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LONG-TERM OUTCOME IN PULMONARY ARTERIAL HYPERTENSION PATIENTS TREATED WITH TREPROSTINIL

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Abstract

Pulmonary arterial hypertension (PAH) is fatal if untreated. Intravenous epoprostenol improves exercise capacity and hemodynamics in PAH, and increases survival in idiopathic PAH (IPAH). To evaluate the effects of subcutaneous (SC) treprostinil, a longer acting prostacyclin analogue, followed by the addition of other PAH therapies if needed, we followed 860 PAH patients treated with SC treprostinil for up to 4 years.

Survival is reported as Kaplan-Meier estimates; for 332 IPAH patients with baseline hemodynamics, observed survival is also compared with predicted survival, using the NIH formula.

Of the total 860 patients, 199 (23%) discontinued due to AEs, 136 (16%) died, 117 (14%) discontinued due to deterioration, 29 (3%) withdrew consent and 11 (1%) underwent transplantation. 97 patients (11%) switched from SC treprostinil to an alternative prostacyclin analogue; bosentan was added in 105 patients (12%) and sildenafil in 25 patients (3%).

Survival was 87%-68% over 1-4 years for all 860 patients and 88%-70% over 1-4 years with SC treprostinil monotherapy. For the IPAH subset with baseline hemodynamics (n=332), 91%-72% over 1-4 years; in contrast, predicted survival was 69%-38% over 1-4 years. The safety profile for long-term SC treprostinil was consistent with previous short-term trials with no unexpected AEs.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a disease that leads to a progressive increase in pulmonary vascular resistance and right heart failure [1, 2]. In 1980, the NIH established an IPAH registry (previously termed primary pulmonary hypertension) that described the characteristics of IPAH and its natural history over a 5-year period. The median survival was 2.8 years, with survival rates of 68%, 48%, and 34% at 1, 3, and 5 years, respectively [3]. Despite therapeutic advances, PAH remains a life threatening disorder without a cure. In 1995, IV epoprostenol was FDA approved for the treatment of severe IPAH and subsequently approved in 2000 for PAH related to the scleroderma spectrum of disease [4, 5]. The first oral therapy, bosentan, an endothelin receptor antagonist, was approved in 2001 [6] and the prostacyclin analogue treprostinil was approved for continuous subcutaneous (SC) infusion in 2002 [7]. In 2004, the prostacyclin analogue iloprost was approved via inhalation [8] and in 2005, the oral phosphodiesterase inhibitor sildenafil was approved [9].

Treprostinil is a prostacyclin analogue that possesses similar pharmacologic actions to epoprostenol, including vasodilatation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation [10,11]. However, epoprostenol therapy is associated with problems due to its short half-life (3-6 minutes) [12], necessitating continuous IV infusion via a central venous catheter. Treprostinil, unlike epoprostenol, is stable at room temperature and neutral pH and has an elimination half-life of 4½ hours (with a distribution half-life of 40 minutes) [13]. These properties permit the delivery of treprostinil via SC infusion. However, SC treprostinil therapy can be limited by pain at the SC infusion site.

A placebo-controlled pilot study evaluating the safety and efficacy of SC treprostinil infusion in 26 PAH patients [13] found favorable trends in exercise capacity, dyspnea and hemodynamics.

Subsequently, two double-blind, randomized, placebo-controlled 12-week studies in a total of 470 patients demonstrated that SC treprostinil therapy improves exercise capacity and hemodynamics [7]. Patients who participated in these controlled studies were eligible to enroll in an open-label extension study; in addition, *de novo* patients were also eligible to enroll in the open-label study. Subjects who participated in these studies received SC treprostinil therapy for up to 4 years. The objectives of this open label study were to retrospectively analyze the effects of SC treprostinil monotherapy (as well as SC treprostinil therapy with the addition of other PAH therapies if needed) on outcomes in PAH. In a subset of patients with IPAH in whom baseline hemodynamic measurements were available, we also compared observed survival with predicted survival, determined using the formula of D'Alonzo et al based on the NIH Registry data [3].

METHODS

Patients

Patients evaluated in these analyses were enrolled in the three placebo-controlled trials of SC treprostinil in PAH [7, 13]; *de novo* patients were also eligible if they met the following entry criteria: NYHA functional class (FC) II, III or IV PAH, either idiopathic or associated with connective tissue disease, congenital heart disease, portal hypertension or HIV. Additional entry criteria included: age ≥8 years, mean pulmonary artery pressure ≥25 mmHg, mean pulmonary capillary wedge pressure ≤15 mmHg, pulmonary vascular resistance >3 units (measured or calculated by right heart catheterization) and 6-minute walk distance 50-450 m. Patients had no previous exposure to prostaglandins or their analogues; background PAH therapies, e.g. anticoagulants, oral vasodilators, cardiac glycosides, diuretics, and supplemental oxygen, were administered at the discretion of the treating physicians. Treprostinil was administered as a continuous SC infusion via an ambulatory micro-infusion pump. Patients randomized to treprostinil in a prior controlled study continued receiving treprostinil at the same dose they were

receiving at the end of that study with subsequent dose adjustments based on investigator discretion. Patients receiving placebo in previous controlled studies and *de novo* patients started treprostinil at a dose of 1.25 ng/kg/min with dose increases based on PAH signs and symptoms, and side effects.

All studies were conducted in accordance with the Amended Declaration of Helsinki in North America, Europe, Australia and Israel sites. Studies were approved by local ethics review committees. Written informed consent was obtained from all patients.

In addition to treatment with chronic SC treprostinil, the use of additional PAH treatments was at the discretion of the treating physicians. Patients continued in the study until: death, transplantation, initiation of intravenous, inhaled or oral prostaglandins or their analogues, or an intolerable adverse event.

Data on vital status, safety and additional or alternative treatments were collected from June 25, 1998 to December 1, 2003 (data cutoff).

