Pharmacokinetics and Steady-State Bioequivalence of Treprostinil Sodium (Remodulin®) Administered by the Intravenous and Subcutaneous Route to Normal Volunteers

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Abstract: Treprostinil sodium is a chemically stable analogue of prostacyclin administered as a chronic, continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension (PAH). There has been significant clinical interest in determining the feasibility of delivering treprostinil by intravenous infusion. Therefore, a bioequivalence and comparative pharmacokinetics study of the two routes of administration was conducted in normal volunteers. A randomized, two-period, crossover study design was employed. Each subject was dosed at 10 ng/kg/min for 72 hours by each route, with the infusions separated by a 4-day wash-out period. In the 51 subjects who received at least 24 hours of treprostinil administered subcutaneously and intravenously, the steady-state ratios of the geometric means (IV/SC) and 90% confidence intervals for AUC_{ss} and $Cmax_{ss}$ were 92.9% (89.8–96.1%) and 106% (99.4–113%), respectively. Secondary pharmacokinetic assessments confirmed the comparability of the two routes of administration at steady state, and also demonstrated that the elimination half-life of treprostinil was 4.4 and 4.6 hours following intravenous and subcutaneous administration, respectively. Based on these findings it was concluded that intravenously and subcutaneously administered treprostinil are bioequivalent at steady state.

Key Words: bioequivalence, pharmacokinetics, prostacyclin analogue, pulmonary arterial hypertension, treprostinil, Remodulin

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Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by dyspnea, chest pain, and syncope. PAH can occur without known cause (primary pulmonary hypertension) or in association with congenital heart disease, connective tissue diseases, or exogenous stimuli such as HIV infection, anorexigens (fenfluramine), or illicit drugs (cocaine). The most significant clinical finding upon right heart catheterization is an elevation in the mean pulmonary arterial pressure (PAP). The main objective of treatment of PAH is to reduce PAP and pulmonary vascular resistance. Prostacyclin and its analogues, because of their favorable effects on pulmonary hemodynamics, are accepted therapies for patients with PAH.

Treprostinil sodium (Remodulin®, United Therapeutics Corporation, Research Triangle Park, North Carolina) is a chemically stable, tricyclic benzindene analogue of prostacyclin that is approved in the United States and in other countries for continuous subcutaneous (SC) administration in the treatment of PAH.[1] In a 12-week, double-blind placebo-controlled, multicenter trial in 470 patients with PAH, treprostinil improved exercise capacity, indices of dyspnea, signs and symptoms of PAH, cardiopulmonary hemodynamics, and the physical dimension of quality of life.[2] Infusion site pain was the most common adverse event attributed to subcutaneous treprostinil administration.

There is significant clinical interest in determining whether treprostinil can be administered as a chronic continuous intravenous infusion via a surgically placed central catheter, which is the route of administration currently employed to administer prostacyclin as epoprostenol sodium (Flolan®, GlaxoSmithKline, Research Triangle Park, North Carolina). Epoprostenol is a safe and efficacious therapy for the treatment of PAH; however, the product has important limitations, many of which are related to its chemical instability and very short elimination half-life. The chemical instability of epoprostenol in solution requires that patients reconstitute vials of lyophilized drug product with diluent. The solution from the vial must be further diluted with an appropriate intravenous buffer to reach the final volume of dosing solution. Additionally, epoprostenol must be kept cold after it is reconstituted and diluted if it is to be used longer than 8 hours, requiring that patients carry cold packs to refrigerate the solution.[3] The very short

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half-life of epoprostenol also leaves patients susceptible to life-threatening complications even from brief interruptions in drug delivery, sudden reductions in dosage, or withdrawal of therapy, according to product labeling.[3]

The additional clinical interest in treprostinil as an alternative intravenous therapy developed due to its superior pharmacokinetic and stability characteristics compared with epoprostenol. These characteristics include: chemical stability at room temperature, allowing for intravenous infusion without the need for ice packs; longer stability in the delivery system (up to 48 hours at room temperature[4]); longer half-life (approximately 4 hours), thus minimizing the pharmacologic impact of unintended interruptions/pump malfunctions; and ease of dosage preparation, given that Remodulin is provided as an aqueous solution for ready dilution. Additionally, intravenous administration will provide an alternative therapy for patients who otherwise benefit from treprostinil, but are unable to continue treatment due to subcutaneous infusion site pain.

