CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	203496
Submission Date	December 27, 2011
Brand Name	TBD
Generic Name	Treprostinil diolamine
Sponsor	United Therapeutic Corporation
Submission Type	505(b)(1)
Therapeutic Class	Prostacyclin analog (vasodilatory action)
Formulation	Oral extended release tablet
(Strengths)	(0.125 mg, 0.25 mg, (b) (4) 1.0 mg, 2.5 mg)
Indication	Pulmonary Arterial Hypertension (PAH)
Dosing Regimen	Initial starting dose of 0.25 mg administered twice-daily with food. Doses titrated based on tolerability. Recommended titration increment is 0.25 mg twice-daily every 3-4 days as tolerated.
Proposed indication	Treatment of PAH (WHO Group 1) by improving the exercise capacity
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
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1. EXECUTIVE SUMMARY

In the current submission, NDA 203496, United Therapeutics Corp. is seeking approval for an oral extended release (ER) formulation of treprostinil, a tricyclic analog of prostacyclin (PGI_2). Treprostinil has shown clinical effectiveness when administered as continuous infusion via intravenous and subcutaneous route (Remodulin®; NDA 21272) and also as intermittent nebulization via the inhaled route (Tyvaso®; NDA 22387).

For the current submission, 3 controlled clinical trials have been performed to demonstrate the effectiveness and safety of treprostinil in patients with pulmonary arterial hypertension (PAH). In study TDE-PH-302, the effectiveness of treprostinil as a front-line therapy was evaluated. Studies TDE-PH-301 and TDE-PH-308 focused on the use of treprostinil as an add-on therapy to other approved oral therapies [oral phosphodiesterase inhibitors (PDE5-I), and/or endothelin receptor antagonists (ERA)].

The clinical pharmacology package for the current submission primarily comprises of a mass balance study, a single and multiple dose pharmacokinetic study, an absolute bioavailability study comparing exposures from oral ER tablet *vs* Remodulin®, a relative bioavailability study comparing the oral ER product *vs* an oral solution, a study each evaluating the pharmacokinetics of treprostinil in renal and hepatic impaired subjects, two food effect studies, and five drug-interaction studies. In addition, since the active moiety of the oral ER tablet is identical to that of the prior approved drug products, Remodulin® and Tyvaso®, data from these products were also used as appropriate in support of the clinical pharmacology package.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) recommends approval of treprostinil as extended release tablets for the treatment of PAH in the monotherapy and adjunctive setting, provided an agreement on labeling is reached with the sponsor. Further, a thrice-daily dosing regimen should be considered for approval. These recommendations are based on the following information:

- Effectiveness of treprostinil has already been established in the prior approved products, Remodulin® and Tyvaso®. No significant change is observed in the metabolic profile of oral treprostinil compared to the prior approved products.

- Similar steady state exposures (plasma treprostinil concentration) are observed upon comparison of the oral ER product and the prior approved intravenous product (Remodulin®).

- A consistent dose-response relationship is observed in the monotherapy and adjunctive settings.

- Based on the pharmacokinetic properties of the current oral ER product, a thrice-daily dosing regimen will provide less peak-to-trough fluctuation in treprostinil systemic exposures.

1.2 Phase 4 Commitments

No specific post-marketing commitments or requirements are proposed by the OCP at this point of time.

1.3. Major Clinical Pharmacology Findings

The important clinical pharmacology and biopharmaceutics findings were,

- The absolute bioavailability of treprostinil oral ER tablet is 17%. This dosage form exhibits extended release characteristics compared to treprostinil administered as an oral solution.

- The dose-normalized steady-state peak and trough concentrations following the administration of treprostinil oral ER tablet spans the average steady-state exposures obtained following the administration of an intravenous infusion. However, the oral ER tablet exhibits a high peak to trough ratio (ranges from 7 to 10 across studies).

- The inter-subject variability of treprostinil for the pharmacokinetic metrics, C_{max} and AUC, is in the range of 40-65%, expressed as percent coefficient of variation (CV%), across various Phase 1 studies. However, the intra-subject variability (25-30%), does not contribute to more than 50% of the overall variability.

- A high calorie, high fat meal delayed the absorption of treprostinil when compared to the fasted state. The systemic exposure to treprostinil, as seen by area under the plasma concentration-time curve (AUC), was increased by 1.5-fold with no significant change in the maximum concentration (C_{max}). Furthermore, the between subject variability in AUC decreased from 50% to 20%, expressed as CV%. No discernible change in the exposures was noted when compared among meals of varying fat and caloric content.

- The systemic exposure to treprostinil is increased in subjects with hepatic impairment. Increases of 2-, 5- and 8-fold were observed in subjects with mild, moderate and severe hepatic impairment respectively compared to otherwise healthy controls. No significant change in exposure to treprostinil was observed in patients with renal impairment.

- Treprostinil is a metabolized predominantly by CYP2C8. Gemfibrozil, a strong inhibitor of CYP2C8 increases the systemic exposure to treprostinil by 2-fold.

- In Study TDE-PH-302 (front-line therapy trial), a trend for dose-dependent increase in percent change from baseline peak 6-minute walk distance (corresponding to the peak treprostinil exposures) at week 12 was observed as a function of the last stabilized dose (body weight normalized) in patients who completed the study. This relationship was consistent for the 6-minute walk distance data at week 11, which corresponds to the trough exposures of treprostinil.

- Similar dose-dependent relationship for the percent change from baseline in peak 6-minute walk distance at week 16 as a function of the last stabilized dose (body weight normalized) was observed for studies TDE-PH-301 and TDE-PH-308 (add-on therapy trials) in completers.

- The relationship is consistent with a trend for dose-dependent increase in percent change from baseline in 6-minute walk distance as a function of cumulative treprostinil dose across all the patients randomized in the study (Study TDE-PH-302, ITT population).

2. QUESTION BASED REVIEW

The clinical pharmacology of treprostinil has been previously reviewed for Remodulin® (NDA 21272, DARRTS date: 03/12/2003) and Tyvaso® (NDA 22387, DARRTS date: 03/04/2009) by Drs. Beasley, Gobburu and Kumi. In the current review, an abbreviated question based review describing the clinical pharmacology aspects pertinent to the oral ER product is presented.

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Treprostinil is a tricyclic analog of prostacyclin (PGI_2). It is synthesized as a diolamine salt which exists as a white to cream colored powder with a molecular weight of 495.6 g/mol. The diolamine salt of treprostinil is freely soluble in water with a solubility of 453 mg/mL. The chemical structure is shown in Fig. 1.

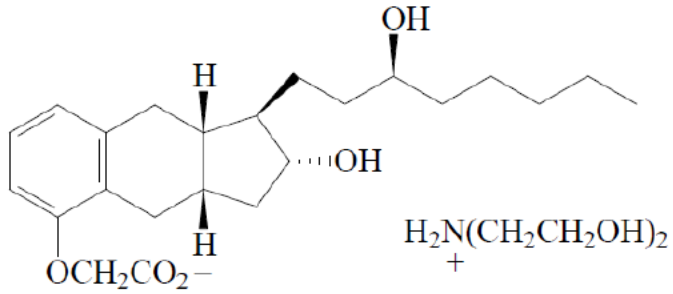

Figure 1: Chemical structure of treprostinil diolamine

Treprostinil diolamine is formulated as an oral extended release (ER) tablet using an osmotic release mechanism. The tablet core (b) (4) is coated by a semi-permeable membrane with a laser drilled aperture. Upon contact with water, the water soluble osmotic excipients swell up, creating hydrostatic pressure within the membrane and force the solubilized drug through the aperture.

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Treprostinil is a tricyclic analog of prostacyclin (PGI_2), which is a potent vasodilator. The pharmacological action of treprostinil pertinent to pulmonary arterial hypertension (PAH) is direct vasodilation of pulmonary and systemic arterial vascular beds.

Treprostinil is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) by improving the exercise capacity.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

The proposed dosage form is a ER tablet for oral use to be administered twice-daily. The ER tablet is available in (b) (4) different strength for the ease of titration i.e., 0.125, 0.25, (b) (4) 1.0 and 2.5 mg.

2.1.4. What is the proposed dose and dosing regimen of treprostinil for the oral ER tablet?

The recommended initial starting dose is 0.25 mg administered twice-daily taken along with food. Doses should be increased over time in a given patient based on tolerability until a beneficial effect is achieved. The recommended titration increment is 0.25 mg twice-daily every 3-4 days as tolerated. If 0.25 mg dose increments are not tolerated, an increment of 0.125 mg is recommended.

2.1.5. What are the previous approved products of treprostinil? What are their recommended doses and dosing regimen?

The two approved products of treprostinil are Remodulin® and Tyvaso®. Remodulin® is an injection for infusion which is administered at a starting dose of 1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated), further titrated based on tolerability in increments of 1.25 ng/kg/min per week for the first 4 weeks and later by 2.5 ng/kg/min per week.

Tyvaso® is a solution for inhalation which is administered as 3 breaths per session for a total of 4 treatment session per day. Each breath of Tyvaso® delivers approximately 6 µg of treprostinil. Tyvaso® is further titrated to a target maintenance dose of 9 breaths per session administered 4 times daily (54 µg x 4 times daily).

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical and clinical pharmacology studies used to support dosing or claims?

Design features of clinical and clinical pharmacology studies are shown in Table 1 and 2, respectively.

Table 1: List and design features of clinical studies supporting this application

Study No.	Description	N	Dose	Duration
TDE-PH-302	Randomized, multi-center, placebo-controlled study in subjects with PAH NOT receiving approved background therapy	349	0.25-1 mg BID starting dose with dose increasing over time	12 Weeks
TDE-PH-301	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	354	0.25-1 mg BID starting dose with dose increasing over time	16 Weeks
TDE-PH-308	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background therapy	310	0.25 mg BID starting dose with dose increasing over time	16 Weeks

Table 2: List and design features of relevant clinical pharmacology & biopharmaceutics studies

Study No.	Study type	Description	N	Treprostinil dose
TDE-PH-107	Mass Balance	OL, mass balance, metabolite profiling and safety study of [^{14}C],[^{3}H] TDE	8	0.5 mg
TDE-PH-104	Single/ Multiple dose PK	OL, R, DB, placebo controlled, parallel group, PK and safety study with TDE oral SR tablet administered over 13 days in escalating doses	36	1 mg BID 2 mg BID 3 mg BID
TDE-PH-114	Absolute Bioavailability	OL, two-sequence, CO study to evaluate the absolute bioavailability of treprostinil administered as a oral SR tablet as compared to an IV infusion of treprostinil sodium	24	1 mg (SR tablet) 0.2 mg (Remodulin®)
TDE-PH-123	Relative Bioavailability	OL, two-sequence, CO study to evaluate the comparative bioavailability of treprostinil administered as a single SR tablet or as a oral solution	24	1 mg and 0.25 mg q2 h x 4 doses
TDE-PH-103	Food Effect	OL, two period, CO, PK and safety study with single doses of treprostinil administered as three tablet prototypes (12 h formulations) in fasted and fed states	30	1 mg
TDE-PH-115	Food Effect	OL, R, single-dose, four-period, CO PK and safety study evaluating the effect of different meal compositions on treprostinil PK	32	1 mg
TDE-PH-112	Hepatic Impairment	OL, single-dose, PK and safety study in three cohorts of subjects with varying degrees of hepatic impairment and one cohort of healthy volunteers	30	1 mg
TDE-PH-120	Renal Impairment	OL, single-dose, two-period, CO, PK, safety and tolerability study in healthy volunteers and patients with ESRD	16	1 mg
TDE-PH-105	Drug Interaction	OL, R, three-period, three sequence, CO study to evaluate the effect of bosentan on steady state treprostinil PK	24	1 mg
TDE-PH-106	Drug Interaction	OL, R, three-period, three-sequence, CO study to evaluate the effect of sildenafil on steady state treprostinil PK	18	1 mg
TDE-PH-109	Drug Interaction	OL, R, single-sequence, CO study to evaluate the effect of repeated rifampin dosing on a single dose of TDE	20	1 mg
TDE-PH-110	Drug Interaction	OL, R, two-period, two-sequence, CO study to evaluate the effect of repeated gemfibrozil or fluconazole dosing on the PK of a single dose of treprostinil	40	1 mg
TDE-PH-116	Drug Interaction	OL, single-sequence, CO study to evaluate the effect of repeated esomeprazole dosing on the PK of a single dose of TDE	30	1 mg

TDE = Treprostinil diethanolamine; OL = Open label; R = Randomized, DB = Double-blind; CO = Crossover

2.2.2. What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The efficacy measures included in the clinical development program are widely used and accepted as clinically meaningful indices for patients with PAH. In studies TDE-PH-301, -302 and -308, the primary efficacy endpoint was change in 6-minute walk distance from baseline to the end of the study i.e., week 12 for study TDE-PH-302 and week 16 for study TDE-PH-301 and -308. Secondary efficacy assessments included changes in 6-minute walk distance at weeks 4, 8, 11 (trough), WHO functional class, Borg dyspnea score, dyspnea-fatigue index, signs and symptoms of PAH and clinical worsening.

2.2.3. What are the key results from the pivotal efficacy trial(s)?

In study TDE-PH-302, where efficacy of treprostinil was evaluated as a monotherapy, the primary endpoint i.e., change in 6-minute walk distance between treatment and placebo groups at week 12 for the entire study population was significant, with a median placebo-corrected treatment effect of +25.5 meters, as reported by the sponsor. The treatment effects at week 4 and 8 were +14 and +20 meters, respectively, and were statistically significant. Additionally, the placebo-corrected treatment effect on 6-minute walk distance at week 11, which was assessed at a time expected to correlate with trough treprostinil concentrations, was also statistically significant with a treatment effect of +17 meters, as reported by the sponsor (Table 3).

In the other two add-on therapy trials, a scenario how treprostinil will be most used if approved, the treatment effect was not statistically significant at week 16 when evaluated as independent trials (Table 3). However, the sponsor reported a statistically significant treatment effect upon pooling both studies (Table 3).