Statistical Analyses

Baseline parameters were recorded at the start of treprostinil treatment. Survival was assessed from the start of treprostinil to death or data cutoff. All treprostinil treated PAH patients were included in the analyses (intent to treat). The Kaplan-Meier method was used to estimate the proportion of patients surviving at each time point. The date of initial treprostinil dosing was used as the index date for determining survival. Patients were censored if they underwent transplantation or discontinued treprostinil. Survival rates were also estimated for patients treated with SC treprostinil monotherapy, censoring patients when additional PAH treatment was added.

A separate analysis of survival was performed for the subgroup of patients with IPAH with available baseline hemodynamics. Expected survival was calculated for each IPAH patient based on the NIH formula [3]. Possible predictors of survival were tested using a proportional hazards model. All variables were fit simultaneously to estimate hazard ratios. Sensitivity analyses were carried out to determine if patients who discontinued due to AEs differed from the remainder of the cohort with respect to baseline demographic and clinical characteristics including known PAH risk factors, e.g. PAH etiology, FC, hemodynamic parameters, or the time from diagnosis to the initiation of SC treprostinil therapy.

Safety was evaluated by adverse events (AEs) and laboratory values. Laboratory values were summarized descriptively at baseline and every 6 months thereafter. Baseline was defined as the measurement just prior to the first dose of treprostinil in either the controlled studies or open-label study. AEs were recorded throughout the study. An AE was considered treatment emergent if it first occurred or worsened following treprostinil initiation, and treatment related if it was considered by the investigator to be possibly or reasonably attributable to treprostinil treatment.

RESULTS

Patient Population

All 860 patients were included in the analyses. Six-hundred-fifty-three patients were female (76%); 711 were Caucasian (83%), 63 Hispanic (7%), 48 African origin (6%), 23 Asian (3%), 11 'Other' race (1%), and 4 Native American (<1%). Mean age was 46 years (range, 5 to 84 years). Thirty-two (4%) patients were ≤16 years of age, and 21 (2%) patients were ≥75 years of age.

PAH history at time of enrollment is summarized for the 860 patients in Table 1. The initial PAH diagnosis was made an average of 42 months before enrollment. The most common diagnosis for the 860 patients was IPAH (48%; 412). Thirteen (2%) patients were HIV positive and HIV status was unknown for an additional 41 (5%) patients. Patients had been at their current NYHA FC for a mean of 15 months before enrollment; the majority of patients were NYHA FC III (76%; 654) at baseline.

Patient Disposition

Patient disposition is summarized in Table 2. A total of 860 patients were treated with SC treprostinil including 423 (49%) who entered from controlled clinical studies and 437 (51%) *de novo* patients. Of the 423 patients who had previously participated in a controlled clinical study, 205 patients had received treprostinil and 218 patients had received placebo.

As of December 1, 2003, 354 (41%) of the 860 treated patients remained on treprostinil and 506 (59%) had discontinued (Table 2). Mean duration of exposure for the 354 patients was 135 weeks (SD 41 weeks). Of the total 860 treated patients, 23% (199/860) discontinued due to AEs, 16% died (136/860), 14% (117/860) discontinued due to deterioration, 3% (29/860) withdrew consent, 1% (11/860) underwent transplantation, 1% (10/860) were withdrawn due to a protocol violation, and <1% (4/860) were lost to follow-up. The 199 AEs that led to discontinuation were predominantly related to study drug, i.e. infusion site pain and/or reaction (n=196). However, the dropout rate for site pain demonstrates (Figure 1) that if the patient discontinued treatment with SC treprostinil due to site pain, it was most likely to occur during the first year of treatment (Figure 2). In addition, sensitivity analyses did not demonstrate any significant differences between the patients who dropped out due to site pain vs. those who did not.

Concomitant PAH Medications

While all patients were started on SC treprostinil as PAH monotherapy, the addition of other PAH treatments was at the discretion of the treating physician. Ninety-eight patients were started on alternative prostacyclin analogues during the study, i.e. IV epoprostenol, n=84, inhaled iloprost, n=8, and oral beraprost, n=6; 97 of these patients were transitioned off SC treprostinil to the alternative prostacyclin analogue; one patient had inhaled iloprost added during the study, however, it was discontinued after 8 days. In addition, during the study, bosentan was initiated in 12% (105/860) of patients and sildenafil was added in an additional 3% (25/860) of patients. None of the patients were treated with both bosentan and sildenafil in addition to SC treprostinil.

Duration of Exposure and Changes in Mean Doses Over Time

Continuous SC treprostinil was administered to 538 (63%) patients for 1 year, 312 (36%) patients for 2 years, 135 (17%) patients for 3 years, and 13 (2%) patients for 4 years. As of December 1, 2003, 860 patients had received treprostinil for a total of 1419 patient-years, with exposure up to 4½ years. The average dose increased from 1.25 ng/kg/min at initiation to 26, 36, 42, and 42 ng/kg/min at 1, 2, 3 and 4 years, respectively.

Survival Analyses

Kaplan-Meier survival rates for the 860 treated patients, including 412 with IPAH and 448 with PAH related to other conditions, were 87%, 78%, 71%, and 68% at 1, 2, 3, and 4 years, respectively (Figure 3). Survival rates with SC treprostinil monotherapy, censoring patients when additional targeted PAH therapy was added (130/860 patients, i.e. 15% of the total cohort

received additional PAH treatment), were 88%, 79%, 73%, and 70% at 1, 2, 3, and 4 years, respectively (Figure 4), not significantly different than for the entire cohort. In addition, due to the significant drop out rate due to site pain during the first year of treatment, survival rates were estimated for patients treated with SC treprostinil for at least one year; survival rates 90%, 82%, and 79% at 2, 3, and 4 years, respectively (Figure 5).

Of the 412 IPAH patients, baseline hemodynamics were available for 332; PAPm: 59 ± 13 (m ± SD) mmHg, RAPm: 10 ± 5 mmHg and cardiac index: 2.2 ± 0.7 L/min/m^2. Baseline clinical characteristics and demographics for these 332 IPAH patients are shown in Table 3. Observed survival rates for these 332 IPAH patients were 91%, 82%, 76% and 72% at 1, 2, 3, and 4 years, respectively; in contrast, expected survival rates (calculated for each patient based on the NIH formula) were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively (Figure 6).