Previous experience with treprostinil established the pharmacokinetic profile of acute intravenous administration while acute and chronic administration was studied for the subcutaneous route. In an acute crossover study in normal volunteers, subcutaneously administered treprostinil was shown to be 100% bioavailable relative to intravenously administered treprostinil at a dose of 15 ng/kg/min for 150 minutes.[5] In a chronic pharmacokinetic study in normal volunteers, subcutaneously administered treprostinil reached steady-state plasma concentrations within 24 hours after initiation of infusion with doses ranging from 2.5 to 15 ng/kg/min[6]; linear pharmacokinetics was established within this dose range. However, a direct comparison of the pharmacokinetics of treprostinil administered by subcutaneous and intravenous administration at steady state had not been conducted. Establishing the steady-state bioequivalence of the 2 routes of administration would demonstrate that plasma exposure is similar irrespective of route of delivery. Therefore, information gained from the subcutaneous treprostinil patient experience (975 patient years) would be directly applicable to the intravenous route of administration.

METHODS

This was a single-center, open-label, two-period crossover study in healthy adult male and female volunteers assessing the steady-state bioequivalence of intravenously and subcutaneously administered treprostinil. The study was conducted between August 2003 and October 2003 at PPD Development (Austin, Texas). All subjects gave written informed consent prior to any study-related assessments. Subjects were eligible if they were nonsmokers, 18 to 65 years of age, weighed 60 to 90 kg, within 15% of their ideal body weight, free of clinically significant abnormal findings, and not taking any prescription (except oral contraceptives) or non-prescription medications (except multivitamins) for 14 and 7 days prior to admission to the clinical research unit, respectively.

Each subject was randomized to receive treprostinil via the subcutaneous or intravenous route during Dosing Period 1 and to receive the alternate route during Dosing Period 2. The subcutaneous infusion site was in the abdomen, while the intravenous infusion site was in a peripheral (arm) vein. The treprostinil dose during each 72-hour dosing period was 10 ng/kg/min, a clinically relevant dose that has been administered previously to normal subjects. Treprostinil was diluted for intravenous administration in normal saline and infused using a Baxter (Deerfield, Illinois), Model AS-50, Syringe Pump. The concentration of treprostinil was adjusted based on each subject's weight, so that 10 ng/kg/min of treprostinil was infused intravenously at a flow rate of 1 mL/h. Treprostinil was administered subcutaneously without dilution using a MiniMed (Sylmar, California) Model 407C pump. The subcutaneous infusion rate was adjusted based on each subject's weight to achieve the 10 ng/kg/min dose. Treatments were separated by a 4-day wash-out period, during which subjects were discharged from the clinic after the conclusion of post-infusion pharmacokinetic sampling and safety assessments; otherwise subjects were confined to the clinic for all study procedures and evaluations.

A total of 36 blood samples (5 mL each) were collected in each dosing period for the determination of plasma treprostinil concentrations. In each dosing period, blood samples were collected prior to study drug administration and at 15, 30, 60, and 90 minutes and 2, 3, 5, 8, 12, 24, 48, 51, 54, 57, 60, 63, 66, 69, and 72 hours after study drug administration. Steady state was defined as hours 48 to 72 of the 72-hour infusion. In addition, blood samples were collected at the following time points after the termination of infusion: 5, 10, 15, 30, 60, and 90 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours. Blood samples were collected by direct venipuncture in K_3-EDTA Vacutainer® or equivalent tubes. The plasma from each blood sample was separated from the red cells by refrigerated centrifugation and frozen.

The frozen plasma samples were shipped on dry ice to Biolytix (Monmouth Jct., New Jersey) for the determination of treprostinil concentrations. A validated liquid chromatography tandem mass spectrometry (LC/MS/MS) assay with a lower limit of quantification (LLOQ) of 10 pg/mL for a 300 μL aliquot of plasma was used to analyze the plasma samples. Assay conditions were modified from the previous method[5,6] to improve the LLOQ from 25 pg/mL to 10 pg/mL. The mean percent accuracy values of quality control samples for the new method were 95%, 92%, and 98% of theoretical values, with coefficient of variation of 5.1%, 6.1%, and 3.4% at 30, 1920, and 3840 pg/mL of treprostinil, respectively. The coefficient of variation was 17.2% at the LLOQ of 10 pg/mL. Plasma samples were extracted using a pentane:dichloromethane (1:1):isopropyl alcohol (9:1) mixture. Extracts were analyzed

using a reverse phase C18 analytical column at a flow rate of 0.4 mL/min with an injection volume of 30 μL. The gradient method was used with Mobile Phase A defined as a 90:10 water:ammonium acetate mixture and Mobile Phase B as a 90:10 acetonitrile:ammonium acetate mixture. Retention times for treprostinil and its internal standard were approximately 2.62 and 4.74 minutes, respectively. Detection was by tandem mass spectrometry (PE-SCIEX API 4000).