Table 3: Display of Hodges-Lehmann estimates of treatment effect for the ITT population across studies TDE-PH-302, -301 and -308

Study	Period	Median 6MWD (meters)		Hodges-Lehmann estimate of treatment effect (95% CIs)	p-value
		Active	Placebo		
Study 302	Week 11 (trough)	351	327	17 (3, 33)	0.0025
	Week 12	370	330	25.5 (10, 41)	0.0001
Study 301	Week 16	381	367	11 (0, 22)	0.072
Study 308	Week 16	370	365	10 (-2, 22)	0.089
Pooled Studies 301 & 308	Week 16	375	366	10 (3, 19)	0.00397

Source: Sponsor submitted study reports of TDE-PH-301, -302 and -308

2.2.4. Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Treprostinil is the only active moiety and its pharmacokinetics is characterized across various Phase 1 studies. Pharmacokinetics of treprostinil was not measured during the Phase 3 trials. However, the PK of treprostinil were assessed in a small subset of patients (N=74) during the open-label safety extension study. For details on bioanalytical method validation, refer to Q 2.8.1.

2.3. Exposure-Response Relationship

2.3.1. How do the exposures compare against the previously approved products?

The average steady state exposures of the oral ER tablet and the currently approved intravenous product of treprostinil are reasonably similar. Fig. 2 shows the dose-normalized mean steady state treprostinil plasma concentrations as box plots for (i) oral ER tablet ($C_{max,ss}$ and $C_{min,ss}$) and (ii) intravenous infusion ($C_{avg,ss}$). Dose-normalization was performed corresponding to the mean dose achieved in the respective pivotal trials (3.4 mg for the oral ER formulation and 9.3 ng/kg/min, for Remodulin®). It can be seen that the average steady state maximum and minimum concentration from the oral ER product spans the average steady state concentration of treprostinil from the previously approved intravenous product, indicative of matching systemic exposures between the two products. It should be noted that the exposures from Tyvaso® (another prior approved product of treprostinil administered via the inhalation route) cannot be used as reference, since, treprostinil is delivered locally and the PK/PD relationship could be different.

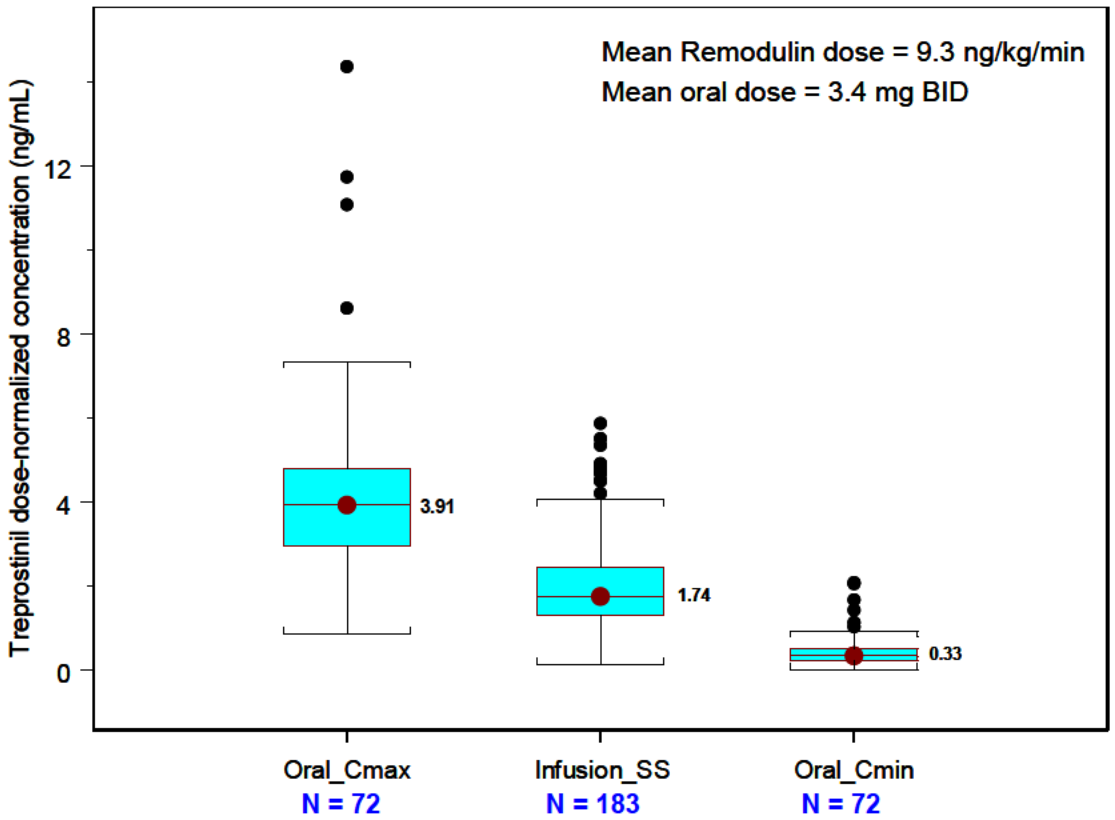

Figure 2: Mean steady state treprostinil concentrations from the oral ER tablet and Remodulin® corresponding to the mean dose achieved in their respective pivotal Phase 3 trial.

2.3.2. What are the characteristics of the dose-response relationship for efficacy?

The phase 3 trials of treprostinil incorporated a titration to tolerability design. Analysis of dose-response, in situations such as these, presents its own challenges and may not be representative of the cleanest form of dose-response such as those resulting out of a parallel fixed-dose study.

Nevertheless, in the current review, the relationship between the last stabilized dose (body weight normalized) and the corresponding percent change from baseline in 6-minute walk distance was explored as the primary analysis. As the trial design employed a titration to tolerability, the last stabilized dose was deemed a relevant metric for this exploration. For the response metric, percent change from baseline in 6-minute walk distance at the end of the study was considered more robust than the absolute change from baseline, since, the former takes into account baseline 6-minute walk distance. This relationship is constructed using the data from patients who completed the study, since a completer analysis is not confounded with imputation methodologies used to account for missing data in the trial. Completers of the study with corresponding peak 6-minute walk distance at week 12 represent about 70% and 75% of the total randomized patients in the treatment and placebo arms, respectively. However, it is important to note that the analysis presented cannot rule out time dependent effects and an interaction between tolerability and the ability to exercise.

As shown in Fig. 3, in Study TDE-PH-302, a trend for dose-dependent increase in the percent change from baseline in peak 6-minute walk distance (corresponding to the peak treprostinil exposures) at week 12 was observed as a function of the last stabilized dose (body weight normalized), upon anchoring to the placebo response. A significant non-zero slope for this relationship was obtained upon assuming a linear trend. The slope for this relationship denotes 1.23% change from baseline in peak 6-minute walk distance per 0.01 mg/kg dose.

A similar relationship (1.35% change from baseline in trough 6-minute walk distance per 0.01 mg/kg dose) was also observed between last stabilized dose (body weight normalized) and percent change in baseline in trough 6-minute walk distance at week 11 as shown in the Fig. 4. Regardless of the analysis of dose-response corresponding to peak (week 12) or trough (week 11) treprostinil concentration, a significant relationship exists which is suggestive of that fact that the effect or the ability to exercise is preserved during the inter-dosing interval.

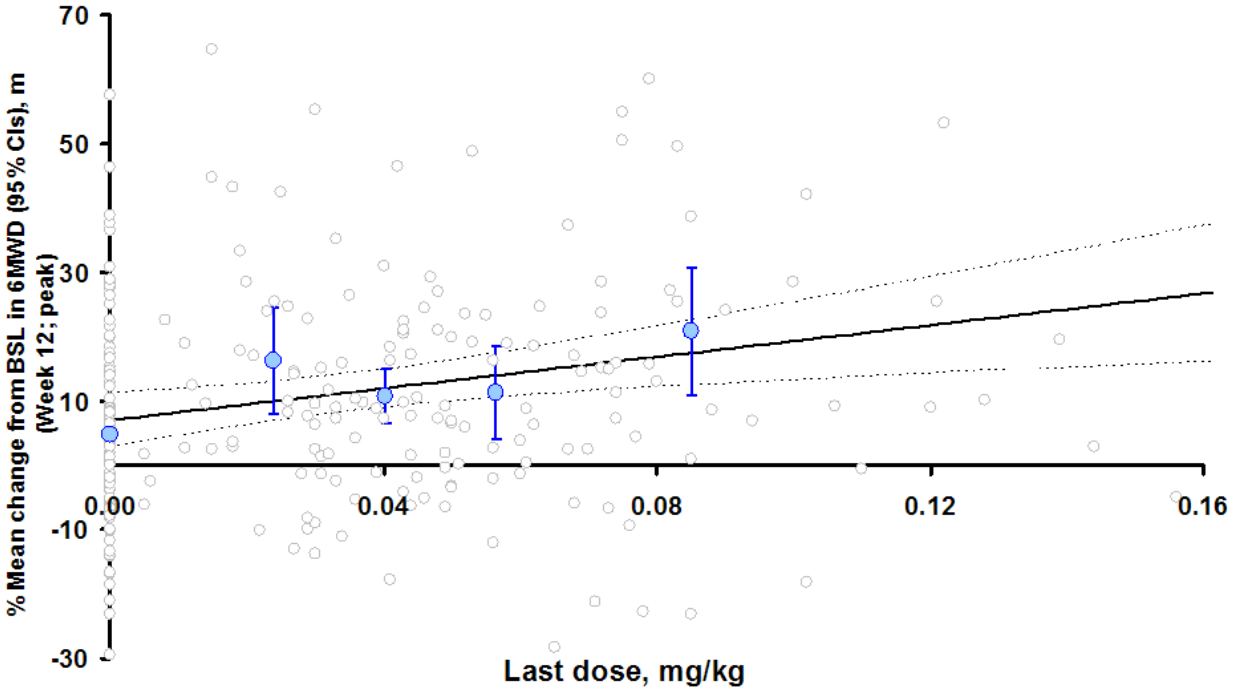

Figure 3: Relationship between last stabilized dose (body weight normalized) and corresponding percent change from baseline in **peak 6-minute walk distance** at week 12 from Study TDE-PH-302 in completers [N = 246; active=160 (40 per bin), placebo=86]. A positive slope for the relationship was observed [Mean and 95% CIs: 1.23 (0.418 – 2.04) as percent change from baseline-per-0.01 mg/kg of treprostinil].

Note: For exposure-response, the gray open circles represent the individual patient data. The blue closed circles and error bars represent the corresponding mean and 95% CIs of percent change from baseline in 6-minute walk distance for each median dose quartile. The solid line represents the linear fit modeled through the entire dataset with 95% CIs represented by dotted lines. Y-axis is truncated to provide an optimum view for the readers to understand this relationship.

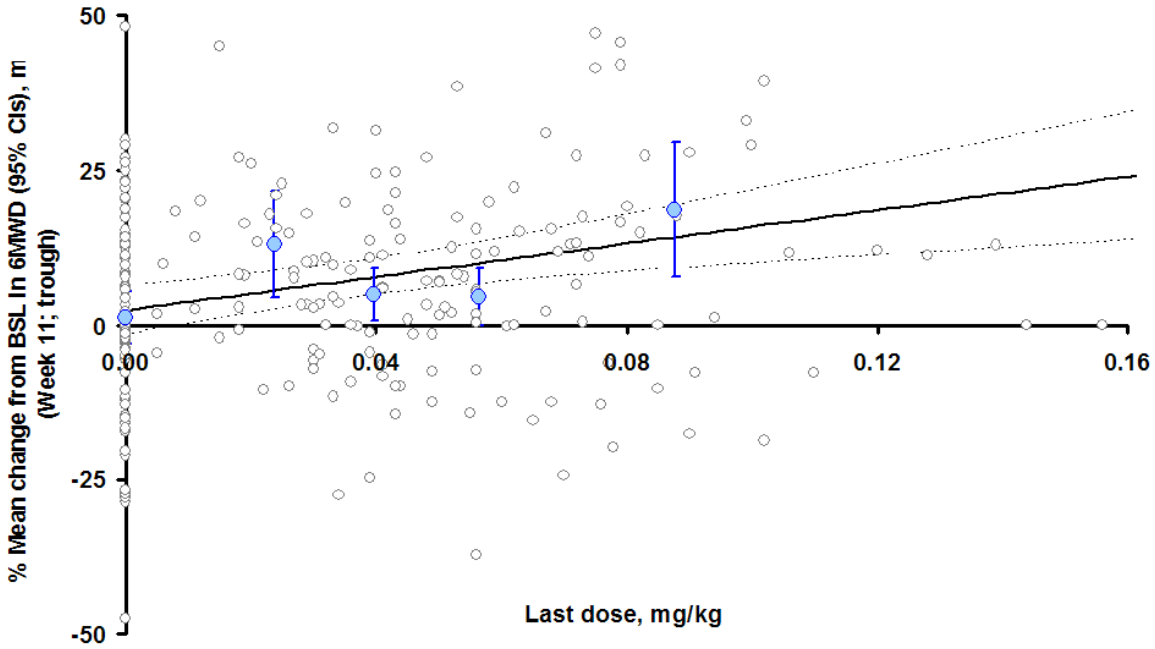

Figure 4: Relationship between last stabilized dose (body weight normalized) and corresponding percent change from baseline in **trough 6-minute walk distance** at week 11 from Study TDE-PH-302 in completers [N = 243; active=159 (~40 per bin), placebo=84]. A positive slope for the relationship was observed [Mean and 95% CIs: 1.35 (0.548 – 2.15) as percent change from baseline-per-0.01 mg/kg of treprostinil].

Assuming a linear relationship, similar dose-dependent trend for the relationship between peak 6-minute walk distance at week 16 as a function of the last stabilized dose (body weight normalized) was also observed for studies TDE-PH-301 and TDE-PH-308 in completers where treprostinil was evaluated in the background of other oral PAH therapies. A non-zero slope for the relationship is shown in Fig. 5 as mean and 95% CIs.