Survival rates were highest for FC II patients (n=128) at study entry, with survival rates of 91%, 84%, 79% and 74% at 1, 2, 3, and 4 years, respectively. Survival rates for FC III patients (n=654) were 88% 79%, 72%, and 70% at 1, 2, 3, and 4 years, respectively, while survival rates for FC IV patients (n=78) were 71%, 62% and 52% at 1, 2 and 3 years, respectively (Figure 7).

Predictors of Survival

Complete baseline demographic, clinical characteristics and hemodynamics were available in 432 PAH patients. Although the associations of both mixed venous oxygen saturation, and pulmonary vascular resistance with survival were statistically significant [p=0.01, HR (95%CI)=0.98 (0.96,0.99) and p=0.04, HR (95% CI)=1.03 (1.002, 1.05) respectively], the

magnitude of these associations was small. However, in the IPAH subset (baseline parameters available in 265 patients), the association between FC and survival was significant statistically and in magnitude [FC IV vs. FC III, p=0.001, HR (95% CI)=5.35 (1.96, 14.56) and FC IV vs. FC II, p=0.002, HR (95% CI)=8.74 (2.23, 34.21)].

Clinical Laboratory Values

All mean chemistry, hematology, coagulation, and urinalysis values were within normal ranges throughout the 4 years of treatment.

Adverse Events

Deaths – A total of 168 patients died during the study or within 30 days after study discontinuation. One death was attributed to treprostinil by the investigator; the cause of this death was reported as progressive PAH; this patient had been receiving treprostinil for 1123 days and was receiving 45 ng/kg/min at the time of death.

Serious Adverse Events (SAEs)– A total of 415 patients had at least one SAE, with 62 (7%) patients having a SAE attributable to treprostinil. Overall, the reported SAEs were typical of patients with PAH and included heart failure (14%; 122), pulmonary hypertension (9%; 76), syncope (4%; 38), pneumonia (4%; 37), and dyspnea (3%; 28). SAEs attributable to treprostinil included site infection (n=9), systemic hypotension (n=8), site pain (n=7), dyspnea (n=4), syncope (n=4), and heart failure (n=4).

Adverse Events (AEs) (Table 4) – The most frequently reported AEs were infusion site pain (92%; 792/860 patients) and site reaction (81%; 700/860). Infusion site reactions were defined

as any local AE other than pain, bleeding or bruising at the infusion site and were most often erythema, swelling, induration, or rash. There were no reported episodes of catheter-related sepsis. Other less frequently observed treatment-related site events were bleeding/bruising (20%; 170) and infection (4%; 35).

Treatment-related events rated as severe in intensity for at least 1% of patients were headache (1.7%; 15), pain (1.4%; 12), diarrhea (1.3%; 11), and nausea (1.2%; 10). Headache was the only treatment-related AE, other than site events, that led to discontinuation for at least 5 (0.6%) patients. Treatment-related events leading to a dose reduction in at least 1% of patients were: diarrhea (6.6%; 57), headache (6.3%; 54), nausea (6.2%; 53), vomiting (2.7%; 23), pain (2.4%; 21), vasodilatation (2.4%; 21), dizziness (2.3%; 20), jaw pain (1.7%; 15), systemic hypotension (1.6%; 14), and anorexia (1.0%; 9).

Prostacyclin-Related Effects – All treatment-emergent AEs reported in at least 10% of the 860 patients were well-characterized side effects of prostacyclin and its analogues, e.g.: diarrhea (42%; 365), nausea (27%; 235), headache (25%; 214), jaw pain (23%; 195), pain (16%; 139), vasodilatation (13%; 115), anorexia (10%; 89), and rash (10%; 88).

Delivery System Complications – Delivery system complications were reported in 30% (255/860) of patients. These complications were most often due to pump malfunction reported in 26% (222/860) of patients, or infusion set complications reported in 9% (74/860) of patients. Pump failures were managed by correcting the alarm condition and/or substituting the backup pump with no reported incidences of clinically significant deterioration occurring in association with the drug delivery system malfunction.

Overdose – Overdoses were reported due to programming errors (3 patients), accidental bolus infusions (4 patients), concentration increases without rate decreases (6 patients), and infusion set replacement following catheter dislodgement (1 patient).

Hemorrhagic Events – Hemorrhagic events not related to the infusion site were epistaxis (2%), ecchymosis (1%), hemoptysis (1%), and hemorrhage (<1%). These events did not appear to be related to the treprostinil dose. One patient was hospitalized for gastrointestinal hemorrhage and one patient for epistaxis. Both of these events resolved without sequelae. These were the only hemorrhagic events rated as severe in intensity, and the gastrointestinal hemorrhage was the only hemorrhagic event leading to discontinuation.

Thrombocytopenia was reported as a treatment-related event for 6 (0.7%) patients with 1 (0.1%) requiring hospitalization and 2 (0.2%) reporting thrombocytopenia as a severe event; all events resolved. One of these 6 patients had PAH associated with portopulmonary hypertension; this patient reported a single, mild episode of thrombocytopenia which resolved in 31 days.

Renal and Hepatic Failure – Renal (n=12) and hepatic failure (n=3) were infrequent and appeared not to be associated with treprostinil.

