Real-world dosing characteristics and utilization of parenteral treprostinil in the outpatient setting

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Abstract
Real-world dosing and titration of parenteral (subcutaneous, SC; intravenous, IV) prostacyclin, a mainstay of pulmonary arterial hypertension (PAH) treatment, is not always consistent with prescribing information or randomized trials and has yet to be adequately characterized. The current study describes real-world outpatient dosing and titration patterns over time, in PAH patients initiated on SC or IV treprostinil. A longitudinal, cross-sectional analysis of medication shipment records from US specialty pharmacy services between 2009 and 2018 was conducted to determine dosing and titration patterns of SC or IV treprostinil in the outpatient setting beginning with the patient’s first shipment. The sample for analysis included shipment records for 2647 patients (IV = 1040, SC = 1607). Although more patients were started on SC treprostinil than IV, median initial outpatient IV treprostinil dose (11 ng/kg/min at month on therapy one [MOT1]) was consistently and statistically significantly higher than initial outpatient SC dose (7.5 ng/kg/min at MOT1; p < 0.01). However, the SC treprostinil dose acceleration rate (DAR) was more aggressive from MOT1 to MOT6, MOT12, and MOT24, leading to a higher dose achieved at later timepoints. All between-group DAR differences were statistically significant (p < 0.001). This study provides evidence that real-world prescribing patterns of parenteral treprostinil in the outpatient setting differs from dosing described in pivotal trials, with important differences between SC and IV administration. Although initial outpatient IV treprostinil dosing was higher, SC titration was accelerated more aggressively and a higher dose was achieved by MOT3 suggesting that factors specific to SC administration (e.g., site pain) may not limit dosing and titration as previously thought.

Keywords
intravenous prostacyclin, pulmonary arterial hypertension (PAH), subcutaneous prostacyclin, titration patterns
INTRODUCTION

Pulmonary arterial hypertension (PAH), a subgroup of pulmonary hypertension, is characterized by vascular proliferation of the small pulmonary arteries, leading to associated elevated pulmonary vascular resistance, right-side ventricular failure, and death. Symptoms of PAH include progressive dyspnea on exertion, fatigue, and exertional chest pain. Although relatively rare, with an estimated prevalence in the United States of 10.6 cases per one million adults, PAH is a devastating disease with a median survival of approximately 7 years, despite new therapeutic options.

Parenteral prostacyclin formulations have become a mainstay of PAH treatment due to their high receptor potency and resultant consistent therapeutic drug levels. Treatment effectiveness in PAH is achieved by delivering the optimal dose, specific to the patient, while carefully mitigating the occurrence and intensity of any adverse effects which could potentially lead to treatment discontinuation. Treprostinil is a prostacyclin analog used in the treatment of PAH and is available in oral, inhaled, and parenteral (subcutaneous, SC; intravenous, IV) formulations. Remodulin® (treprostinil) Injection was approved by the United States (US) Food and Drug Administration in May 2002 for the treatment of PAH, based on multicenter, randomized studies, completed in 1999. As the ideal prostacyclin dose for individual patients varies extensively, dose titration is essential to achieve and maintain the maximum therapeutic benefit. Per prescribing information, the recommended initial dose for patients new to prostacyclin infusion therapy is 1.25 ng/kg/min and should be increased by 1.25 ng/kg/min per week for the first 4 weeks of treatment followed by 2.5 ng/kg/min per week for the remaining duration of infusion. This dose can be tailored and titrated to clinical response and tolerability, with no ceiling dose.

Despite nearly 20 years of clinical experience with IV and SC treprostinil, real-world dosing and titration patterns, in both the inpatient and outpatient settings, are not always consistent with guidance provided in the prescribing information or cited from randomized clinical trials. As well, reports from the contemporary literature have described the IV and SC doses of treprostinil to be considerably higher than those evaluated in the pivotal studies. Moreover, implementation of treatment paradigms has evolved as clinical experience deepens, guidelines are revised, and tolerability management improves.

Real-world dosing of SC and IV treprostinil has yet to be adequately characterized, therefore the objective of the current study is to describe general trends in real-world outpatient dosing and titration patterns in clinical practice, over time, in patients initiated on SC or IV treprostinil therapy for PAH.