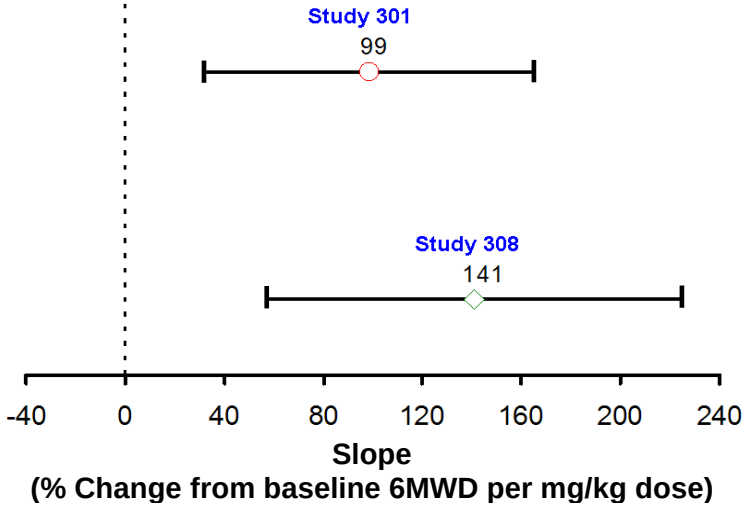

Figure 5: Relationship between last stabilized dose (body weight normalized) and corresponding percent change from baseline in peak 6-minute walk distance at week 16 from studies TDE-PH-301 [N=246; active=118, placebo=128] and TDE-PH-308 [N=249; active=120, placebo=129] in patients who completed the study. Data is represented as slope [mean and 95% CIs].

One of the drawbacks of evaluating the relationship between last stabilized dose (body weight normalized) and corresponding percent change from baseline in 6-minute walk distance is that it ignores the time-course of dose titration. It is possible for patients to have the same last stabilized dose but differing in the duration at that dose. In order to further evaluate the exposure-response relationship, percent change from baseline in 6-minute walk distance as a function of cumulative treprostinil dose was constructed in all randomized patients i.e., the intent-to-treat (ITT) population as a sensitivity analysis. The last observed 6-minute walk distance data was used in patients who dropped out during the trial with their cumulative doses truncated until the day of the last observed response data. Baseline 6-minute walk distance data was carried forward for patients who dropped prior to week 4. As shown in Fig. 6, upon anchoring to placebo response, the relationship was consistent with a significant non-zero slope (2.5% change from baseline in 6-minute walk distance per 100 mg cumulative treprostinil dose). Moreover, as expected, it can be observed that the non-completers with lower cumulative exposures have correspondingly lower percent change from baseline 6-minute walk distance.

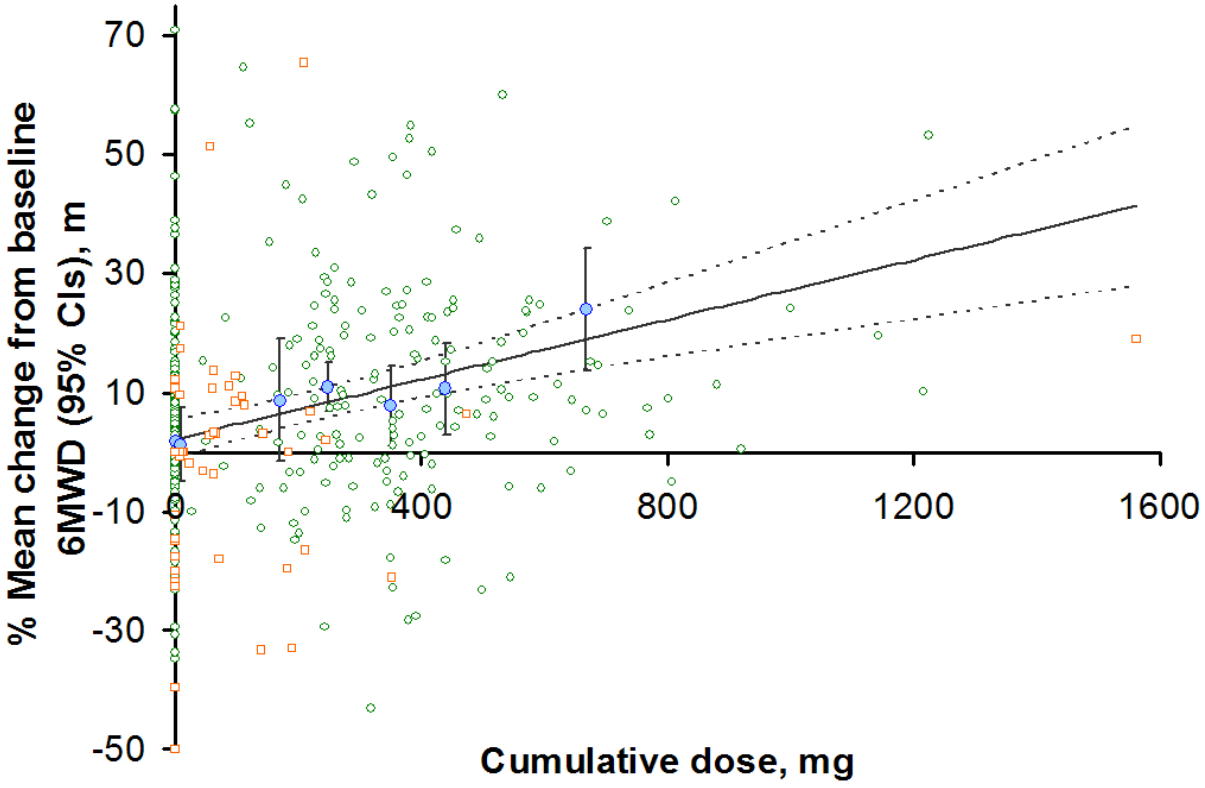

Figure 6: Relationship between cumulative treprostinil dose and corresponding percent change from baseline from Study TDE-PH-302 in all randomized patients (ITT population) [N = 349; active=233 (~40 per bin), placebo=116]. A positive slope for the relationship was observed [Mean and 95% CIs: 2.50 (1.50 – 3.50) as percent change from baseline-per-100 mg of cumulative treprostinil dose]. The green open circles represent individual patient data from completers and the orange open squares represent the individual patient data from non-completers.

2.3.3. What are the characteristics of the dose-response relationships for safety?

Since treprostinil is titrated to tolerability, no specific exposure-response analyses for safety were conducted.

2.3.4. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Following twice-daily dosing of the oral ER tablet, treprostinil displays a huge peak-to-trough ratio (ranges between 7 to 10) based on mean concentration-time courses from various Phase 1 studies. Although the average steady state C_{max} and C_{min} from the oral ER tablet spans the average steady-state exposures seen from administering treprostinil via the intravenous route (Fig. 2), the fluctuation around the mean is large. As treprostinil has significant tolerability issues, as seen by high drop out rates in the Phase 3 trial, a more frequent dosing regimen delivering the same total daily dose e.g., TID dosing, will result in lower maximum concentration (31% reduction in $C_{max,ss}$ compared to twice-daily dosing) and lesser fluctuation (peak-to-trough ratio = 2.4) (Fig. 7), thereby potentially allowing patients to better tolerate and successfully titrate up, assuming the tolerability issues are associated with a higher C_{max}.

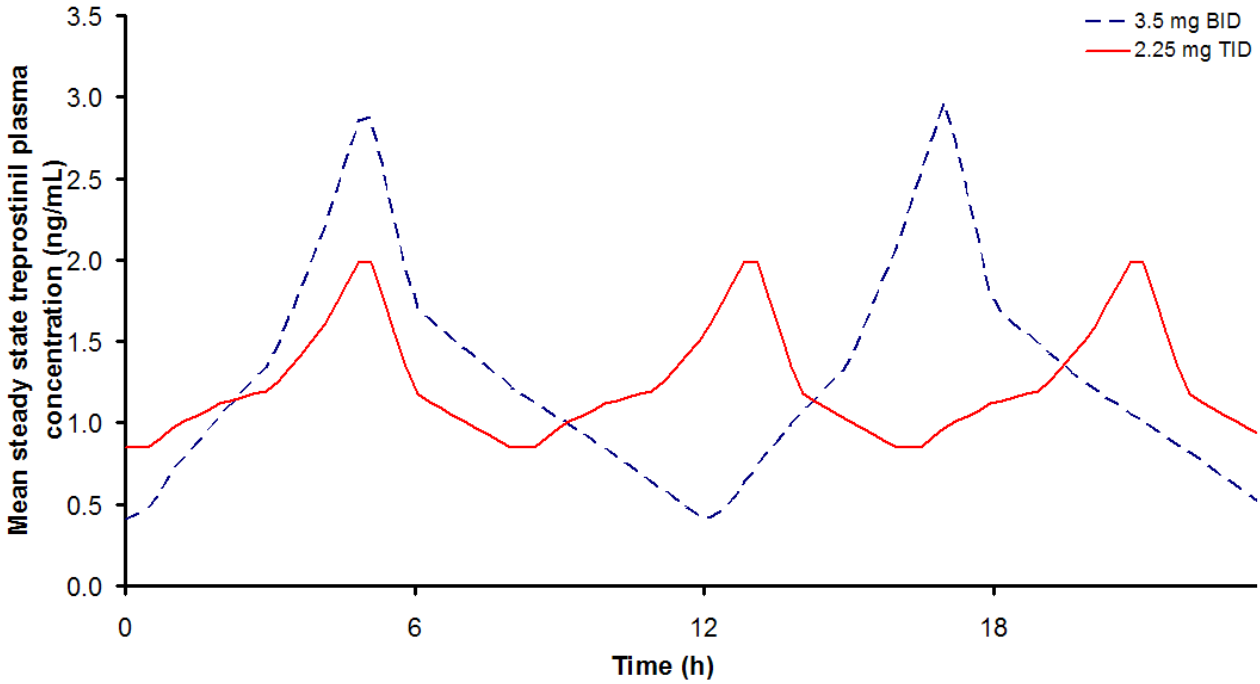

Figure 7: Comparison of mean steady state treprostinil concentration-time profile administered as 3.5 mg BID and 2.25 mg TID. Steady state concentration-time courses following oral administration of treprostinil were simulated using non-parametric superposition of the mean data obtained subsequent to administration of 1 mg treprostinil from a healthy Phase 1 study.

2.3.5. Does this drug prolong the QT or QTc interval?

Treprostinil has been shown to prolong QT. Based on the TQT study conducted with the inhaled formulation (Tyvaso®), a mean effect of 8.5 ms and an upper bound of the 90% CI of 11.3 ms for the supra-therapeutic dose was reported. The systemic exposure achieved with the supra-therapeutic dose of Tyvaso®, 1.8 ng/mL, is lower than the therapeutic exposures achieved after maximal therapeutic doses of the oral ER tablet. It should be noted that Tyvaso® systemic exposure does not reflect local concentration in the heart, which is expected to be higher. Nevertheless, a potential to cause QT prolongation exists when treprostinil is administered orally. An appropriate precautionary statement in the product insert for Brandname is suggested in the QT-IRT review by Dr. Fiszman (DARRTS date: 06/11/2012).

2.4. Pharmacokinetics

2.4.1. What are the pharmacokinetic characteristics of treprostinil diolamine?

Absorption: The absolute bioavailability of treprostinil following oral administration of treprostinil ER tablet is 17.6%. The relative bioavailability of treprostinil following oral ER tablet relative to the oral solution is approximately 70%. When administered with food, the time to reach maximum plasma concentration of treprostinil following oral administration of the ER tablet is 4-6 h. Absorption of treprostinil is affected by food (refer Q 2.7.3). Pharmacokinetics of treprostinil in PAH patients is linear with a dose-proportional increase for AUC_{0-t} and less than dose-proportional increase for C_{max} in the dose range of 0.5-15 mg. Upon repeat dosing, the pharmacokinetic parameters are not significantly affected, thus suggesting minimal accumulation.

Distribution: Treprostinil is highly bound to plasma proteins with approximately 96% of the drug being bound, as seen from *in vitro* protein binding studies. The diolamine component is minimally bound to plasma proteins (<10%). The protein binding is not concentration dependent for both the components i.e., treprostinil and diolamine, in the range of 0.01-10 µg/mL.

Metabolism: Treprostinil undergoes significant first-pass metabolism in the liver. Metabolism is primarily mediated by the cytochrome P450 enzymes, largely by CYP2C8. CYP2C9 also plays a role in the metabolism of treprostinil, but the relative contribution is small. Other CYP450 enzymes tested such as CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A11 do not affect the metabolism of treprostinil. Six major metabolites were identified from mass balance studies formed via processes such as oxidation, oxidative cleavage, dehydration and glucuronidation. The metabolites of treprostinil are not active.

Elimination: Treprostinil and its metabolites are primarily eliminated by the kidneys. The half-life of treprostinil following oral administration of ER tablet could not be reliably estimated due to a high degree of variability in the absorption of treprostinil. However, the effective half-life of treprostinil from studies using Remodulin® administered intravenously or using an oral solution of treprostinil is about 2 h.

2.4.2. What is the mass balance of treprostinil diolamine following oral administration?

Mass balance was studied following oral administration of radioactive treprostinil diolamine solution in eight healthy male volunteers [Study TDE-PH-107]. To differentiate between the two components, treprostinil administered at a dose of 0.5 mg was labeled as [^{14}C] and diolamine at a corresponding dose of 0.14 mg was labeled as [^{3}H]. Recovery of radioactivity administered as [^{14}C] treprostinil-derived was near to complete, with 95.2% of the administered dose accounted in urine and feces over a collection period of 288 h (12 d) (Table 4). However, only 64.3% of the radioactivity administered as [^{3}H] diolamine-derived was accounted over a 576 h (24 d) collection period, indicating that the recovery of diolamine was incomplete. The predominant route of excretion for both [^{14}C] treprostinil- and [^{3}H] diolamine-derived radioactivity following oral administration was via urine which accounted for 78.2% and 62.1% of the total dose administered, respectively, through the last collection interval. Feces accounted for 18.6% and 2.25% of the total dose administered as [^{14}C] treprostinil- and [^{3}H] diolamine-derived radioactivity, respectively, through the last collection interval. Unchanged parent drug i.e., [^{14}C] treprostinil accounted for only 1.32% of the total administered dose, with 1.13% detected in feces and 0.19% in urine (Table 4).

Following oral administration of treprostinil diolamine, the active moiety [^{14}C] treprostinil was extensively metabolized with metabolism occurring on the side chain of the molecule via oxidation, oxidative cleavage, dehydration and glucuronidation (Fig. 8). Six metabolites were identified in urine, feces and plasma which accounted for 78% of the total administered radioactivity (Table 4). There was no significant change in the metabolic profile of treprostinil following oral route, except for one new metabolite, M388, which accounted for only 0.5% of the total administered dose.