DISCUSSION

In the present study, the observed survival rates over 1 to 4 years were 87% to 68% for the entire cohort of 860 PAH patients treated with SC treprostinil. Survival rates with SC treprostinil monotherapy were 88% to 70% over 1 to 4 years, not significantly different than for the entire cohort nor for the cohort of patients excluding those who received combination therapy in whom survival rates were 84% to 63% over 1 to 4 years (data not shown). For the IPAH patients,

observed survival rates over 1 to 4 years were 91% to 72% compared with predicted survival rates of 69% to 38% [3]. Survival was also evaluated in this study by FC at treatment initiation. This analysis was performed because poor survival has been associated with FC in various studies, e.g. IPAH patients from the NIH Registry, IPAH patients treated with IV epoprostenol, and IPAH patients treated with oral bosentan [3, 14, 15, 16]. Historically, survival for FC III and IV patients from the NIH Registry was 32 and 6 months, respectively [3]. Results in the present study were consistent with the NIH Registry with improved survival rates for patients who were FC II at study entry (observed survival 91%, 84%, 79%, and 74% at 1, 2, 3, and 4 years, respectively; n=128) vs. FC III (88%, 79%, 72%, and 71% at 1, 2, 3, and 4 years, respectively; n=654) or FC IV (71% at 1 year, 62% at 2 years and 52% at 3 years; n=78).

Observational studies have demonstrated a survival benefit in IPAH with warfarin [17, 18], and with chronic calcium channel blockers in the small subset of IPAH patients who demonstrate acute pulmonary vasoreactivity [19]. In the 12-week randomized open-label trial of 81 FC III and IV IPAH patients, survival was improved in patients treated with IV epoprostenol compared with patients treated with conventional therapy alone [4]. Since that study, several observational studies have confirmed a long term survival benefit in FC III and IV IPAH patients treated with IV epoprostenol when compared with either historical controls or predicted survival based on the NIH Registry equation [14, 15]. In a recently published literature review from 1992-2002, survival rates were reported for IPAH patients treated with conventional therapy alone vs. IV epoprostenol plus conventional medical therapy; the 1, 2, and 3 year survival rates were 72%, 53%, and 48%, respectively, for patients who did not receive IV epoprostenol vs. 82%, 74% and 62%, respectively, for patients who received IV epoprostenol [2]. The observed and predicted survival rates from the observational epoprostenol studies are similar to the observed and predicted survival rates for the IPAH patients in our study. However, life-threatening AEs

associated with IV epoprostenol, such as sepsis and drug interruption, are unlikely to occur with SC treprostinil.

Subsequently, McLaughlin et al reported improved survival in 169 IPAH patients treated with oral bosentan: the 1, 2, and 3 year observed survival rates were 96%, 89%, and 86%, respectively, compared with NIH predicted survival rates of 69%, 57%, and 48%, respectively [16]. In addition, survival in IPAH patients treated with first-line bosentan has been compared with first line IV epoprostenol [20]. Thus, while these survival rates are similar to those we report in the present study with SC treprostinil, clinical trials cannot be directly compared with each other (Table 5).

More recently, Provencher et al reported that in an IPAH cohort treated with bosentan, many patients required the addition of another targeted PAH therapy during long term follow-up [21]; in addition, Opitz et al have also reported the need to add another PAH therapy in a cohort of IPAH patients treated with first-line inhaled iloprost [22]; both studies, not inconsistent with the observations made in the present study.

In the SC treprostinil 12-week randomized clinical trials, although 84% of patients on active drug reported site pain, 27% of patients on placebo also reported site pain. Site pain is a major drawback with SC treprostinil therapy. In this open-label extension study, 23% of the patients discontinued due to adverse events with 98% of these discontinuations due to site pain. However, almost 70% of these dropouts occurred within the first year. For those patients who remained on SC treprostinil for one year, survival rates were 90% to 79% at 2 to 4 years. For the majority of patients, long-term SC treprostinil therapy was well tolerated in patients who had minimal site pain. Prostacyclin-related side effects were controlled by dose adjustment, and no

clinically significant changes in laboratory values were observed. The longer half-life of treprostinil makes an exacerbation of PAH symptoms resulting from abrupt cessation of drug less likely to occur with treprostinil than with epoprostenol. In addition, serious complications associated with a continuous IV infusion, e.g. sepsis, thromboembolic events, are unlikely to occur with a SC infusion treatment. In 2004, treprostinil was also FDA approved for continuous IV administration, an alternative option for patients intolerant to SC treprostinil as well as an alternative to IV epoprostenol. Potential advantages of IV treprostinil over IV epoprostenol include better stability, easier drug preparation and longer duration of activity [23, 24].

There are several important limitations to this observational study. The use of the NIH Registry equation as opposed to a parallel placebo-treated or historical control group is a significant limitation. The NIH equation is based on data from the 1980s and background practice patterns have changed over the past 2 decades. In addition, the 23% discontinuation rate during the study due to AEs (predominantly site pain) cannot exclude a selection bias. However, analyzing the patients who dropped out due to site pain vs. those that did not, did not demonstrate any significant differences between the two groups with respect to know PAH risk factors, such as FC, PAH etiology, or hemodynamic parameters at the time of SC treprostinil initiation. Additional limitations in this observational study include: as the treprostinil doses these patients were on are lower than the overall doses patients are currently on, whether higher doses may have affected outcome remains to be studied. In addition, with either bosentan or sildenafil initiated in 15% of patients, this study cannot adequately address the effects of SC treprostinil monotherapy on survival in PAH.

In conclusion, having multiple therapeutic options available for PAH patients should improve the efficacy in treating PAH. The selection of an “optimal” medical regimen for an individual

patient should be based on a risk-benefit assessment of all treatment options available. While SC treprostinil may not be the drug of first choice for most PAH patients, having SC treprostinil as a therapeutic option may improve outcome in PAH.