METHODS

Study design

This was a longitudinal, cross-sectional, retrospective analysis of patient medication shipment records from specialty pharmacy services (SPS) between January 1, 2009, and August 15, 2018. This review was designed to describe evaluable differences in general outpatient dosing and titration patterns of parenteral treprostinil by route of administration (SC or IV), prescriber geography, dose acceleration rate (DAR) by route of administration, and dosing based on the patient's clinical characteristics at the time of referral, where available. Changes in dosing, titration patterns, and utilization over time were also characterized and compared.

Study population

Outpatient medication shipment records were included for review and analysis of patients within the United States who received at least one shipment of parenteral treprostinil from their SPS between January 1, 2009, and August 15, 2018. Shipment record data was not available before January 1, 2009.

Record data was available for 3132 patients that were classified as naïve to parenteral treprostinil and were not transitioning from other treprostinil formulations, such as inhaled or oral therapy.

Records were excluded from the analysis if the route of treprostinil administration was not specified as parenteral and if dosing information was not available for the initial outpatient medication shipment or absent for all recorded shipments. Records were also excluded if the shipment date was noted to have occurred later than the discontinuation date if no discontinuation date was noted but the last shipment occurred 4 months or earlier, if duplicate discontinuation information was recorded, if shipment dates were missing, if the initial shipment date was >90 days from the initial start date, or if more than one start date was recorded.

The records for 2647 patients that were administered treprostinil (IV = 1040, 39%; SC = 1607, 61%) met the inclusion criteria and were included in the analysis.

Aside from the shipment delivery method, no other covariates were introduced.

Statistical analyses

Descriptive statistics were performed on all study variables. Continuous variables were summarized as
TABLE 1  Baseline characteristics at time of referral

|                | Overall | SC (n = 1607) | IV (n = 1040) | p value |
|----------------|---------|---------------|--------------|---------|
| WHO FC, n (%)  | N = 626 | N = 399       | N = 227      | 0.05*   |
| I              | 4 (0.6) | 2 (0.5)       | 2 (0.9)       |         |
| II             | 47 (7.5)| 33 (8.3)      | 14 (6.2)     |         |
| III            | 273 (43.6)| 187 (46.9)   | 86 (37.9)     |         |
| IV             | 302 (48.2)| 177 (44.4)   | 125 (55.1)    |         |
| Etiology, n (%)| N = 620 | N = 378       | N = 242      | <0.01   |
| Idiopathic     | 242 (39.0)| 139 (36.8)   | 103 (42.6)    |         |
| CHD            | 70 (11.3)| 59 (15.6)     | 11 (4.5)      |         |
| CTD            | 160 (25.8)| 90 (23.8)     | 70 (28.9)     |         |
| HIV            | 12 (1.9) | 6 (1.6)       | 6 (2.5)       |         |
| Portal hypertension | 28 (4.5)| 20 (5.3)   | 8 (3.3)       |         |
| Other          | 57 (9.2) | 40 (10.6)    | 17 (7)        |         |
| None           | 50 (8.1) | 24 (6.3)     | 26 (10.7)     |         |
| >1 etiology specified | 1 (0.2) | 0 (0)      | 1 (0.4)       |         |
| 6MWD (m)       | N = 114 | N = 72        | N = 42        | 0.08    |
| Mean (SD)      | 289 (137.8)| 306 (147.4) | 260 (115.6)  |         |
| Median (IQR)   | 302 (180, 369)| 307 (181, 405)| 264 (180, 342) |         |
| mPAP (mmHg)    | N = 638 | N = 402       | N = 236      | 0.77**  |
| Mean (SD)      | 53.9 (13.1)| 54.1 (14.1) | 53.7 (11.2)   |         |
| Median (IQR)   | 53 (46, 61)| 53 (45, 62) | 53 (48, 60)   |         |

Abbreviations: 6MWD, six-minute walk distance; CHD, congenital heart disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; IQR, interquartile range; IV, intravenous; mPAP, mean pulmonary artery pressure; SC, subcutaneous; SD, standard deviation; WHO FC, World Health Organization functional class.

*Exact test.

**Nonparametric test.

Means ± standard deviations, medians, and ranges. Categorical variables were summarized as frequency distributions and percentages. Wilcoxon rank–sum tests were used for the comparison of two treprostinil groups nonparametrically.

For analysis, geographic regions of prescribers were defined per United States Census regions and included Northeast, South, Midwest, and West. When available, patient characteristics at the time of referral were collected and summarized.