Table 4: Treprostinil and metabolites in urine and feces following oral administration. Results are expressed as percent of total radioactivity administered.

Compound	% of administered dose		
	Urine	**Feces**	**Total**
Treprostinil (parent)	0.19	1.13	1.32
M392	12.9	4.42	17.3
M334	23.6	0.99	24.6
M348	20.2	3.50	23.7
M374	8.14	1.21	9.35
M388*	0.39	0.11	0.50
M566	2.40	0.14	2.54
Other unknowns combined	10.6	5.30	15.9
Total	**78.4**	**16.8**	**95.2**

* New metabolite by oral route compared to intravenous administration

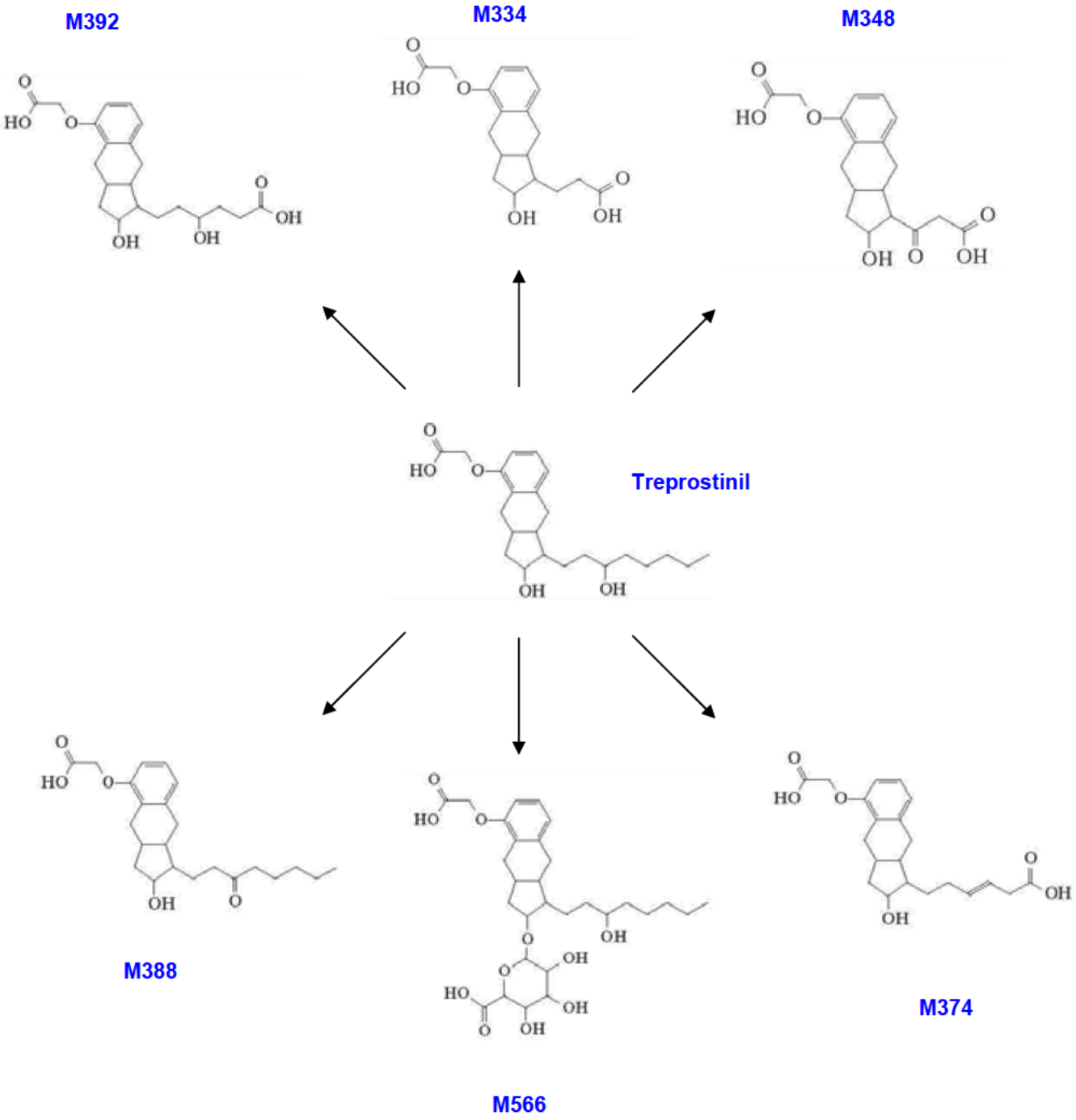

Figure 8: Metabolites of treprostinil following oral administration.

2.4.3. What are the single dose and multiple dose PK parameters?

The concentration-time course of treprostinil following both single and multiple dose regimen is shown in Fig. 9. Pharmacokinetic summary metrics of treprostinil following 1 mg treprostinil administered orally as a single dose and as twice-daily repeat dose for 13 days is shown in Table 5. It is seen that the time to reach maximum concentration is achieved between 3-4 h. The concentration-time course of treprostinil is highly variable across individual which prevents a reliable estimation of the elimination half-life and other pharmacokinetic parameters. However, based on the mean concentration-time profile, the effective half-life of treprostinil seems to be approximately 2 h. The summary metrics of treprostinil exposure i.e., both C_{max} and AUC_{0-t} is similar following single and multiple doses of 1 mg treprostinil suggesting minimal accumulation.

Table 5: Important pharmacokinetic metrics following 1 mg oral administration of treprostinil on day 1 (single dose) and day 13 (twice-daily repeat dose)

Parameter	Mean (%CV)	
	Single dose (N=9) 1 mg, Day 1	Multiple dose (N=9) 1 mg BID, Day 13
C_{max} (ng/mL)	0.99 (61)	0.87 (40)
T_{max} (h)†	4.01	3.20
AUC_{0-t} (ng.h/mL)	3.79 (64)	4.07 (38)

† Median

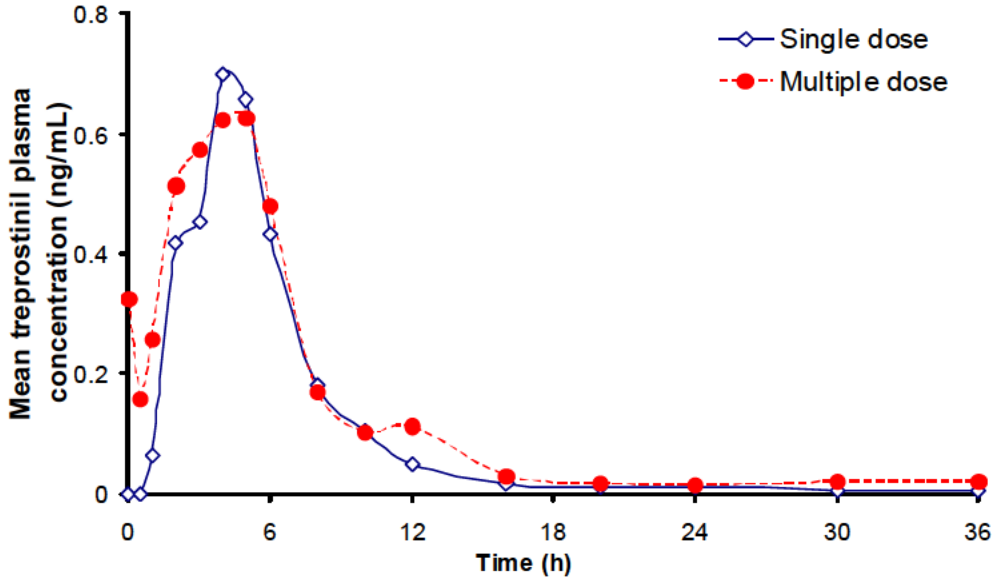

Figure 9: Mean concentration-time course of treprostinil following 1 mg oral administration on day 1 (single dose) and day 13 (twice-daily repeat dose)

2.4.4. How does the PK of treprostinil in healthy volunteers compare to that in patients?

Due to high variability in the concentration-time courses of treprostinil in both healthy volunteers and PAH patients, it was not possible to fit an appropriate pharmacokinetic model to describe the observed data across patients individually. Hence, pharmacokinetic parameters such as clearance (CL/F) and volume (V/F) could not be reliably estimated to make this comparison. However, there is no physiological basis or hypothesis that the pharmacokinetics should be different between healthy volunteers and PAH patients.

2.4.5. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability of treprostinil for the PK metrics, C_{max} and AUC, is in the range of 40-65%, expressed as percent coefficient of variation, across various Phase 1 studies. This is reflected by the highly variable concentration-time courses for treprostinil across different subjects (Fig. 10). A high degree of variability is observed in the absorption of treprostinil resulting in multiple peaks. This phenomenon may be due to erratic release patterns of the drug from the extended release dosage form or varying gastrointestinal transit times between patients. Due to this reason, it is difficult to model the observed data to describe the pharmacokinetics of treprostinil.

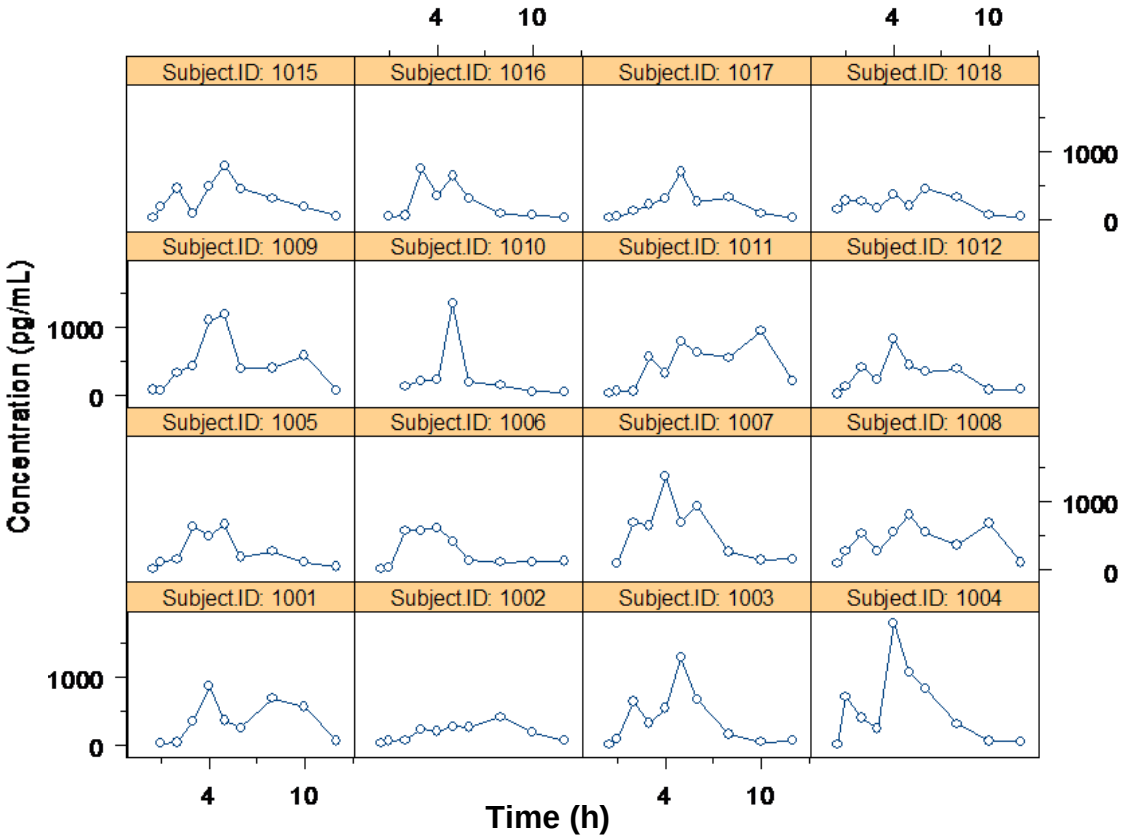

Figure 10: Concentration-time courses of treprostinil as seen across healthy volunteers following single oral dose of 1 mg treprostinil diolamine ER tablet [*Source*: treprostinil diolamine ER tablet arm from Study TDE-PH-116]

However, as treprostinil will be titrated to tolerability, an assessment of intra-subject variability is important. An estimate of the intra-subject variability can be obtained from Study TDE-PH-104, where 1 mg treprostinil diolamine was administered to healthy volunteers as a single dose followed by twice-daily repeat dose for 13 days. Since, there is no significant accumulation as shown by similar C_{max} and AUC values in Table 4, pharmacokinetic parameters can be compared between day 1 and day 13. As shown in Fig. 11, there is reasonable product consistency as seen by the shape of the pharmacokinetic profiles within the same subjects on day 1 and day 13. Based on this small study (n=8), the root mean square error (RMSE; which provides a fair estimate of the intra-subject variability) is 31% and 25% for C_{max} and AUC, respectively. A comparison within the same study shows that the intra-subject variability contributes to approximately 50% of the overall variability.