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TABLE 1.
PAH History

Total enrolled, n	860
Idiopathic Pulmonary Arterial Hypertension, n (%)	412 (48)
Idiopathic Pulmonary Arterial Hypertension associated with –	
Congenital systemic to pulmonary shunts, n (%)	177 (21)
Diffuse cutaneous systemic sclerosis, n (%)	72 (8)
Thromboembolic disease, n (%)	49 (6)
Portopulmonary hypertension, n (%)	43 (5)
Systemic lupus erythematosus, n (%)	35 (4)
Limited cutaneous systemic sclerosis, n (%)	28 (3)
Mixed connective tissue disease, n (%)	27 (3)
HIV, n (%)	13 (2)
Overlap syndrome, n (%)	4 (<1)
Months Since Diagnosis	
Mean (SD)	42 (74)
Human Immunodeficiency Virus	
No, n (%)	806 (93)
Yes, n (%)	13 (2)
Unknown, n (%)	41 (5)
NYHA Functional Class at Baseline	
II, n (%)	128 (15)
III, n (%)	654 (76)
IV, n (%)	78 (9)
Months at Baseline WHO Functional Class	
Mean (SD)	15 (31)

TABLE 2.
Patient Disposition

Total enrolled, n	860
Total enrolled in previous controlled study, n (%)	423 (49)
Randomized to receive treprostinil in previous study, n	205
Randomized to receive placebo in previous study, n	218
De novo patients, n (%)	437 (51)
Completed[†], n (%)	331 (38)
Prematurely discontinued, n (%)	506 (59)
Ongoing (as of 01 December 2003), n (%)	23 (3)
Reason for premature discontinuation, n (% of total; % of discontinuations)	
Death	136 (16; 27)
Transplantation	11 (1; 2)
Clinical deterioration/rescue therapy	117 (14; 23)
Withdrew consent	29 (3; 6)
Adverse event	199 (23; 39)
Protocol violation	10 (1; 2)
Lost to follow-up	4 (<1; 1)

[†]transitioned to commercial drug

TABLE 3.
Baseline Demographics and Clinical Characteristics in IPAH Patients[†]

Subjects n	332
Age yrs	45 ± 15
Sex n (%)	
Male	74 (22)
Female	258 (78)
Months from diagnosis	28 ± 45
NYHA Functional class at baseline n (%)	
II	53 (16)
III	262 (79)
IV	17 (5)
Months at baseline WHO functional class	13 ± 21
PAPm mmHg	59 ± 13
RAPm mmHg	10 ± 5
CI L/min/m^2	2.2 ± 0.7

m ± SD
[†]IPAH patients with baseline hemodynamic parameters
PAPm = mean pulmonary artery pressure; RAPm = mean right atrial pressure; CI = cardiac index.

TABLE 4. Adverse Events		**Number of patients (n=860)** **n (%)**
Serious adverse events		415 (48)
	Heart failure	122 (14)
	Pulmonary hypertension	76 (9)
	Syncope	38 (4)
	Pneumnoia	37 (4)
	Dyspnea	28 (3)
Serious adverse events attributable to treprostinil		62 (7)
	Site infection	9 (1)
	Systemic hypotension	8 (1)
	Site pain	7 (1)
	Dyspnea	4 (<1)
	Syncope	4 (<1)
	Heart failure	4 (<1)
Adverse events		
	Infusion site pain	792 (92)
	Site reaction	700 (81)
	Bleeding/bruising	170 (20)
	Infection	35 (4)
Treatment related events		
	Headache	15 (2)
	Pain	12 (1)
	Diarrhea	11 (1)
	Nausea	10 (1)
Treatment related events leading to dose reduction		
	Diarrhea	57 (7)
	Headache	54 (6)
	Nausea	53 (6)
	Vomiting	23 (3)
	Pain	21 (2)
	Vasodilatation	21 (2)
	Dizziness	20 (2)
	Jaw Pain	15 (2)
	Systemic hypotension	14 (2)
	Anorexia	9 (1)
Prostacyclin related effects		
	Diarrhea	365 (42)
	Nausea	235 (27)

	Headache	214 (25)
	Jaw pain	195 (23)
	Pain	139 (16)
	Vasodilation	115 (13)
	Anorexia	89 (10)
	Rash	88 (10)
Delivery system complications		255 (30)
	Pump malfunction	222 (26)
	Infusion set complications	74 (9)
Overdose		
	Programming error	3 (<1)
	Accidental bolus	4 (<1)
	Concentration increase without rate decrease	6 (1)
	Infusion set replacement following catheter dislodgement	1 (<1)
Hemorrhagic events		
	Epistaxis	(2)
	Ecchymosis	(1)
	Hemoptysis	(1)
	Hemorrhage	(<1)
	Thrombocytopenia	6 (1)
	Thrombocytopenia related hospitalization	1 (<1)
	Severe thrombocytopenia	2 (<1)
Renal and hepatic failure		
	Renal failure	12 (1)
	Hepatic failure	3 (<1)

TABLE 5. [14, 16, 20]
IPAH Patients Treated With Intravenous Epoprostenol, Oral Bosentan, or Subcutaneous Treprostinil: Baseline Characteristics, Observed Survival and Predicted Survival (NIH Registry)

	IV Epoprostenol (n=162)[1]		Oral Bosentan (n=169)[2]		SC Treprostinil (n=332)		IV Epoprostenol (n=83)[3]	Oral Bosentan (n=83)[3]
PAPm mmHg	61 ± 13		57 ± 16		59 ± 13		59 ± 15	57 ± 15
RAPm mmHg	14 ± 6		10 ± 6		10 ± 5		10 ± 5	10 ± 5
CI L/min/m^2	1.8 ± 0.6		2.4 ± 0.8		2.2 ± 0.7		2.1 ± 0.6	2.2 ± 0.6
NYHA Class n (%)								
I/II	--		15 (9)		53 (16)		--	--
III	75 (46)		139 (82)		262 (79)		83 (100)	83 (100)
IV	87 (54)		15 (9)		17 (5)		--	--
Survival Rates %	Observed	NIH Predicted	Observed	NIH Predicted	Observed	NIH Predicted	Observed	Observed
1 year	88	59	96	69	88	69	93	95
2 years	76	46	89	57	80	56	89	87
3 years	63	35	86	48	74	46	78	82
4 years	56	NA	NA	NA	69	38	NA	NA

1. McLaughlin et al. Circulation 2002
2. McLaughlin et al. ERJ 2005
3. Sitbon et al. Thorax 2005

m ± SD; NA = not available

PAPm = mean pulmonary artery pressure; RAPm = mean right atrial pressure; CI = cardiac index.