Clinical laboratory parameters (hematology, serum chemistry, and urinalysis) were documented at screening and at the end of each treatment period. Systolic and diastolic blood pressure, heart rate, and respiratory rate were taken at pre-dose and at approximately 15, 30, 60, 90, and 120 minutes and 12, 24, 48, and 72 hours after the initiation of infusion; and at 30, 60, and 120 minutes and 12 and 24 hours after the termination of infusion. Physical examinations were performed at screening and at the end of the study. Adverse events were monitored continuously.

Individual subject plasma concentration versus time data for treprostinil was subjected to non-compartmental pharmacokinetic analysis. The primary analysis of the maximal plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) during steady state was performed after log-transformation. An analysis of variance was performed on $Cmax_{ss}$ and AUC_{ss} data using the General Linear Models (GLM) procedures in SAS. The statistical model included effects for Sequence, Subjects (nested within Sequence), Period, and Treatment. Similar analyses of $Cmin_{ss}$ (the lowest observed plasma concentration during steady state), $Cavg_{ss}$ (arithmetic average of steady state plasma concentrations), and fluctuation at steady state ($[Cmax_{ss} - Cmin_{ss}]/Cavg_{ss}$) were also performed.

The primary end point of the study was to assess bioequivalence via analysis of steady-state pharmacokinetics. Specifically, bioequivalence was deemed to have been established for the intravenous and subcutaneous routes if the 90% confidence intervals around the point estimates of the ratio of adjusted geometric means (IV/SC) for AUC_{ss} and $Cmax_{ss}$ meet the established confidence interval boundaries of 80 to 125%. Subjects who received treprostinil for greater than 24 hours by both routes of administration were included in the pharmacokinetic analysis.

Cmax, time to peak plasma concentration (Tmax), AUC_{0-96h}, AUC_{inf}, elimination phase rate constant (λ_z), elimination phase half-life ($T_{1/2}$), plasma clearance (CL), and volume of distribution (V_z) were also determined for each treatment. All pharmacokinetic parameters for each treatment were summarized using descriptive statistics. Presentations included both the arithmetic means (with standard deviations as the associated measure of variability) and geometric means (with the coefficient of variation as the associated measure of variability) so data could be interpreted in relation to both a normal distribution and a log-normal distribution.

Subjects who received a treprostinil infusion for any duration were included in the safety analysis. The safety data collected in this study were summarized using descriptive statistics.

RESULTS

Study Population

Fifty-five subjects received study medication and were included in the safety analysis; however only 51 subjects received treprostinil for greater than 24 hours by both routes of administration and were included in the pharmacokinetic analyses. One subject was replaced shortly after initiation of treprostinil infusion as a result of unwillingness to undergo repeated venipuncture for pharmacokinetic sampling.

Of the 55 subjects included in the safety analysis 60% (33 of 55) were male; 51% (28 of 55) were White, 29% Hispanic, 16% Black, 2% Asian, and 2% American Indian. All subjects were between 18 and 63 years of age (mean age = 36.2 years). The mean body weight was 73.9 kg (range = 58.4–90.8 kg), and the mean height was 171.3 cm (range = 156–187 cm). Concomitant medications used during the study included oral contraceptives (4 subjects), ibuprofen (2 subjects), and gatifloxacin (1 subject).

Pharmacokinetic Results

Figures 1A and 1B show the mean plasma treprostinil concentration profiles, plotted on both a linear and log-linear scale, respectively, during and after IV and SC infusion. The pharmacokinetic profiles of the 2 routes appear similar during the entire infusion profile, including the steady-state period (hours 48–72). The only noticeable difference is the delay in the first 8 to 10 hours of the elimination phase after subcutaneous administration, relative to intravenous administration, that may be attributable to a subcutaneous depot effect resulting in continued absorption of drug from the subcutaneous tissues.