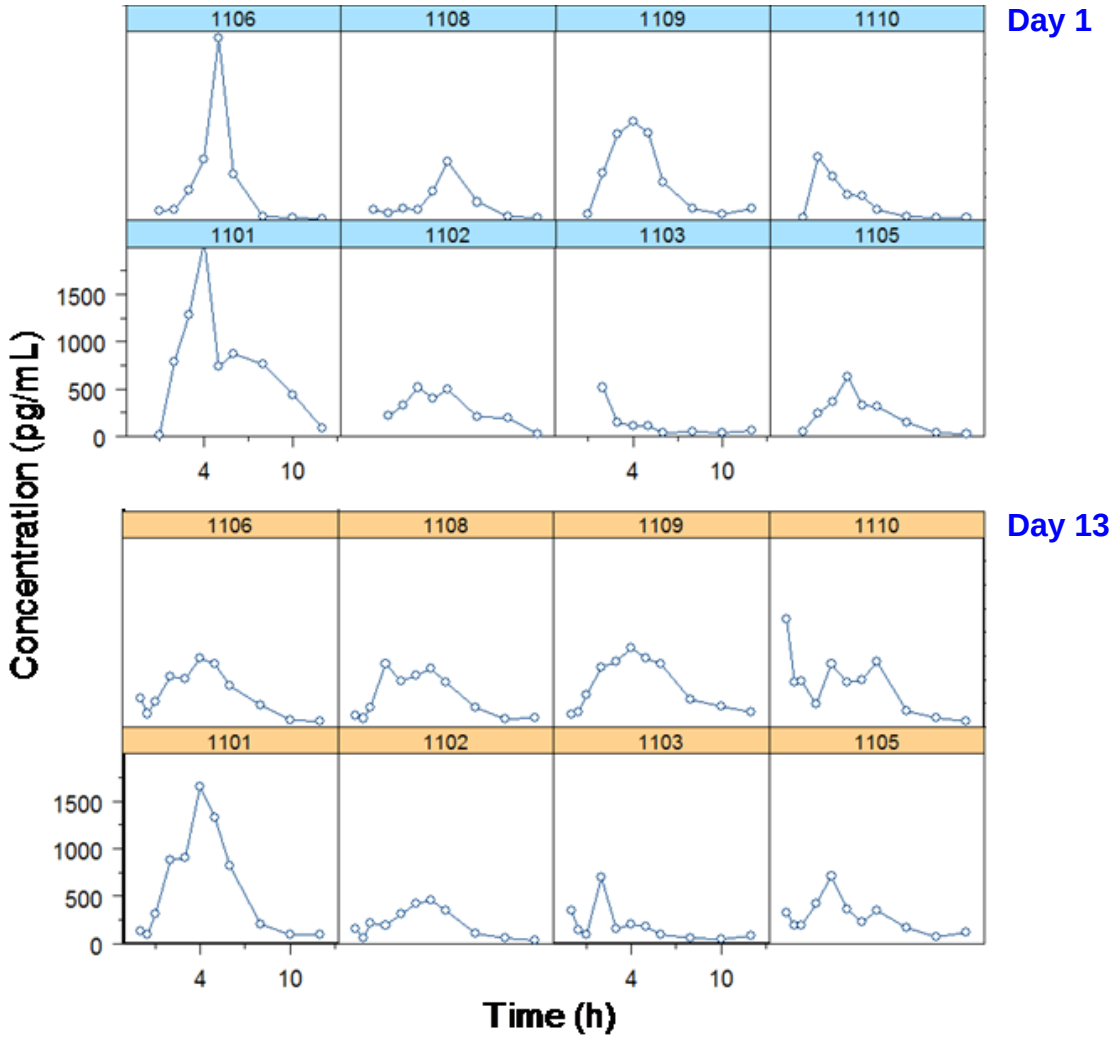

Figure 11: Concentration-time courses of treprostinil as seen within healthy volunteers following single oral dose of 1 mg treprostinil diolamine ER tablet on day 1 (top panel) and day 13 (bottom panel) [*Source*: treprostinil diolamine ER tablet arm from Study TDE-PH-104]

2.5. Intrinsic Factors

2.5.1. What intrinsic factors (age, gender, race, weight, disease, genetic polymorphism, pregnancy, and organ dysfunction) impact the systemic exposure to treprostinil? Do any of these factors warrant a dosing recommendation?

No specific pharmacokinetic studies were performed to study the impact of age, gender and weight on the systemic exposure to treprostinil. Most of the Phase 1 studies did not show any major differences in the pharmacokinetics of treprostinil which enrolled both male and female healthy volunteers with a body mass index of 19 to 40 kg/m^2. Moreover, multivariate analysis with the data obtained from Phase 3 trials, did not show any significant differences in efficacy based on age, gender, or weight.

In order to understand the impact of organ impairment on the systemic exposure to treprostinil, pharmacokinetic studies were performed in both renal and hepatic impaired subjects in comparison to healthy controls.

Renal impairment: Pharmacokinetics of treprostinil was studied in end stage renal disease (ESRD) patients in comparison to matched healthy controls to evaluate the impact of renal impairment. A total of 16 subjects were enrolled, with 8 subjects each in the ESRD and healthy volunteer group. Further, ESRD subjects were allocated to two sequences, one where treprostinil was administered immediately post-dialysis and the other where treprostinil was administered 4 h prior to dialysis procedure. Comparison of pharmacokinetic metrics between ESRD subjects dosed immediately following dialysis *vs* healthy controls in Table 6, did not show a significant impact of renal impairment on the systemic exposure to treprostinil. There was no change in C_{max} and a 23% decrease in AUC_{inf}, which is not clinically relevant given treprostinil is titrated to tolerability/target response. These results are consistent with the mass balance study results which showed <1.0% of the total administered dose excreted unchanged in the urine. Moreover, comparison of ESRD patients who were dosed 4 h prior to dialysis *vs* healthy controls also showed similar results, suggesting no major impact of hemodialysis in the clearance of treprostinil. Therefore, no dose-adjustments are warranted in renal impaired patients.

Table 6: Impact of renal impairment on the pharmacokinetics of treprostinil

	Geometric mean ratio	
	ESRD (dosing post-dialysis) *vs* Healthy	ESRD (dosing pre-dialysis) *vs* Healthy
C_{max}	1.07	0.72
$AUC_{0\text{-}inf}$	0.77	0.61

Hepatic impairment: Pharmacokinetics of treprostinil was studied in subjects with varying degrees of hepatic impairment [mild (n=8), moderate (n=8) and severe (n=6)] in comparison to matched healthy controls (n=8). There was a significant increase in the systemic exposure to treprostinil in the hepatic impaired groups with C_{max} and AUC values increased by 1.6-, 4-, 4.8-fold and 2.1-, 4.8-, 7.6-fold, respectively (Table 7). This increase in systemic exposure to treprostinil in hepatically impaired subjects is consistent with the fact that treprostinil is extensively metabolized by the liver and contributed predominantly by changes in the first pass effect.

Table 7: Impact of hepatic impairment on the pharmacokinetics of treprostinil

	Fold increase		
	Mild HI *vs* Healthy	Moderate HI *vs* Healthy	Severe HI *vs* Healthy
C_{max}	1.6	3.6	4.7
$AUC_{0\text{-}inf}$	2.2	4.6	8.2

Dosing recommendation: Following dosing recommendations are proposed for patients with different degrees of hepatic impairment:

- Mild: Lower starting dose of 0.125 mg twice daily with dose titrations made with either 0.125 mg every 3-4 days.
- Moderate: Since, increase in exposures is primarily driven by F (fraction bioavailable), a 4-fold lower dose is required for dose-adjustment. Due to the unavailability of a strength lower than 0.125 mg, the recommendation is to avoid use in patients with moderate hepatic impairment.
- Severe: Contraindicated.

2.6. Extrinsic Factors

2.6.1. What drug interactions impact the systemic exposure to treprostinil? Do any of these interactions warrant a dosing recommendation?

Treprostinil is primarily metabolized by cytochrome P450 enzymes in the liver. The major enzyme responsible for the metabolism of treprostinil is CYP2C8, which accounts for 95% of disappearance, based on *in vitro* studies using human hepatic microsomes. CYP2C9 accounts for 22% disappearance and is a minor enzyme in the metabolic pathway. Co-administered drugs which are inhibitors or inducers of these enzymes could potentially affect the systemic exposure to treprostinil. Table 8 shows the list of compounds which were tested to interact with treprostinil. On the other hand, treprostinil had no inhibitory effects on the CYP isozymes CYP2A6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 in concentrations ranging from 0.1 to 10,000 ng/mL. Also, no notable induction of enzyme activities associated with CYP1A2, 2B6, 2C9,

2C19 or 3A4 was observed upon exposure of human hepatocytes to 1,000 to 5,000 ng/mL treprostinil diolamine. Apart from metabolic drug interactions, there is a potential for proton pump inhibitors to cause an increase in the solubility of a weakly acidic drug such as treprostinil which could result in higher systemic exposures.

Table 8: List of compounds tested for potential drug interaction with treprostinil following administration of 1 mg treprostinil diolamine ER tablet

Co-administered drug	Interaction type
Gemfibrozil	CYP2C8 inhibitor
Fluconazole	CYP2C9 inhibitor
Rifampin	CYP2C8 and CYP2C9 inducer
Sildenafil	CYP2C9 inhibitor (weak)
Bosentan	CYP2C9 inducer
Esomeprazole	Potential improvement in the solubility of treprostinil

As shown in the Fig. 12, gemfibrozil, a specific inhibitor of CYP2C8, increased the systemic exposure to treprostinil by 2-fold, which confirms CYP2C8 to be the major enzyme in the metabolic pathway. There was no significant change in the systemic exposure to fluconazole (C_{max} ↔, AUC_{inf} 15%↓), a specific CYP2C9 inhibitor, suggesting that metabolism via CYP2C9 is very minor. Moreover, when rifampin, an inducer of both CYP2C8 and 2C9 was co-administered with treprostinil, there was a 17% and 22% decrease in C_{max} and AUC_{inf}, respectively. However, this decrease might not be of clinical significance since treprostinil is titrated to tolerability or target response.

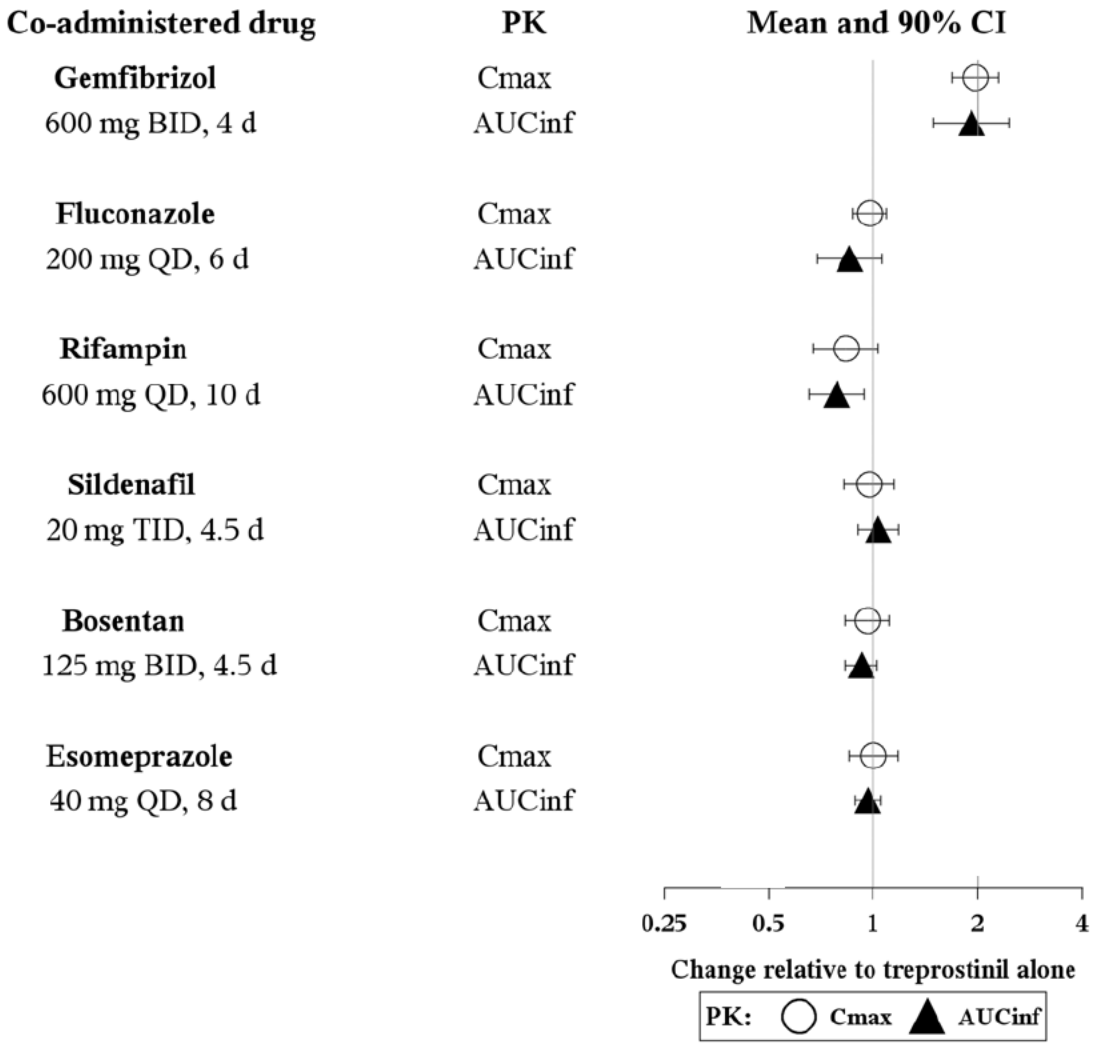

Figure 12: Impact of co-administered drugs on systemic exposure to treprostinil relative to 1.0 mg treprostinil diolamine administered alone. Data represented as mean change in PK metrics, C_{max} and AUC_{inf}, with 90% confidence intervals.

Other commonly co-administered drugs such as sildenafil and bosentan, former a weak CYP2C9 inhibitor and latter a CYP2C9 inducer, did not affect the systemic exposures to treprostinil, again indicating that the contribution of CYP2C9 to the metabolism of treprostinil is minor if not negligible. Conversely, there was no impact of treprostinil on the systemic exposures to bosentan and sildenafil including the active metabolites (data not shown). Finally, there was no effect of esomeprazole, a potent proton pump inhibitor, on the systemic exposures to treprostinil.

Dosing recommendation: Due to a 2-fold increase when co-administered with gemfibrozil, treprostinil when co-administered with CYP2C8 inhibitors, should be started at a lower dose of 0.125 mg and titrated in steps of 0.125 every 3-4 days. All other drug interactions do not require dose-adjustments.

2.7. General Biopharmaceutics

2.7.1. Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

(b) (4)

2.7.2. Does this formulation qualify as a extended release dosage form?

To qualify, typically, the concentration-time course data from a modified release dosage form is compared against an existing immediate release product of the drug to ensure features such as prolonged absorption and lower peak-to-trough fluctuations. In case of treprostinil, both the approved products, Remodulin® and Tyvaso®, are administered via non-oral routes and there is no solid oral dosage form available for comparison. However, there is a relative bioavailability study [Study TDE-PH-123] comparing treprostinil diolamine administered as 1 mg ER tablet *vs* oral solution administered as 4 x 0.25 mg dose staggered every 2 h. Since, immediate release dosage forms rapidly disintegrate to provide drug in solution, the pharmacokinetic profile following administration of the oral solution could serve as an appropriate reference to compare the extended release characteristics of the ER tablet.