Figure Legends:

Figure 1. Kaplan-Meier Time to Discontinuation Due to Site Pain in all SC Treprostinil-treated PAH Patients (n=860). Discontinuation estimates (95% CIs) were 83% (81%, 86%) at 1 year, 75% (72%, 78%) at 2 years, 70% (66%, 74%) at 3 years and 67% (62%, 72%) at 4 years.

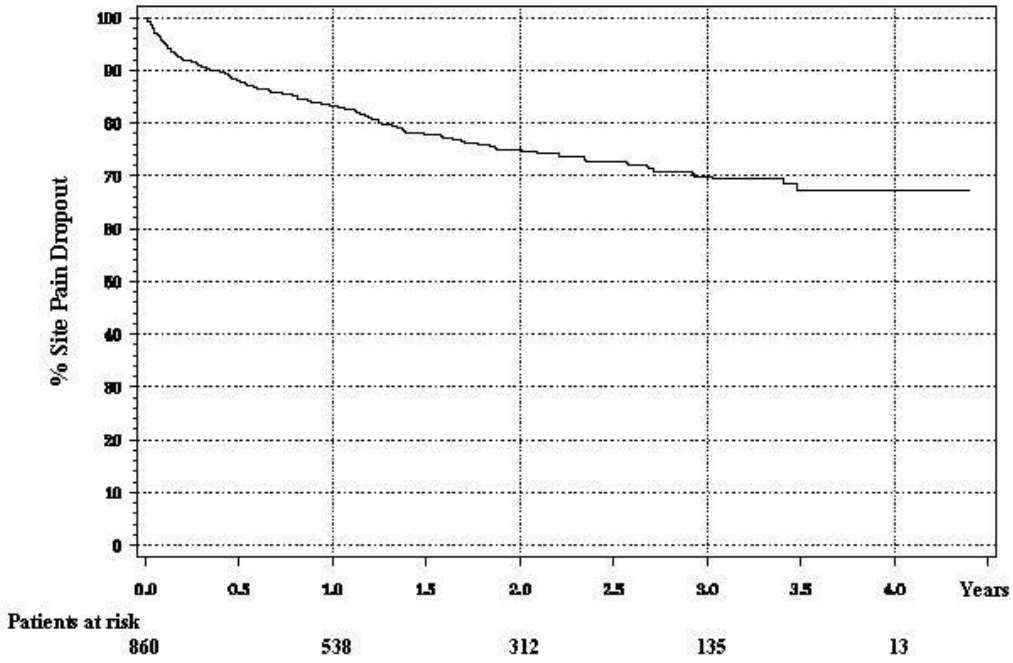


Figure 2. Kaplan-Meier Estimate of Time to Discontinuation due to Site Pain in the 196 Patients who Discontinued SC Treprostinil Therapy Due to Site Pain. Time to

discontinuation estimates (95% CIs) were 34% (27%, 40%) at 1 year, 9% (6%, 14%) at 2 years and 1.5% (0.4%, 4%) at 3 years.

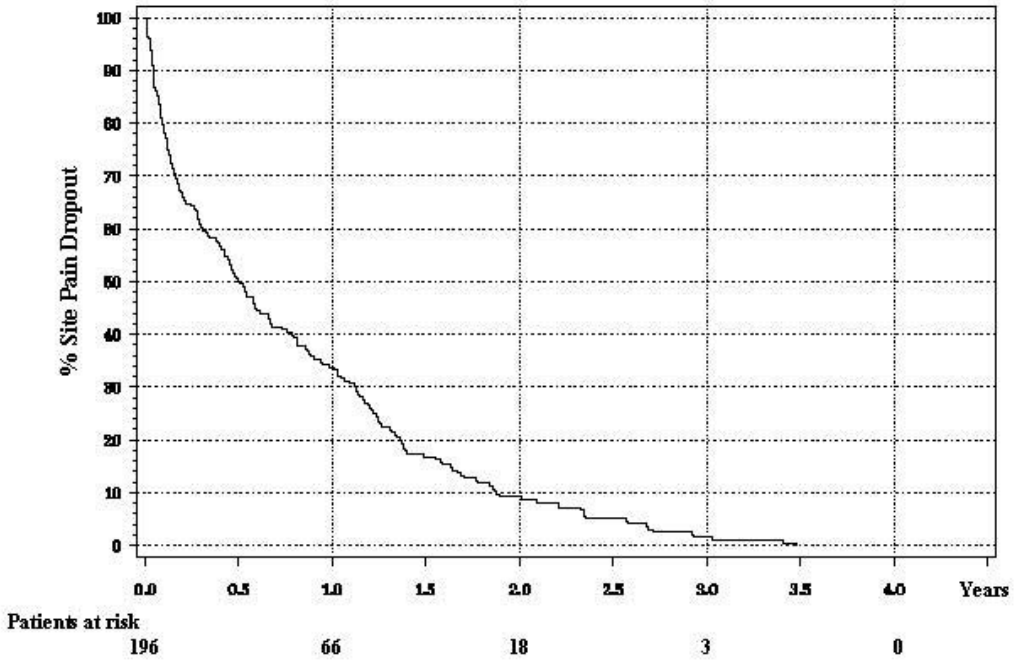


Figure 3. Observed Survival in All SC Treprostinil-treated PAH Patients (n=860). Survival estimates (95% CIs) were 87% (84%, 89%) at 1 year, 78% (75%, 81%) at 2 years, 71% (67%, 75%) at 3 years and 68% (63%, 73%) at 4 years.

