary arterial hypertension. J Heart Lung Transplant. 2019;38(7):748–56.
30 Gabrielli L, Ocaranza MP, Sitges M, Kanacri A, Saavedra R, Sepulveda P, et al. Acute effect of iloprost inhalation on right atrial function and ventricular dyssynchrony in patients with pulmonary artery hypertension. Echocardiography. 2017;34(1):53–60.
31 Li JH, Zhang HD, Wang ZZ, Lu QQ, Li D, Lian TY, et al. Acute iloprost inhalation improves right ventricle function in pulmonary artery hypertension: a cardiac magnetic resonance study. Front Pharmacol. 2018;9:1550.
32 Tello K, Seeger W, Naeije R, Vanderpool R, Ghofrani HA, Richter M, et al. Right heart failure in pulmonary hypertension: diagnosis and new perspectives on vascular and direct right ventricular treatment. Br J Pharmacol. 2021;178(1):90–107.
33 Zeineh NS, Bachman TN, El-Haddad H, Champion HC. Effects of acute intravenous iloprost on right ventricular hemodynamics in rats with chronic pulmonary hypertension. Pulm Circ. 2014;4(4):612–8.
34 Tello K, Axmann J, Ghofrani HA, Naeije R, Narcin N, Rieth A, et al. Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension. Int J Cardiol. 2018;266:229–35.
35 Richter MJ, Rako ZA, Tello K. Ratio between right ventricular strain and systolic pulmonary artery pressure as a surrogate for right ventricular to pulmonary arterial coupling: validation against the gold standard. Eur Heart J Cardiovasc Imaging. 2023;24(3):e50–e52.

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