It can be seen from the mean concentration-time courses in Fig. 13, that the oral solution resulted in rapid absorption of the drug with relatively higher C_{max} values. In contrast, the mean pharmacokinetic profile of the ER tablet showed sustained release of treprostinil from the dosage form, resulting in prolonged absorption with a subsequent blunt in the maximum concentration achieved. Moreover, on an average level data, the apparent elimination half-life of treprostinil following extended release tablet is prolonged when compared to rapid decline in concentration following oral solution, suggesting flip-flop pharmacokinetics which is a characteristic feature for extended release dosage forms. Therefore, the drug product given in a twice-a-day dosing regimen, qualifies as a extended release dosage form.

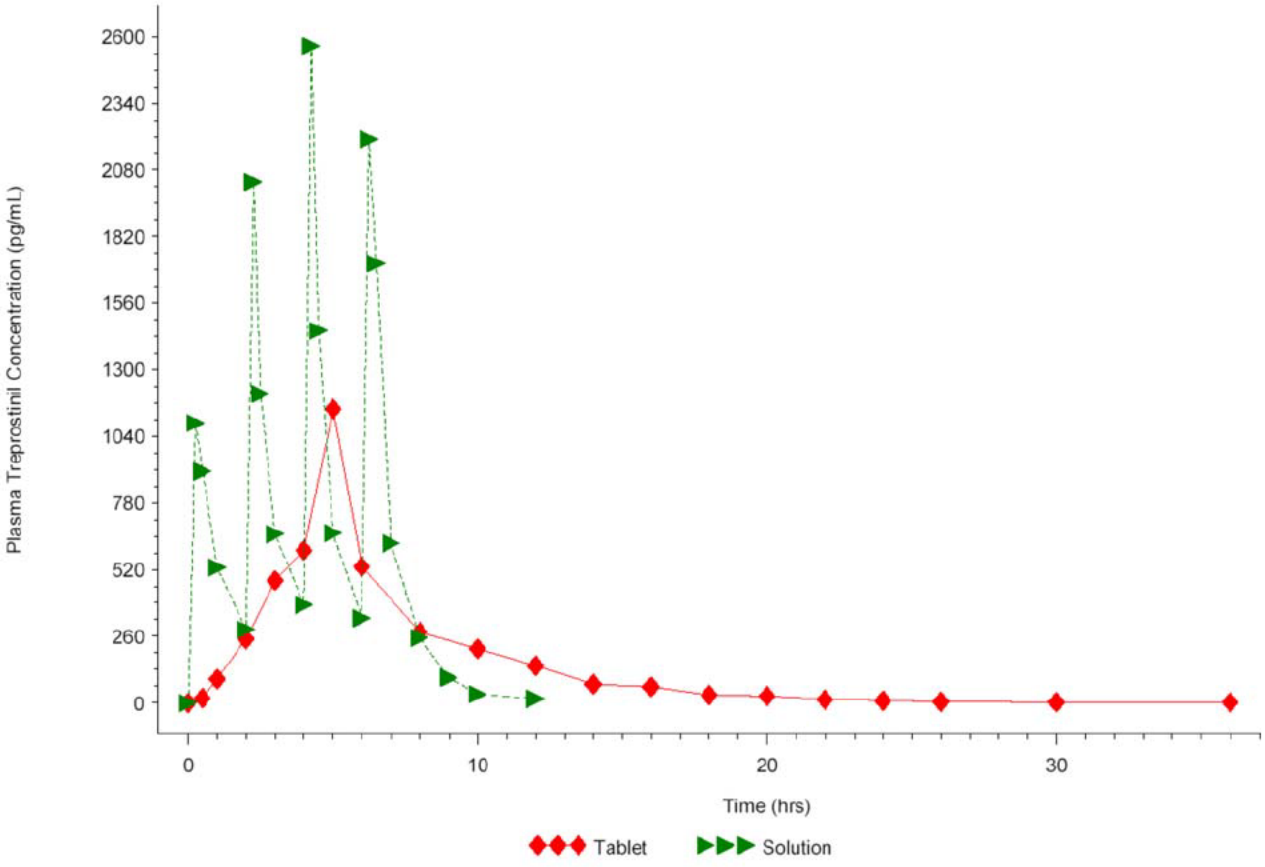

Figure 13: Mean concentration-time course following oral administration of (i) 1 mg ER tablet (ii) solution administered as 4 x 0.25 mg dose staggered every 2 h.

2.7.3. What is the effect of food on the bioavailability (BA) of treprostinil from the ER dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Meal affects the pharmacokinetic performance of the ER tablet. As shown in Fig. 14, a high calorie, high fat meal [Study TDE-PH-103] delayed the absorption to provide sustained treprostinil exposure during the 12 h inter-dosing interval when compared to fasted state. Food affected the systemic exposure to treprostinil as seen by an increase in AUC by 1.5-fold with no change in the maximum concentration achieved (Fig. 14). Moreover, food caused a decrease in the inter-subject variability in the PK metrics of treprostinil.

Further, no significant differences in the systemic exposure to treprostinil was observed when compared across meals varying in caloric and fat content [Study TDE-PH-115] as shown in Fig. 15.

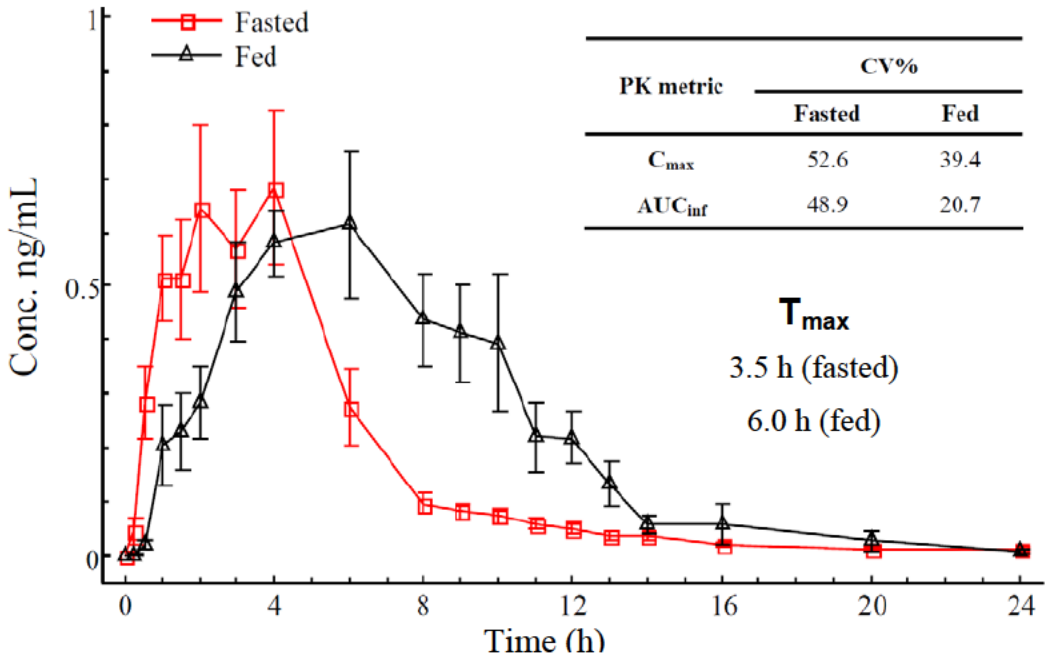

Figure 14: Mean concentration-time course of treprostinil administered as 1 mg oral ER tablet in fed (high calorie, high fat) *vs* fasted state.

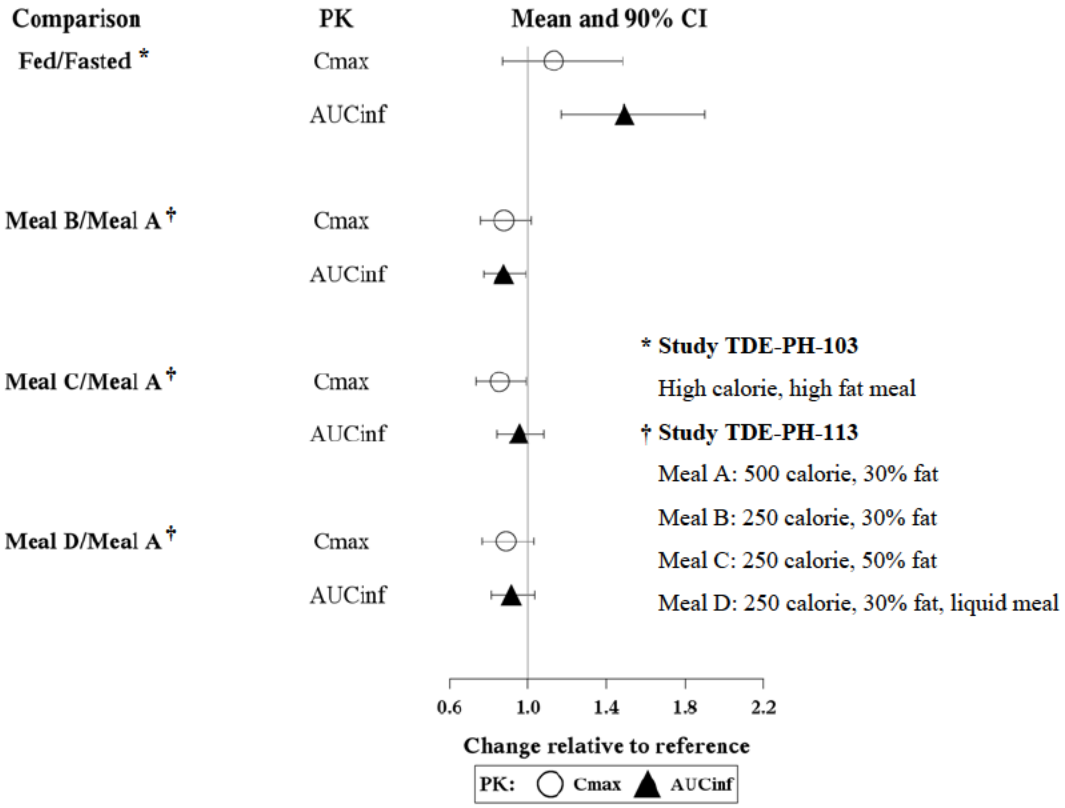

Figure 15: Impact of food and the effect of varying caloric/fat content on the systemic exposure to treprostinil.

2.8. Bioanalytical method validation

2.8.1. How are the active moieties identified and measured in the plasma? Are the bioanalytical methods that are used to assess concentrations validated?

Plasma concentrations of treprostinil were quantified by a validated ultra performance liquid chromatography/mass spectrometry/mass spectrometry (UPLC/MS/MS) method operated in negative TurboIonSpray® mode. Standard curves were constructed in the range of 10 pg/mL (lower limit of quantification, LLOQ) to 5000 pg/mL. The accuracy and precision values of the quality control samples from all supporting bio-analytical reports were equal to or better than 15% (20% at the LLOQ). All the supporting bio-analytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is therefore acceptable.

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SUDHARSHAN HARIHARAN
10/02/2012

SATJIT S BRAR
10/02/2012

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10/02/2012

Appendix: Individual study reviews

This appendix is an addendum to the clinical pharmacology review checked in DARRTS on 10/02/2012.

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Apparent permeability of UT-15C through Caco-2 monolayers

Study report: 7049-123	**Report issued:** 01/26/2005	EDR Link

TITLE

Determination of apparent permeability of UT-15C (treprostinil diolamine) through Caco-2 monolayers

OBJECTIVES

The objective of this study was to assess the extent and nature of intestinal transport of UT-15C (treprostinil diolamine) utilizing the human carcinoma cell line (Caco-2) as a model of human intestinal permeability.

METHODS

Test: UT-15C (treprostinil diolamine)

Marker compounds: Mannitol (paracellular marker), Caffeine (transcellular marker), Vinblastine (positive control for P-glycoprotein), Verapamil (P-gp inhibitor)

Test system: Caco-2 monolayers (passage 22, cultured for 26 days)

Procedure

1. Pre-incubation with verapamil (100 µM) for 30 min as in appropriate dosing chambers
2. Addition to UT-15C (10 µM) on to the dosing chamber
3. Samples were collected at 30 and 60 min post-incubation from the receiver chamber
4. Apparent permeability was calculated by the following equation:

$$P_{app} = \frac{\delta Q}{\delta t} \times \frac{1}{60AC_0} \text{ cm/s}$$

Where:

P_{app}	Apparent permeability
$\frac{\delta Q}{\delta t}$	Transport rate (pmol/minute)
A	Monolayer surface area (cm^2)
C_0	Initial donor concentration (pmol/mL)

5. The efflux ratio was calculated as:

P_{app} (basolateral to apical)/P_{app} (apical to basolateral)

RESULTS

Table 1: Apparent permeability through Caco-2 cell monolayers

Compound	Mean Papp x 10^6 (cm/second)		Efflux
	Apical to Basolateral	Basolateral to Apical	
UT-15C	3.07	3.74	1.22
UT-15C + Verapamil	2.04	2.32	1.14
Mannitol	0.561	0.574	1.02
Mannitol + Verapamil	0.530	0.487	0.919
Caffeine	36.9	51.1	1.38
Caffeine + Verapamil	37.1	NR	NA
Vinblastine	0.635	6.15	9.69
Vinblastine + Verapamil	0.857	3.62	4.22

NR No result.
NA Not applicable.

CONCLUSION

- The apparent permeabilities of paracellular and transcellular marker compounds were as expected and confirmed the maturity of the monolayers.
- Vinblastine, a positive control for P-gp, showed that it undergoes active efflux which is inhibited in the presence of verapamil, a P-gp inhibitor, and confirmed active efflux mediated by P-gp in the Caco-2 monolayers used.
- The efflux ratio of UT-15C was close to unity, suggesting that the transport of treprostinil is via passive diffusion and is independent of active mechanisms.
- The apparent permeability of UT-15C was 3.07 x 10^{-6} cm/s.