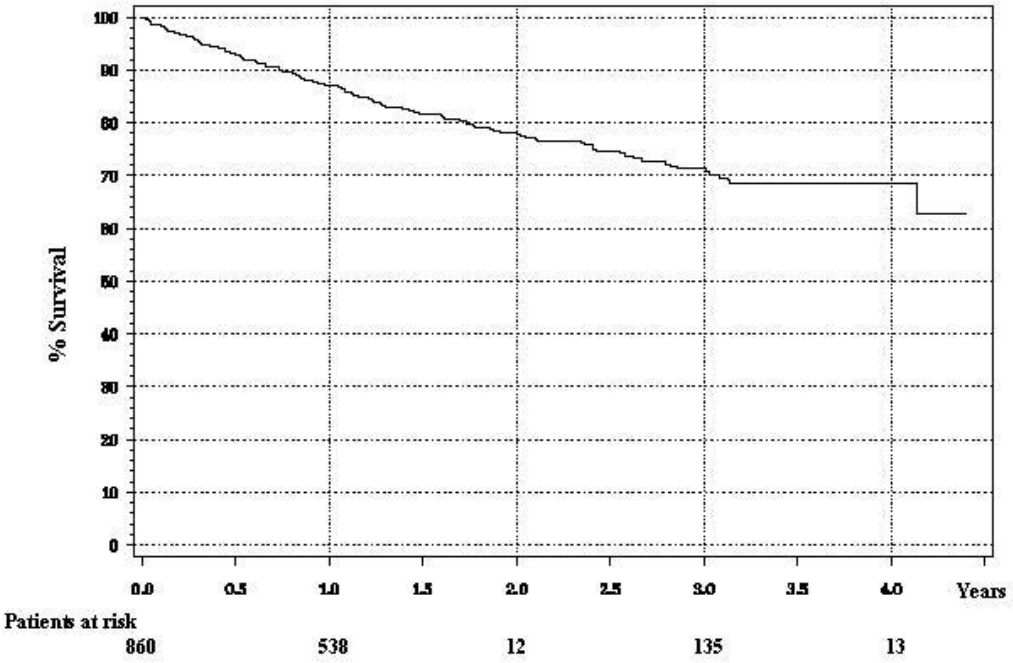


Figure 4. Observed Survival With SC Treprostinil Monotherapy. Patients were censored when additional PAH therapies were initiated. Survival estimates (95% CIs) were 88% (85%, 90%) at 1 year, 79% (76%, 82%) at 2 years, 73% (69%, 77%) at 3 years and 70% (64%, 74%) at 4 years.

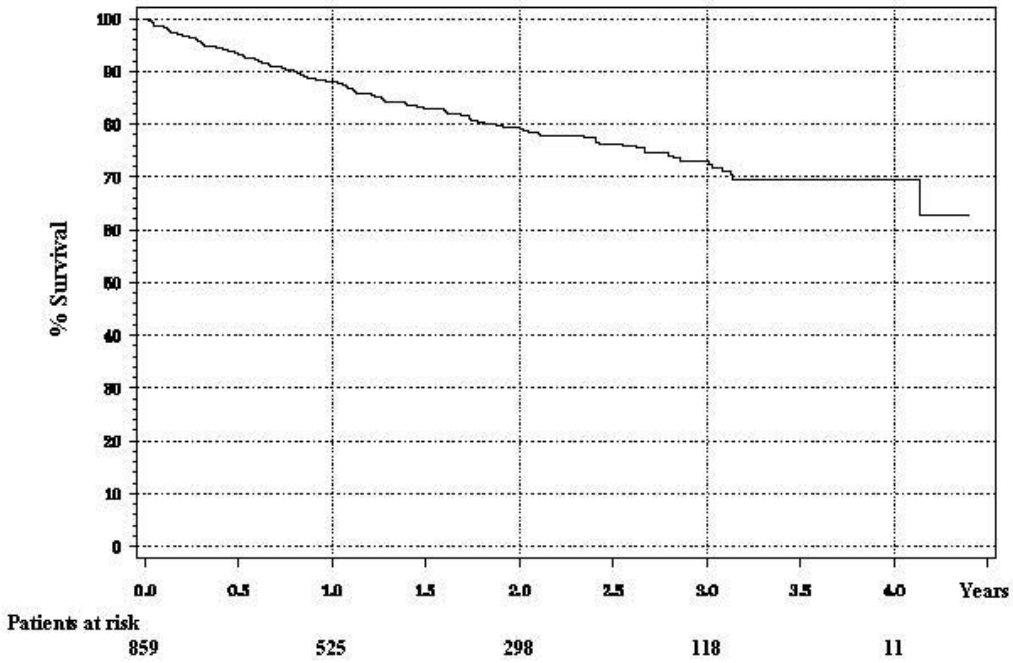


Figure 5. Observed Survival for Patients Who Were Treated with SC Treprostinil for at Least One Year (n= 538). Survival estimates (95% CIs) were 90% (86%, 92%), 82% (77%, 86%) and 79% (73%, 83%) at 2, 3 and 4 years, respectively.