Dosing reported in SPS shipments were documented as outpatient month on therapy (MOT), which corresponded to the dose noted by the SPS at the beginning of each month. It does not provide detail of dose changes that may have occurred over the course of the month. For patients on ongoing therapy whose shipment records were missing dose specifications, analysis was undertaken using the last observed values and repeated with the last observation carried forward method for imputation of missing dose values. MOT1 outpatient dosing data suggests many patients were initiated on therapy in the inpatient setting.

Dose titration was determined by calculating the DAR, assessing the slope of dose increase between MOT1 and the end of the time period assessed. DAR was compared for each group using Wilcoxon rank–sum tests.

RESULTS

Patient characteristics at the time of referral were available for a small subset of patients in the SC and IV cohorts (Table 1). Etiology was available in 620 patient records (SC = 376; IV = 242). Of those with data available, idiopathic PAH was the most common etiology overall. Compared to the IV treprostinil cohort, congenital heart disease (CHD) was more prevalent in the SC cohort. WHO FC at time of referral was available in
626 patient records (SC = 399; IV = 227). A greater proportion of patients receiving SC treprostinil were WHO functional class III (46.9%), compared to 37.9% in the IV group. Those receiving IV treprostinil had a higher proportion (55.1%) of WHO functional class IV patients than the SC group (44.4%). Due to the limited availability of data on FC at the time of referrals, these findings must be interpreted cautiously.

Geographic variations were evaluated on the basis of the prescriber’s ZIP Code and defined by the geographic regions per US Census regions, including Northeast, South, Midwest, and West. The number of patients per prescriber region is listed in Figure 1. Notably, the distribution of IV and SC between the regions was statistically significant. The majority of patients included in the SC cohort were attributed to prescribers in the West, whereas most patients in the IV cohort were attributed to prescribers in the Midwest.

Dosing

At each year included in the analysis, there were consistently more SC treprostinil starts than IV treprostinil starts, with the highest ratio of SC:IV observed in 2010 at 2.23 and the lowest ratio of 1.27 in 2011 (Figure 2). Although more patients initially received SC treprostinil, the median outpatient starting dose for those receiving IV treprostinil was consistently higher across all years included in the analysis, a finding that was statistically significant for all years between 2010 and 2018, inclusive (Figure 3).

The median outpatient dose, presented as ng/kg/min, for both cohorts at each MOT are shown in Table 2. A higher initial outpatient dose of IV treprostinil, 11 ng/kg/min, was observed at MOT1, compared to the initial SC treprostinil dose of 7.5 ng/kg/min (p < 0.01). At MOT2, the median dose was 17 ng/kg/min for IV treprostinil and 17.1 ng/kg/min for SC treprostinil (p = 0.91). Median doses for both cohorts are shown in Table 2 and Figure 4. Over the study duration, median doses of SC treprostinil trended higher than IV doses (50 vs. 46.4 ng/kg/min, p = 0.02) at MOT12, (58 vs. 50 ng/kg/min, p = 0.01), MOT18, and MOT24 (62 vs. 52 ng/kg/min, p = 0.01).

Dose titration was determined by calculating the DAR, assessing the slope of dose increase between MOT1 and the end of the time period assessed. A comparison of the DAR for each cohort (ng/kg/min/month) is shown in Table 3. Dosing in the SC treprostinil group was accelerated more aggressively from MOT1 to MOT6, MOT12, and MOT24. The differences in all DARs between the two groups were statistically significant (p < 0.001).

Dosing was also characterized by prescriber region and notably, prescribers located in the Northeast region were found to have prescribed the highest doses to patients in the SC treprostinil group, whereas those in the West region prescribed their highest doses in IV treprostinil patients.

![Route of Administration by Prescriber Region](image.png)

*distribution of region is significantly different by route of administration type (p<0.01).
IV: intravenous; SC: subcutaneous

**FIGURE 1** Patients by prescriber region. IV, intravenous; SC, subcutaneous
In addition, overall dosing trends were analyzed to assess changes in dosing patterns as a function of distinct time periods. Any differences observed were considered clinically negligible.

**DISCUSSION**

Achieving the ideal dose of treprostinil parenteral therapy in PAH is critical for effectiveness but must also balance the occurrence and intensity of side effects. The optimal dose of treprostinil can vary widely among individuals, requiring careful dose titration for each patient. Dose titration guidance provided by the prescribing information is based on pivotal studies and may not reflect current clinical practice. These longitudinal data illustrate real-world dosing patterns of patients initiated on SC and IV treprostinil in clinical practice over time. As noted, however, these data are limited to dosing information collected from outpatient medication shipment records and in many cases did not include specific demographic details of patient (age, gender) or disease state (PAH etiology or FC) characterization. The median doses recorded for MOT1 in both the SC and IV cohorts may suggest that patients were started on treprostinil therapy in the inpatient setting, however, this cannot be confirmed from shipment records alone. Furthermore, as some patients remained on therapy at the time of the analysis, discontinuation rates could not be assessed from the current sample.