In vitro protein binding

Study report: 7049-127	**Report issued:** 05/08/2007	EDR Link

TITLE

The *in vitro* protein binding and protein binding interaction of [^{14}C] treprostinil and [^{3}H] diolamine components of UT-15C (treprostinil diolamine) in human plasma

OBJECTIVES

The purpose of the study was to determine, *in vitro*, the extent of protein binding of [^{14}C] treprostinil and [^{3}H] diolamine components of UT-15C to human plasma proteins and the potential for protein binding interactions between UT-15C and warfarin and digoxin in human plasma.

METHODS

Matrix	Experiment	Concentrations	Test Article or Ligand
Plasma (human)	Time-to-equilibrium	10 µg/mL (1, 3, 5, and 7 hours)	^{14}C-Treprostinil with Diethanolamine
		10 µg/mL (1, 3, 5, and 7 hours)	Treprostinil with ^{3}H-Diethanolamine
Plasma (human)	Concentration Dependence	0.01, 0.1, 1, and 10 µg/mL	^{14}C-Treprostinil with Diethanolamine
		0.01, 0.1, 1, and 10 µg/mL	Treprostinil with ^{3}H-Diethanolamine
Plasma (human)	Interactions	0 and 25 ng/mL	UT-15C
		2500 ng/mL	[^{3}H]Warfarin
		2 ng/mL	[^{3}H]Digoxin
Plasma (human)	Interaction Confirmation	0, 1, 2, 10, and 25 ng/mL	UT-15C
		2 ng/mL	[^{3}H]Digoxin

The protein binding of [^{14}C] treprostinil with diolamine and of [^{3}H] diolamine with treprostinil in human plasma was determined by equilibrium dialysis for 5 h at treprostinil concentrations of 0.01, 0.1, 1, and 10 µg/mL. *Note*: Time to equilibrium was determined to be 5 h for both radiolabeled components of UT-15C.

The protein binding of [^{3}H] warfarin (2500 ng/mL) in the presence and absence of UT-15C (25 ng/mL) was determined by equilibrium dialysis. Similarly, the protein binding of [^{3}H] digoxin (2 ng/mL) in the presence and absence of UT-15C (1, 2, 10 and 25 ng/mL) was determined.

Concentrations of warfarin and digoxin studies are in the therapeutic concentration range.

RESULTS

Table 1: Concentration dependent protein binding of [^{14}C] treprostinil and [^{3}H] diolamine

Treprostinil Concentration (µg/mL)	Percent ^{14}C-Treprostinil Bound		Percent ^{3}H-Diethanolamine Bound	
	Mean	SD	Mean	SD
0.01	96.1	0.4	6.07	4.93
0.1	96.3	0.1	-1.95	1.89
1	96.1	0.2	0.22	1.25
10	96.2	0.1	0.99	0.80

Table 2: Protein binding interaction between warfarin and UT-15C

Ligand	Test (ng/mL) UT-15C	% Radioactivity bound	
		Mean	SD
[^{3}H] warfarin 2500 ng/mL	0	99.0	0.1
	25	99.1	0.0

Table 3: Protein binding interaction between digoxin and UT-15C

Ligand	Test (ng/mL) UT-15C	% Radioactivity bound	
		Mean	SD
[^{3}H] digoxin 2 ng/mL	0	32.7	2.1
	1	30.6	4.0
	2	35.7	3.1
	10	36.3	3.9
	25	42.9	4.8

CONCLUSION

- The [^{14}C] treprostinil component of UT-15C was highly bound to human plasma proteins, with mean binding ranging from 96.1 to 96.3%.
- The [^{3}H] diolamine component of UT-15C was minimally bound to human plasma proteins, with the greatest mean percent bound value of 6.07% observed at 0.01 µg/mL of treprostinil.
- There was no evidence for concentration dependent protein binding of either component of UT-15C over the target treprostinil concentration range of 0.01 to 10 µg/mL.
- UT-15C (25 ng/mL) had no effect on the extensive binding of [^{3}H] warfarin to human plasma proteins confirming that UT-15C does not affect warfarin plasma protein binding.
- The protein binding of [^{3}H] digoxin seem to increase with increase in concentration of UT-15C. However, the reason for this interaction is unclear.

Mass Balance		
Study report: TDE-PH-107	**Study period:** 11/03/2006 - 11/30/2006	EDR Link
TITLE		
A single center, open-label, mass balance, metabolite profiling, and safety study of [^{14}C],[^{3}H]UT-15C (treprostinil diolamine) following single oral dose administration in healthy male subjects		
OBJECTIVES		
• To determine whole blood and plasma radioactivity of [^{14}C]treprostinil and [^{3}H]diolamine • To determine urinary and fecal recovery of total radioactivity for [^{14}C]treprostinil and [^{3}H]diolamine • To characterize and identify major metabolites		
STUDY DESIGN		
Single center, open label, mass balance and metabolite profiling study. **Test product:** [^{14}C],[^{3}H]UT-15C as an oral solution. The radioactive dose was equivalent to 0.5 mg treprostinil and 0.14 mg diolamine.		
PK Sampling		
Blood samples for pharmacokinetic analysis were obtained at the following time points: 0 h (pre-dose), and 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, and 240 h (day 11) post-dose. An aliquot of whole blood was assayed for radioactivity analysis; an aliquot of plasma was utilized for radioactivity analysis; additional aliquots of plasma were frozen for possible treprostinil parent and/or metabolite analysis. Urine samples for radio analysis were collected during the following time intervals: pre-dose catch and post-dose during the following intervals - 0 to 3 h, 3 to 6 h, 6 to 12 h, 12 to 24 h, and during each 24 h interval thereafter until the end of study or early withdrawal. Fecal samples for radio analysis of were collected pre-dose and during every 24 h interval thereafter until the end of study or early withdrawal.		
Statistical method		
Descriptive statistics (mean, SD, CV) were calculated on derived PK parameters for both [^{14}C] treprostinil and [^{3}H] diolamine. No formal statistical analyses were conducted.		
Population		
N = 8; healthy adult male volunteers Seven subjects completed the study.		

RESULTS

PK summary statistics

Table 1: Summary of mean (CV%) pharmacokinetic measures for total radioactivity in plasma and whole blood

PK metric	Plasma		Whole blood	
	[^{14}C]	[^{3}H]	[^{14}C]	[^{3}H]
C_{max} (ng eqv/mL)	17.4 (16)	1.33 (28)	8.78 (14)	1.22 (28)
T_{max} (h)†	0.5	0.25	0.375	0.25
$AUC_{0\text{-}inf}$ (h*ng eqv/mL)	33.4 (28)	151 (23)	16.5 (23)	147 (21)
$t_{1/2}$ (h)	1.4 (55)	195 (20)	0.9 (10)	228 (15)

† *Median*

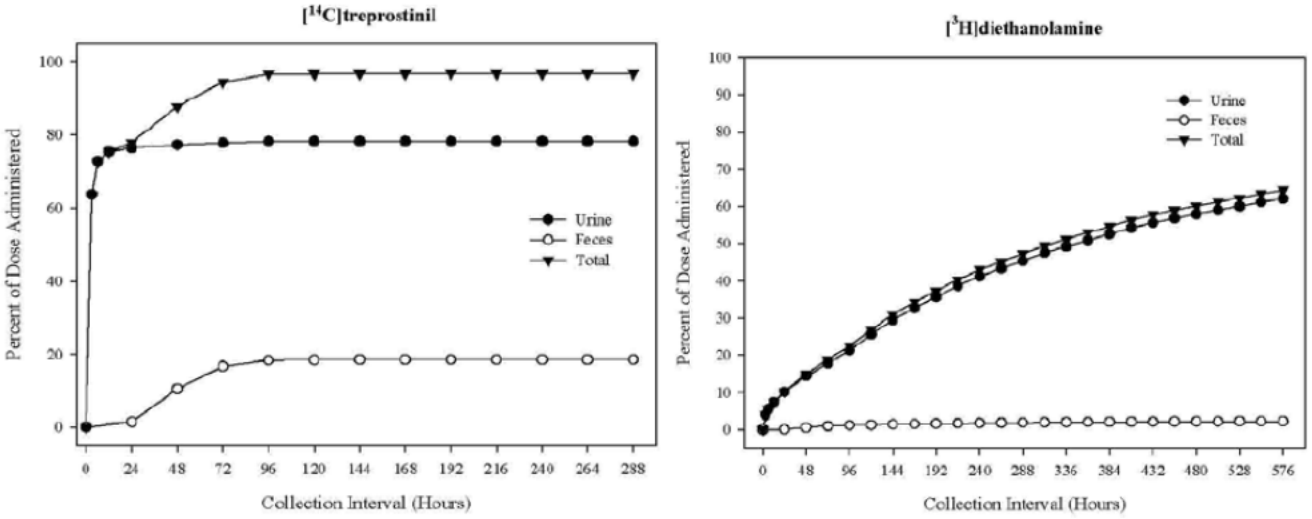


Figure 1: Mean recovery of [^{14}C] treprostinil-derived and [^{3}H] diolamine-derived radioactivity.

Table 2: Treprostinil and metabolites in urine and feces following oral administration. Results are expressed as percent of total [^{14}C] radioactivity administered.

Compound	% of administered dose		
	Urine	Feces	Total
Treprostinil (parent)	0.19	1.13	1.32
M392	12.9	4.42	17.3
M334	23.6	0.99	24.6
M348	20.2	3.50	23.7
M374	8.14	1.21	9.35
M388*	0.39	0.11	0.50
M566	2.40	0.14	2.54
Other unknowns combined	10.6	5.30	15.9
Total	**78.4**	**16.8**	**95.2**

* New metabolite by oral route compared to intravenous administration

Metabolite profiling

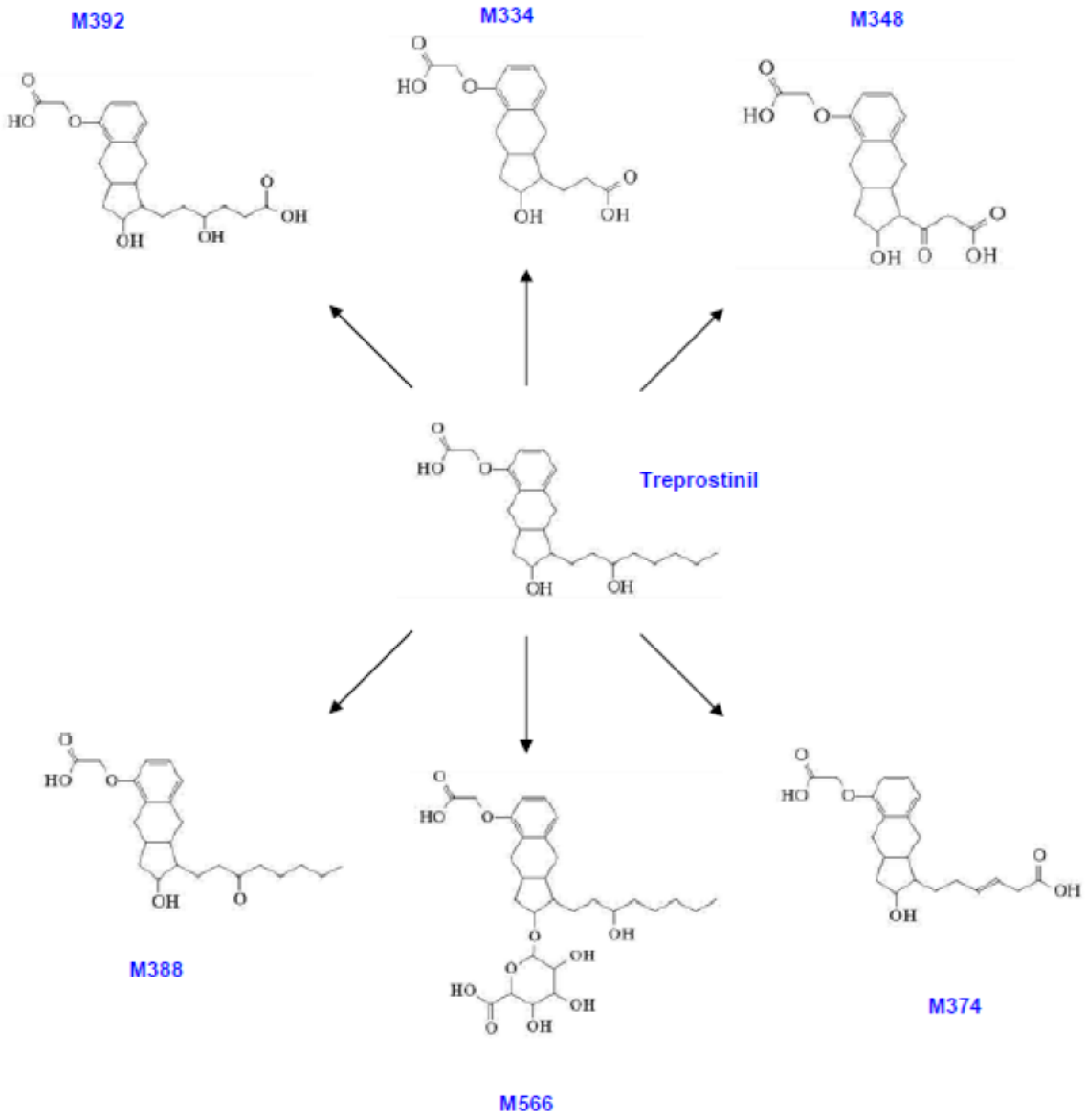


Figure 1: Metabolites of treprostinil following oral administration

CONCLUSION

- Comparison of mean AUC values for plasma and whole blood indicate that [^{14}C] treprostinil-derived radioactivity is not highly associated with red blood cells.
- Recovery of [^{14}C] treprostinil-derived radioactivity was near to complete (> 95%) within 96 h of study drug administration. However, the overall mean recovery of [^{3}H] diolamine-derived radioactivity was only 64.3% over day 24, suggesting that diolamine-derived radioactivity was incomplete.
- The predominant route of excretion of [^{14}C] treprostinil-derived radioactivity following oral administration was via urine. A mean of 78.2% of the dose was excreted in urine; however the unchanged parent drug represented only 0.19% of the total administered dose, suggesting that renal elimination is a minor pathway for treprostinil. Feces accounted for 16.8% of [^{14}C] treprostinil-derived radioactivity.
- The predominant route of excretion of [^{3}H] diolamine-derived radioactivity following oral

administration was also via urine. A mean of 62.1% of the dose was excreted in urine and 2.25% was excreted in feces.