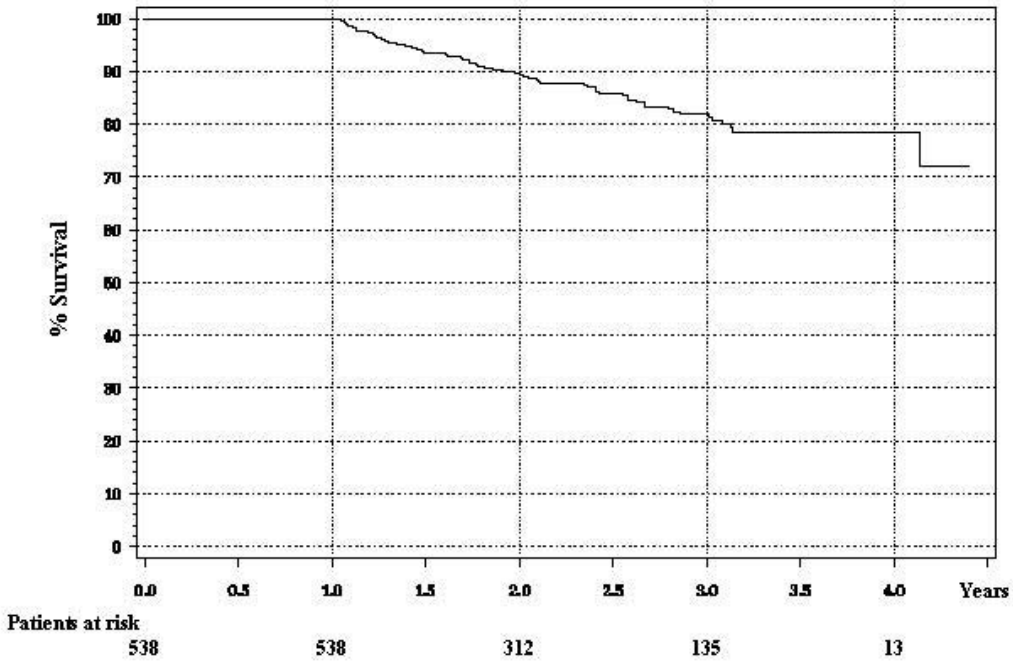


Figure 6. Observed Survival in SC Treprostinil-treated IPAH Patients (n=332 with baseline hemodynamic parameters available) versus Predicted Survival by the NIH equation[9]. Survival estimates (95% CIs) were 91% (87%, 84%) at 1 year, 82% (76%, 86%) at 2 years, 76% (69%, 81%) at 3 years and 72% (65%, 78%) at 4 years versus predicted survival rates of 69% at 1 year, 56% at 2 years, 46% at 3 years and 38% at 4 years.

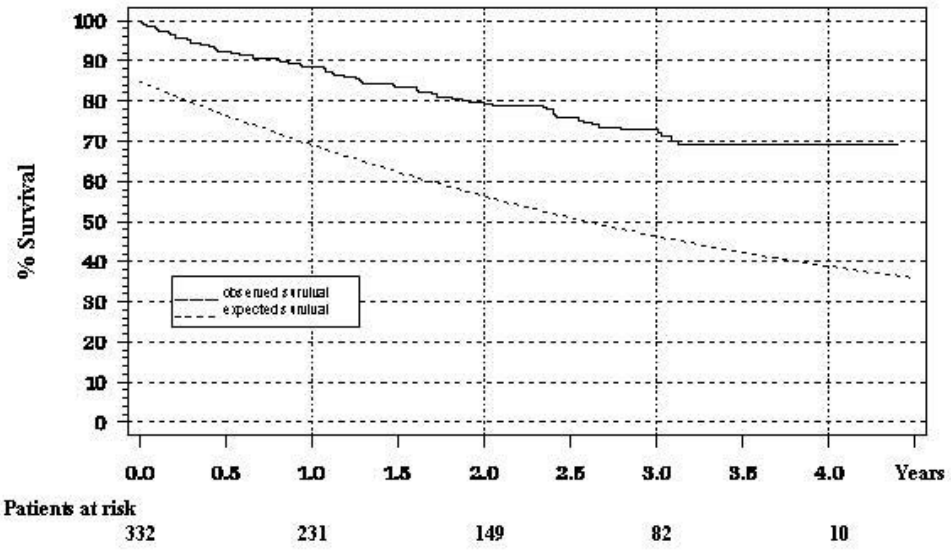
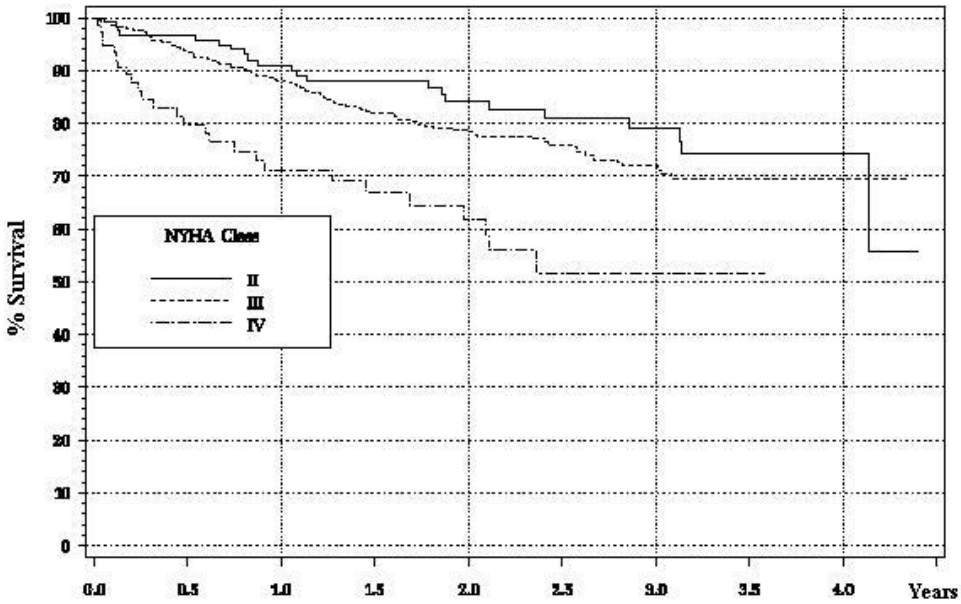


Figure 7. Observed Survival in All SC Treprostinil-treated PAH Patients (n=860) Based on NYHA Functional Class (FC) at Time of Treprostinil Initiation. Survival rates for FC II patients (95% CIs) were 91% (84%, 95%) at 1 year, 84% (75%, 90%) at 2 years, 79% (68%, 86%) at 3 years and 74% (62%, 83%) at 4 years (n=128). Survival rates for FC III patients (95% CIs) were 88% (85%, 91%) at 1 year, 79% (75%, 82%) at 2 years, 72% (67%, 76%) at 3 years and 70% (64%, 75%) at 4 years (n=654). Survival rates for FC IV patients (95% CIs) were 71% (58%, 81%) at 1 year, 62% (48%, 73%) at 2 years, and 52% (36%, 66%) at 3 years (n=78).



Patients at Risk

Class II	128	91	59	34	5
Class III	654	409	230	96	8
Class IV	78	38	23	5	0