Our findings demonstrate that despite patients in the IV treprostinil group having a higher initial outpatient dose, those patients in the SC treprostinil group achieved higher doses after MOT2. These differences in dosing were observed when stratified by patient characteristics (e.g., PAH etiology) and prescriber characteristics (e.g., geography), however, we acknowledge that this information was not available for all patients within the sample.

A greater proportion of patients receiving SC treprostinil were WHO functional class III (46.9%), compared to 37.9% in the IV group. Those receiving IV treprostinil had a higher proportion (55.1%) of WHO functional class IV patients than the SC group (44.4%). Improved outcomes are associated with higher treprostinil doses, which interestingly, were achieved on SC therapy as early as MOT2.

Patients receiving SC administration continued to attain higher doses than those receiving IV therapy at 6 months, 1 year, and 2 years of treprostinil therapy. Additionally, SC treprostinil was titrated more aggressively than IV from MOT1 to MOT6, MOT12, and MOT24, highlighting the differences in parenteral treprostinil dosing and titration as a function of route of administration. These results suggest that factors attributed to SC administration (e.g., site pain) may not limit dosing and titration.11,12

![FIGURE 2](image)  
**FIGURE 2** Ratio of subcutaneous (SC) treprostinil starts (initial shipment) compared to intravenous (IV) treprostinil starts by year of data collection

Given the dose–response relationship and the ability to titrate with no ceiling dose, systemic prostacyclin therapy has been well recognized as an effective, long-term therapeutic option with the potential to outpace
When comparing dose levels with the mean doses from pivotal trials, we found that in the real-world outpatient setting, the mean dose of SC treprostinil achieved was 30.2 ± 19.9 ng/kg/min (median 26.0 ng/kg/min) at MOT3, notably higher than the mean dose in the SC treprostinil pivotal study of 9.3 ng/kg/min at 12 weeks.6 These results suggest SC treprostinil titration is much more rapid in the contemporary, real-world, clinical setting. This trend extends well beyond the initial 3 months of therapy. Our SC treprostinil group achieved a mean (±SD) dose of 54.6 (±28) ng/kg/min (median 50.0 ng/kg/min) at MOT12, while in the two open-label extension (OLE) studies of SC treprostinil (2006), the mean dose at 1 year on therapy was 26 and 26.2 ± 1.2 (SD) ng/kg/min, half of the dose of this present study.8,10 The dose in our present analysis continued to be higher than doses observed in OLE studies at 2–4 years on therapy, further supporting the finding that real-world titration of SC treprostinil is variable and dosing more aggressive than previously reported.

The higher doses achieved in our SC treprostinil group may result in improved clinical outcomes, however, outcomes data was not included in shipment records. A recent publication from Ramani et al.13 reported that in their analysis of data from pivotal SC and oral treprostinil studies, higher doses of treprostinil were associated with significantly longer times to first PAH-related and all-cause hospitalization. Additionally, they noted a trend towards improvements in 6-min walk distance with higher doses.13 Although analysis of shipping records does not indicate whether dose titration is a result of disease progression or drug tolerance, achieving a high dose within a short period of time, as we observed with the more aggressive up-titration in our SC treprostinil group, has also been associated with achieving better outcomes. Preston and Farber14 presented their findings at the 2013 ISHLT Annual Meeting, reporting that those patients receiving parenteral treprostinil at higher doses had a lower risk of death, and the highest risk of death was found to be in those patients that did not achieve a dose of at least 20 ng/kg/min within the first 3 months of therapy.

### FIGURE 3
Median outpatient subcutaneous (SC) treprostinil dose (ng/kg/min) at month on therapy 1 (MOT1) (initial shipment) compared to intravenous (IV) treprostinil by year of data collection.