Geometric mean data for the primary pharmacokinetic endpoints of AUC_{ss} and $Cmax_{ss}$ are presented in Table 1. The ratios of the adjusted geometric means (IV/SC) and 90% confidence intervals about the ratios for AUC_{ss} and $Cmax_{ss}$ were 92.9% (CI 89.8–96.1%) and 106% (CI 99.4–113%), respectively. The confidence intervals for these ratios are well within the established bioequivalence boundaries (80–125%) for both AUC_{ss} and $Cmax_{ss}$. Individual ratios for AUC_{ss} ranged from 0.682 to 1.403, while $Cmax_{ss}$ ratios ranged from 0.647 to 2.381.

In addition to the primary endpoints used to evaluate steady-state bioequivalence, secondary pharmacokinetic parameters including $Cmin_{ss}$, $Cavg_{ss}$, and fluctuation at steady state, were evaluated and are presented in Table 2. While $Cmin_{ss}$ and $Cavg_{ss}$ are similar, the degree of fluctuation at steady state was somewhat higher for intravenous dosing compared with subcutaneous dosing.

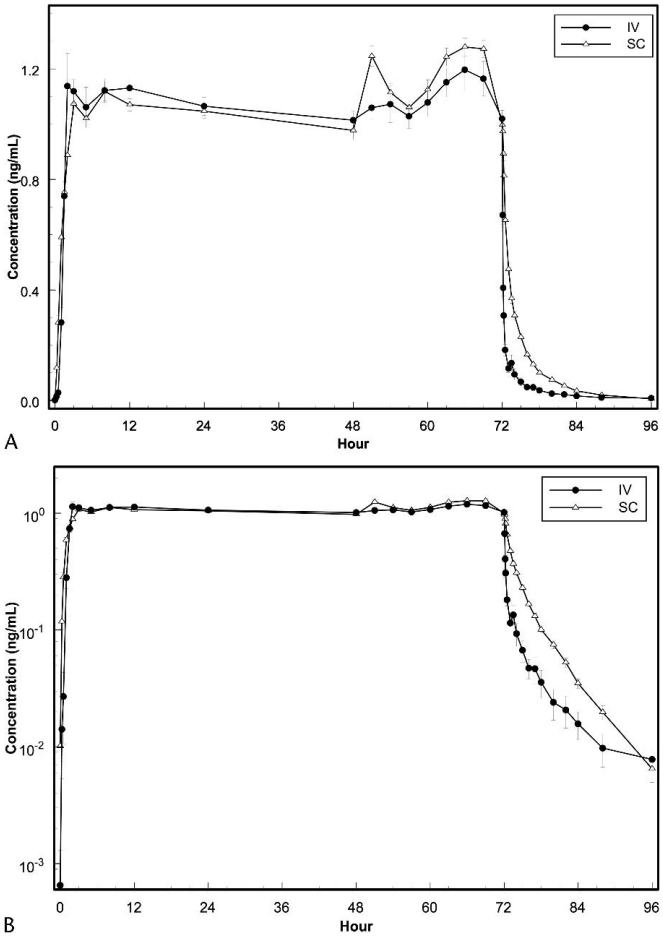

FIGURE 1. (A) Mean plasma concentration of treprostinil following IV infusion and SC infusion (linear plot). (B) Mean plasma concentration of treprostinil following IV infusion and SC infusion (log-linear plot).

Table 3 summarizes the PK parameters determined for the entire 72-hour treprostinil infusion for each route of administration: AUC_{inf}, $AUC_{0\text{-}96h}$, Cmax, Tmax, λ_z, $T_{1/2}$, CL, and V_z. Generally the parameters were comparable between the 2 routes of administration, with the exception of Tmax, which occurred at an average time of 36.4 hours for intravenous dosing and 50.3 hours for subcutaneous dosing. The mean elimination half-life following the termination of the infusion was 4.4 hours and 4.6 hours for intravenous and subcutaneous administration, respectively.