### TABLE 2
Median dosing of subcutaneous (SC) treprostinil compared to intravenous (IV) treprostinil at each month on therapy (MOT)

| Dose (ng/kg/min), median (interquartile range) | SC (N = 1607) | IV (N = 1040) | p value* |
|-----------------------------------------------|---------------|---------------|----------|
| MOT1                                          | 7.5 (2, 17)   | 11 (7, 20)    | <0.01    |
| MOT2                                          | 17.1 (11, 27) | 17 (11, 25)   | 0.91     |
| MOT3                                          | 26 (18, 36)   | 22 (16, 36)   | <0.01    |
| MOT4                                          | 31 (21, 43)   | 27 (18, 40)   | <0.01    |
| MOT5                                          | 36 (24, 50)   | 30 (20, 48)   | <0.01    |
| MOT6                                          | 40 (27, 54)   | 34 (23, 50.4) | <0.01    |
| MOT12                                         | 50 (35, 70)   | 46.4 (31, 62.8) | 0.02 |
| MOT18                                         | 58 (40, 80)   | 50 (35, 70)   | <0.01    |
| MOT24                                         | 62 (40, 83)   | 52 (39, 75)   | <0.01    |

*Nonparametric test; treprostinil IV versus treprostinil SC.

disease progression. When comparing dose levels with the mean doses from pivotal trials, we found that in the real-world outpatient setting, the mean dose of SC treprostinil achieved was 30.2 ± 19.9 ng/kg/min (median dose 26.0 ng/kg/min) at MOT3, notably higher than the mean dose in the SC treprostinil pivotal study of 9.3 ng/kg/min at 12 weeks.6 (Table 4) These results suggest SC treprostinil titration is much more rapid in the contemporary, real-world, clinical setting. This trend extends well beyond the initial 3 months of therapy. Our SC treprostinil group achieved a mean (±SD) dose of 54.6 (±28) ng/kg/min (median 50.0 ng/kg/min) at MOT12, while in the two open-label extension (OLE) studies of SC treprostinil (2006), the mean dose at 1 year on therapy was 26 and 26.2 ± 1.2 (SD) ng/kg/min, half of the dose of this present study.8,10 The dose in our present analysis continued to be higher than doses observed in OLE studies at 2–4 years on therapy, further supporting the finding that real-world titration of SC treprostinil is variable and dosing more aggressive than previously reported.

The higher doses achieved in our SC treprostinil group may result in improved clinical outcomes, however, outcomes data was not included in shipment records. A recent publication from Ramani et al.13 reported that in their analysis of data from pivotal SC and oral treprostinil studies, higher doses of treprostinil were associated with significantly longer times to first PAH-related and all-cause hospitalization. Additionally, they noted a trend towards improvements in 6-min walk distance with higher doses.13 Although analysis of shipping records does not indicate whether dose titration is a result of disease progression or drug tolerance, achieving a high dose within a short period of time, as we observed with the more aggressive up-titration in our SC treprostinil group, has also been associated with achieving better outcomes. Preston and Farber14 presented their findings at the 2013 ISHLT Annual Meeting, reporting that those patients receiving parenteral treprostinil at higher doses had a lower risk of death, and the highest risk of death was found to be in those patients that did not achieve a dose of at least 20 ng/kg/min within the first 3 months of therapy.
therapy. Additionally, Benza et al.\textsuperscript{15} reported that survival was significantly higher for those receiving treprostinil doses $\geq 40$ ng/kg/min and every 10-ng/kg/min increase was associated with further improvements in long-term survival. For comparison, patients in our SC and IV groups achieved median doses of 26 and 22 ng/kg/min, respectively, by Month 3.

Although there were consistently more SC treprostinil starts than IV treprostinil starts at each year included in our analysis, the median starting dose for those receiving IV treprostinil was higher across all years included in the analysis. Somewhat surprisingly, this analysis did not find any significant differences in SC or IV treprostinil dosing trends over time, when results were considered by year or in groupings of 2–5 years. We had anticipated that potential differences may have been apparent as clinical practice patterns have evolved, however, no significant differences were noted.

A more recently published OLE study of IV treprostinil therapy in 16 de novo patients reported a mean $\pm$ SD dose of $41 \pm 4$ ng/kg/min at 12 weeks, whereas our data showed a mean dose of $28.9 \pm 23.2$ ng/kg/min (median 22.0 ng/kg/min) in our IV group at MOT3.\textsuperscript{9} Our IV treprostinil patients achieved a mean $\pm$ SD dose at MOT11 of $50.7 \pm 29.3$ ng/kg/min (median 45.0 ng/kg/min) compared to $98 \pm 9$ ng/kg/min at 48 weeks in the same OLE study.\textsuperscript{9} However, it is important to note that the population in the present analysis is larger and includes multiple sites, compared to the single-site experience presented in the OLE study. Taken together, these findings support that real-world use of parenteral treprostinil has evolved since its initial approval demonstrating that parenteral treprostinil is dosed much higher and titrated more rapidly than has been observed in the pivotal trials.

The authors acknowledge the inherent limitations of a study using data collected from outpatient shipping documentation. Data captured in shipment records is limited to only outpatient doses and does not account for patients whose therapy was initiated in an inpatient setting. Unlike similar studies utilizing shipping records that often lack insight into the baseline characteristics of patients, we were able to access patient data that was entered at the time of referral; however, this was limited by the availability of detail on the patient referral form. Although the patients included in the current analyses were classified as naïve to parenteral treprostinil and not transitioning from another treprostinil formulation, some patients may have been transitioning from other prostanoid class therapies. Our sample size did decrease over the course of the study as patients discontinued therapy or shipping records were unavailable. Only patients that continued on treprostinil therapy were included in the analysis, leading to a selection bias.

This study provides evidence that real-world prescribing patterns of outpatient parenteral treprostinil differs from dosing described in pivotal trials, with

![FIGURE 4](image_url) Median outpatient dosing of subcutaneous (SC) treprostinil compared to intravenous (IV) treprostinil at each month on therapy

| TABLE 3 | Median dose acceleration rate (DAR) of SC treprostinil compared to IV treprostinil |
|-----------------|-----------------|-----------------|-------------------|
| DAR (ng/kg/min/month), median (IQR) | SC | IV | $p$ value* |
| MOT1–MOT6 | 5.2 (2.8, 8) | 3.8 (1.6, 6) | <0.001 |
| MOT1–MOT12 | 3.4 (1.8, 5.1) | 2.6 (1.3, 4.1) | <0.001 |
| MOT1–MOT24 | 2 (1.1, 3) | 1.6 (0.8, 2.5) | <0.001 |

Abbreviations: IQR, interquartile range; MOT, month on therapy.
*Nonparametric test.
important differences demonstrated between SC and IV routes of administration. While initial outpatient dosing of IV treprostinil was higher, titration of SC treprostinil was accelerated more aggressively. In addition, a higher dose was achieved at Month 3 and continued to Month 6, resulting in a significant difference in dose acceleration rate, suggesting that factors specific to SC administration (e.g., site pain) may not be as limiting as previously thought. It may also be a reflection of physicians’ increasing experience with higher treprostinil doses and their ability to more effectively manage potential adverse events since the era of initial approval.

ACKNOWLEDGMENTS
This study was sponsored by United Therapeutics Corporation. The authors would like to thank Youlan Rao, Ph.D. (United Therapeutics Corporation) for statistical expertise and Charlie McPherson (United Therapeutics Corporation) for the analytical support provided in the conduct of the study.

CONFLICT OF INTERESTS
Lana Melendres-Groves has received honoraria and/or fees for consultancy and advisory committees from United Therapeutics Corporation, outside of the submitted work; Zeenat Safdar has received honoraria and/or fees for consultancy and advisory committees from United Therapeutics Corporation, Bayer Pharmaceuticals, Actelion Pharmaceuticals, Boehringer Ingelheim, and Genentech, outside the submitted work. Margaret R. Sketch, Meredith Broderick, and Andrew C. Nelsen are employees of United Therapeutics Corporation. Dasom Lee has nothing to disclose. Vijay P. Balasubramanian has received research support, honoraria, and/or fees for consultancy and an advisory committee from United Therapeutics Corporation, speaker bureau, and advisory committee honoraria and/or fees from Bayer Pharmaceuticals, and speaker bureau honoraria and/or fees from Boehringer Ingelheim, outside the submitted work.

ETHICS STATEMENT
Not applicable.

AUTHOR CONTRIBUTIONS
Lana Melendres-Groves, Zeenat Safdar, and Vijay P. Balasubramanian contributed to the study design, data analysis, and writing of the manuscript. Margaret R. Sketch, Meredith Broderick, and Andrew C. Nelsen contributed to the study design, data analysis, writing of the manuscript, and acquisition of funding. Dasom Lee contributed to the study design and data analysis.

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How to cite this article: Balasubramanian VP, Safdar Z, Sketch MR, Broderick M, Nelsen AC, Lee D, Melendres-Groves L. Real-world dosing characteristics and utilization of parenteral treprostinil in the outpatient setting. Pulm Circ. 2022;12:e12016. https://doi.org/10.1002/pul2.12016