Safety Results

The incidence of adverse events was comparable between intravenous and subcutaneous routes of administration. Most adverse events were considered treatment-related; there were no serious or severe adverse events reported during the study. Three subjects discontinued the study because of intolerable, possibly treatment-related adverse events (ie, infusion site pain, nausea and vomiting, and rectal bleeding). Most adverse events were related to the infusion site for both routes of administration (ie, infusion site pain (59% SC, 57% IV), infusion site erythema (67% SC, 55% IV), infusion site edema (43% IV), and infusion site reaction (30% SC)). Other adverse events occurring in greater than 10% of subjects were mostly those related to the pharmacologic effects of treprostinil, including headache (61% SC, 53% IV), jaw pain (30% SC, 26% IV), and nausea (22% SC, 23% IV), and occurred in a similar percentage of subjects irrespective of the route of administration. These adverse events have been reported previously in subjects receiving epoprostenol and prostacyclin analogues.[1–7] No clinically significant changes in laboratory parameters, physical examinations, or vital signs occurred during the course of the study.

DISCUSSION

The main objective of this study was to determine the bioequivalence of intravenous and subcutaneous treprostinil at steady state. Since treprostinil is administered to patients as a continuous infusion and titrated to an effective and tolerable dose, steady-state pharmacokinetic parameters are most relevant in the analysis of bioequivalence data. Plasma treprostinil concentrations were given 48 hours to reach steady state prior to evaluation of the primary variables—AUC and Cmax at steady state (hours 48 to 72).

The primary pre-specified pharmacokinetic analysis included any subject who received at least 24 hours of treprostinil for each route of administration. In the 51 subjects who received at least 24 hours of treprostinil administered subcutaneously and intravenously the ratios of the adjusted geometric means (IV/SC) and confidence intervals about the ratios for AUC_{ss} and $Cmax_{ss}$ were 92.9% (CI 89.8–96.1%) and 106% (CI 99.4–113%), respectively. This study used a novel approach to the concept of bioequivalence, which is most often used in trials comparing the pharmacokinetic profiles of formulations of a new "generic" dosage form versus the "innovator" dosage form after single oral doses. In this case, 2 parenteral dose routes were compared during and after 72-hour infusions using a single formulation of treprostinil. The results clearly establish that subcutaneous and intravenous treprostinil administration are bioequivalent at steady state, thereby demonstrating the relatedness of both routes of parenteral administration.

With respect to the other pharmacokinetic parameters, both routes yielded similar values. Following intravenous administration, the half-life was 4.4 hours while following subcutaneous administration the half-life was 4.6 hours. In previous, smaller studies in 15 subjects, the elimination half-life for treprostinil was calculated to be 1.4 to 2.9 hours following subcutaneous administration and 52 minutes following intravenous administration.[5,6] This difference may be due in part to

TABLE 1. Summary of Primary Steady-State Pharmacokinetic Parameters

Parameter	Statistic	IV	SC	Bioequivalence Comparison*
AUC_{ss} (hr · ng/mL)	Geom LS Mean	25.67	27.63	92.9 (89.8, 96.1)
	Geom Mean	25.69	27.63	
	CV (%)	22.00	16.22	
$Cmax_{ss}$ (ng/mL)	Geom LS Mean	1.47	1.39	106.0 (99.4, 113.0)
	Geom Mean	1.47	1.39	
	CV (%)	37.51	16.06	

*Bioequivalence comparisons are based on a general linear model for a 2-period crossover design fit using PROC GLM of SAS. Numbers displayed are the ratio of geometric Least Square (LS) means with 90% CI for N = 51 subjects.

assay sensitivity as in the previous studies the lower limit of quantification was 25 pg/mL, compared with 10 pg/mL in this study. In addition previous studies involving intravenous administration were not conducted at steady state.

Treprostinil administered at a dose of 10 ng/kg/min was well tolerated by most subjects. The majority of adverse events reported were mild in severity and all resolved. Adverse events commonly associated with prostacyclin administration were common for both infusion routes and included headache, jaw pain, and nausea. These events occurred at similar rates for each route of administration, thus demonstrating the equivalent systemic safety profile of the 2 routes of administration.

The most prevalent adverse events were related to the treprostinil infusion site when administered by either route. Typical SC infusion events included infusion site pain, infusion site erythema, and an infusion site reaction around the placement of the SC catheter. Peripheral IV infusion events included infusion site erythema, infusion site pain, and infusion site edema. These intravenous infusion site events were similar to findings that have been reported when epoprostenol was administered peripherally.[7] The findings may be a result of the peripheral placement of the IV catheter with possible infiltration of the perivenous tissues resulting in locally occurring adverse events. These events would not be of concern during infusion through a surgically placed central catheter, the route that is employed in patients with PAH.[8] The peripheral route was used for this study because it is inappropriate to administer IV treprostinil to healthy volunteers via a central line due to the risks associated with central venous catheter placement.

TABLE 2. Summary of Secondary Steady-State Pharmacokinetic Parameters

Parameter	Route	Mean	SD	Geom. Mean	CV (%)
$Cavg_{ss}$ (ng/mL)	IV	1.09	0.23	1.06	21.24
	SC	1.15	0.19	1.13	16.27
$Cmin_{ss}$ (ng/mL)	IV	0.76	0.21	0.73	27.05
	SC	0.90	0.19	0.88	20.90
Fluctuation	IV	0.708	0.421	NA	NA
	SC	0.443	0.150	NA	NA

NA, not applicable; N = 51.

From a therapeutic perspective, the pharmacokinetic properties and stability characteristics of treprostinil are potentially advantageous, relative to epoprostenol, with regard to patient convenience and safety. These characteristics include: chemical stability at room temperature, allowing for intravenous infusion without the need for ice packs; longer stability in the delivery system (up to 48 hours at room temperature), which may require patients to mix dosing formulations less frequently; longer half-life (approximately 4 hours), thus minimizing the pharmacologic impact of unintended interruptions/pump malfunctions; and ease of dosage preparation, given that Remodulin is provided as an aqueous solution for ready dilution.

In clinical practice patients with PAH should be transitioned between subcutaneous and intravenous treprostinil with careful monitoring. It is possible that disease symptoms, comorbidities, and concomitant medications could increase individual patient differences in pharmacokinetic parameters compared with healthy volunteers. As is customary practice, dosing of chronic, parenteral therapies in PAH patients must always be conducted under close supervision to titrate the dose to achieve maximal therapeutic benefit with tolerable side effects.

The bioequivalence findings suggest that the safety and efficacy data for subcutaneous treprostinil are directly relevant in evaluating the anticipated safety and efficacy of intravenously administered treprostinil in patients. Treprostinil has been administered by chronic continuous intravenous infusion via a surgically placed central catheter in an ongoing study in

TABLE 3. Summary of Pharmacokinetic Parameters Related to the Full Profile (0–96 hours)

	Intravenous (n = 51)					Subcutaneous (n = 51)				
Parameter	Mean	SD	Geom. Mean	CV (%)	Range	Mean	SD	Geom. Mean	CV (%)	Range
AUC_{inf} (hr · ng/mL)	77.38	12.63	76.37	16.32	55.9–102.7	79.31	11.95	78.44	15.06	58.9–110.3
AUC_{0-96h} (hr · ng/mL)	77.26	12.61	76.25	16.32	55.8–102.6	79.21	11.96	78.34	15.10	59.9–110.2
C_{max} (ng/mL)	1.82	0.94	1.68	51.57	0.95–6.73	1.43	0.22	1.41	15.70	1.0–1.9
T_{max} (hr)	36.39	27.28	21.29	74.96	2.0–69.0	50.27	23.43	36.47	46.61	2.0–69.1
λ_z (1/hr)	0.238	0.123	0.201	51.80	0.03–0.5	0.182	0.068	0.168	37.21	0.04–0.4
$T_{1/2}$ (hr)	4.41	3.98	3.45	90.21	1.4–23.4	4.61	2.72	4.13	59.04	1.9–18.0
CL (mL/min/kg)	9.56	1.59	9.43	16.61	7.0–12.9	9.28	1.39	9.18	14.95	6.5–12.2
V_z (L/kg)	3.65	3.22	2.82	88.29	0.95–16.8	3.71	2.42	3.28	65.22	1.6–16.5

patients with PAH.[8] Preliminary data demonstrates that the intravenous route of administration produces similar effects on exercise capacity compared with subcutaneous administration.

CONCLUSION

Intravenously and subcutaneously administered treprostinil are bioequivalent at steady state. In the 51 subjects who received at least 24 hours of treprostinil administered subcutaneously and intravenously the ratios of the adjusted geometric means and 90% confidence intervals about the ratios of the mean for AUC_{ss} [92.9% (CI 89.8–96.1%)] and $Cmax_{ss}$ [106% (CI 99.4–113%)] met the established guidelines for bioequivalence.

Treprostinil administered by both subcutaneous and intravenous infusion over 72 hours at a rate of 10 ng/kg/min was well tolerated. Systemic (headache, jaw pain, nausea) and infusion site-related adverse events were comparable between the 2 routes of administration and consistent with the known pharmacologic profile of treprostinil.

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