- Following administration of UT-15C, the active moiety, [^{14}C] treprostinil was extensively metabolized with metabolism occurring on the side chain of the molecule. Processes involved oxidation, oxidative cleavage, dehydration, and glucuronic acid conjugation. Six metabolites of treprostinil were identified, with quantities ranging from 0.5 to 24.6% of dose.
- There was no significant change in the metabolic profile of treprostinil following oral route, except for one new metabolite, M388, which accounted for only 0.5% of the total administered dose.

Absolute bioavailability

Study report: TDE-PH-114	**Study period:** 12/06/2008 - 12/15/2008	EDR Link

TITLE

An open label, randomized, crossover comparative pharmacokinetic and absolute bioavailability study of 1 mg UT-15C (treprostinil diolamine) ER tablet and administration of Remodulin® by continuous intravenous infusion to normal healthy volunteers

OBJECTIVE

To assess the absolute bioavailability of treprostinil diolamine ER oral tablet

STUDY DESIGN

Open-label, single center, single-dose, two-period, two-sequence, crossover pharmacokinetic study in healthy volunteers.

	Period 1	Period 2
Seq. 1	TDE ER 1 mg (SD)	0.2 mg Remodulin® administered as *i.v.* infusion over 4 h
Seq. 2	0.2 mg Remodulin® administered as *i.v.* infusion over 4 h	TDE ER 1 mg (SD)

A 7-day wash-out separates both the periods.

PK Sampling

In each dose period, blood samples for PK assessments were carried out at 0 (pre-dose), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42 and 48 h post-dose.

Statistical method

ANOVA model on log transformed parameters AUC to calculate the absolute bioavailability. LS mean and the 90% CI for absolute bioavailability is constructed.

Population

Healthy subjects.
N = 24 adult male and female healthy volunteers were enrolled in the study. All twenty four subjects completed the study.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-0.3 to 0.8 %
Precision	2.8 to 9.5 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER 1 mg (Oral)**	**Remodulin® 0.2 mg, i.v. infusion 4 h**
C_{max} (ng/mL)	0.775 (40)	1.40 (14)
T_{max} (h)†	4.0	3.5
$AUC_{0\text{-}last}$ (h*ng/mL)	3.55 (29)	4.11 (16)
$AUC_{0\text{-}\infty}$ (h*ng/mL)	3.63 (29)	4.12 (16)
$t_{1/2}$ (h)	5.31 (75)	1.03 (67)

† *Median*

Table 2: Absolute bioavailability of treprostinil diolamine ER tablet

	Least square means			
PK metric	**TDE ER 1 mg (Oral)**	**Remodulin® 1 mg, i.v. infusion (dose-normalized)**	**Absolute bioavailability (F)**	**90% CI**
$AUC_{0\text{-}\infty}$ (h*ng/mL)	3.47	20.36	0.17	(0.16, 0.19)

Concentration-time profile

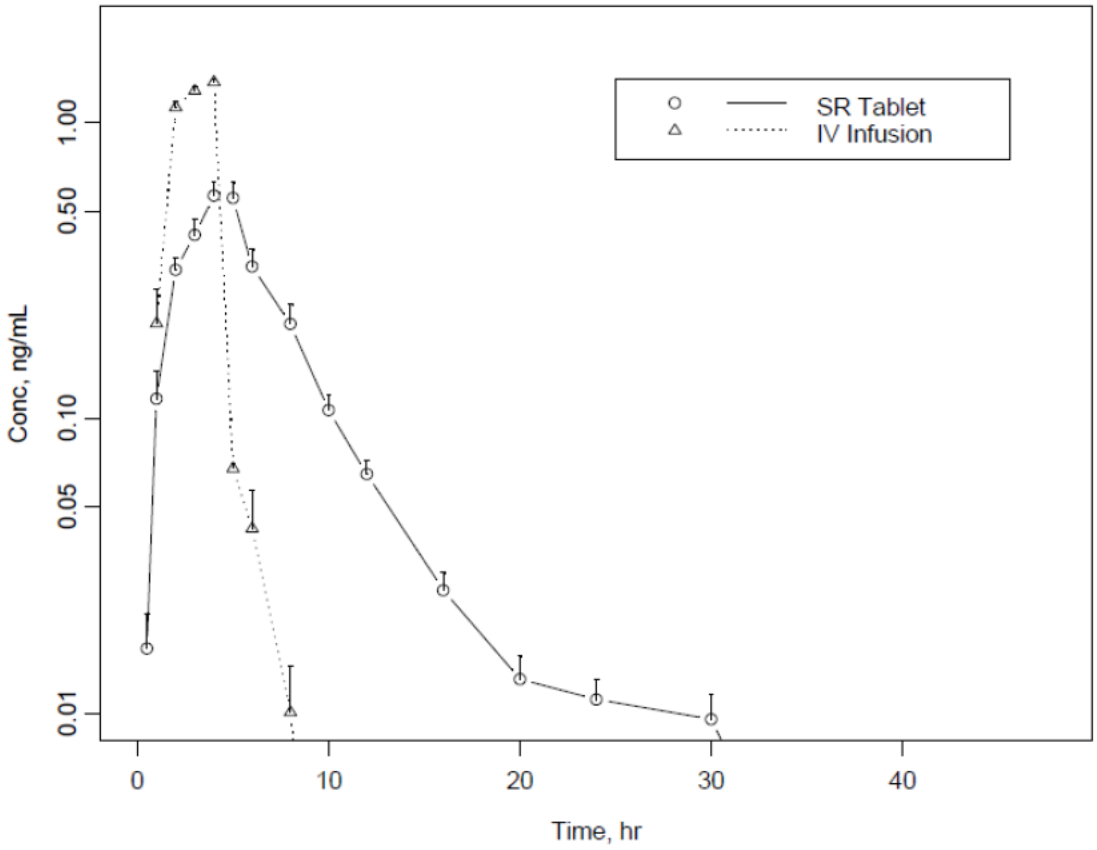


Figure 1: Mean treprostinil plasma concentration-time profile following 1 mg single-dose treprostinil diolamine and 0.2 mg Remodulin® administered as continuous infusion for 4 h.

CONCLUSION

- The absolute bioavailability of treprostinil is 17%.

Relative bioavailability

Study report: TDE-PH-123	**Study period:** 08/14/2010 - 08/22/2010	EDR Link

TITLE

A comparative bioavailability study of UT-15C (treprostinil diolamine) ER oral tablets and UT-15C administered as an oral solution in healthy volunteers

OBJECTIVE

To assess the relative bioavailability of treprostinil administered as oral ER tablet *vs* solution

STUDY DESIGN

Open-label, single center, two-period, two-sequence, crossover pharmacokinetic study in healthy volunteers.

	Period 1	Period 2
Seq. 1	TDE ER 1 mg (SD)	0.25 mg treprostinil oral solution administered every 2 h x 4 times
Seq. 2	0.25 mg treprostinil oral solution administered every 2 h x 4 times	TDE ER 1 mg (SD)

A 7-day wash-out separates both the periods.

PK Sampling

In each dose period, blood samples for PK assessments were carried out at 0 (pre-dose), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30 and 36 h post-dose.

Statistical method

ANOVA model on log transformed AUC to calculate relative bioavailability. LS mean and the 90% CI for relative bioavailability is constructed.

Population

Healthy subjects.
N = 24 adult male and female healthy volunteers were enrolled in the study. All twenty four subjects completed the study.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-5.0 to -2.0 %
Precision	2.8 to 5.5 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER 1 mg (oral tablet)**	**TDE 1 mg (oral solution)**
C_{max} (ng/mL)	1.25 (44)	3.19 (41)
T_{max} (h)†	5.0	0.5
$AUC_{0\text{-}last}$ (h*ng/mL)	5.02 (40)	6.97 (25)
$AUC_{0\text{-}\infty}$ (h*ng/mL)	5.11 (39)	7.01 (25)
$t_{1/2}$ (h)	3.94	1.03

† *Median*

Table 2: Relative bioavailability of treprostinil diolamine ER tablet

	Least square means		Relative bioavailability (F)	90% CI
PK metric	**TDE ER 1 mg (oral tablet)**	**TDE 1 mg (oral solution)**		
$AUC_{0\text{-}\infty}$ (h*ng/mL)	4.75	6.80	0.699	(0.624, 0.783)

Concentration-time profile

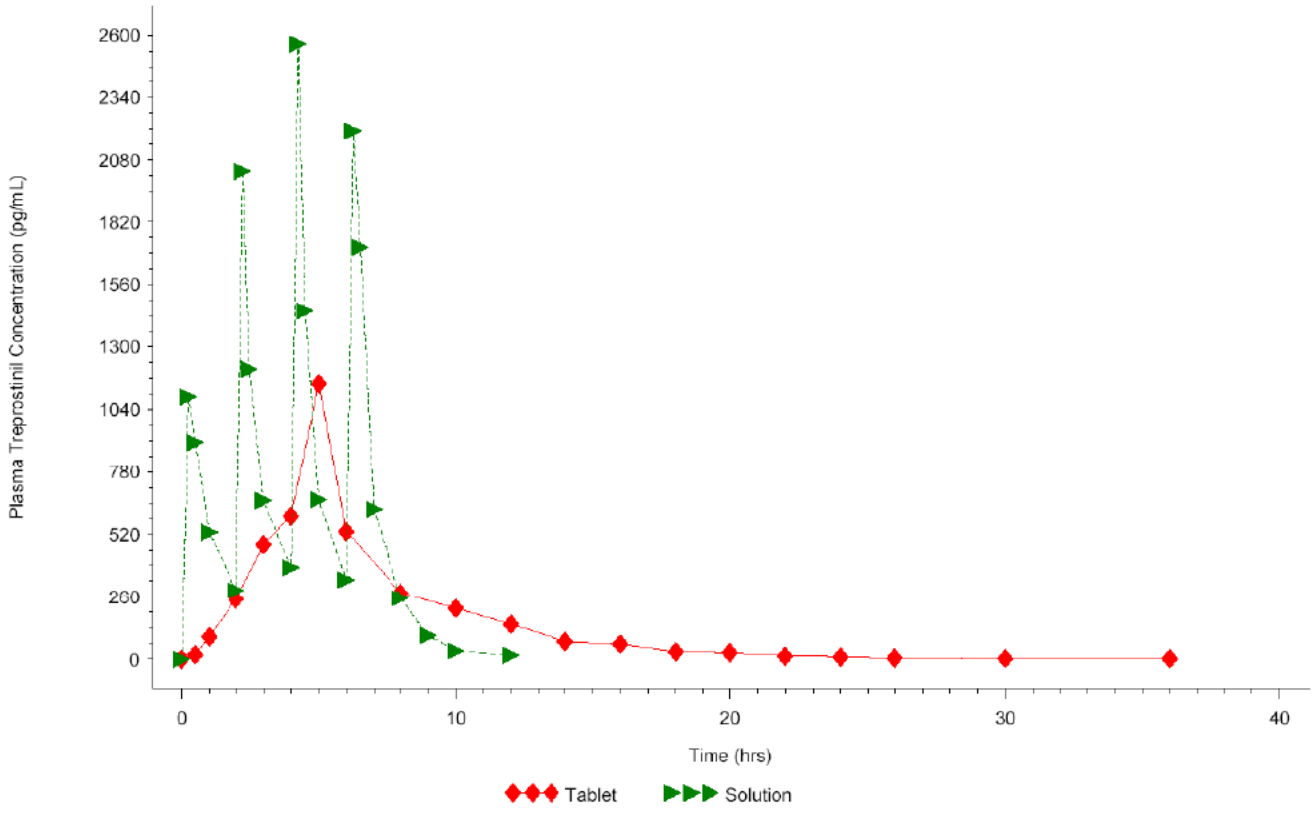


Figure 1: Mean treprostinil plasma concentration-time profile following 1 mg single-dose treprostinil diolamine and 0.25 mg treprostinil diolamine oral solution administered every 2 h x 4 times.

CONCLUSION

- The relative bioavailability of treprostinil ER oral tablet relative to oral solution is 70%.

Single- and multiple-dose PK

Study report: TDE-PH-104	**Study period:** 08/17/2005 - 08/31/2005	EDR Link

TITLE

A 14-day randomized, double-blind, placebo-controlled, parallel-group study evaluating the pharmacokinetics and safety of a sustained release tablet of UT-15C (treprostinil diolamine) administered in fixed and escalating doses in healthy volunteers.

OBJECTIVE

To evaluate the pharmacokinetics and safety of sub-chronic administration of treprostinil diolamine ER tablet at a fixed dose and upon dose escalation over a 14-day period

STUDY DESIGN

Single center, randomized, double-blind, placebo-controlled, parallel group study

Cohort 1: 23 doses of TDE ER 1 mg (or placebo) administered over 13 days
Cohort 2: 12 doses of TDE ER 1 mg (or placebo) administered over 7 days and
11 doses of TDE ER 2 mg (or placebo) administered over six days, if tolerated
Cohort 3: 12 doses of TDE ER 2 mg (or placebo) administered over 7 days and
11 doses of TDE ER 3 mg (or placebo) administered over six days, if tolerated

PK Sampling

Blood samples for pharmacokinetic analysis were obtained at the following time points on days 1 and 13: 0 (pre-dose), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, and 36 h post-dose. Additional samples at 42 and 48 h were collected on day 13.

Statistical method

N/A

Population

N = 36, healthy adult volunteers; 12 per cohort.
One subject withdrew consent and discontinued the study after the first dose; there were no associated AEs. Thirty five subjects received 23 doses of study drug and completed the study; however, six of these subjects required a reduction of the prescribed dose due to AEs.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5120
QCs (pg/mL)	30, 1920, 3840
Accuracy/Bias	-1.7 to 4.0 %
Precision	9.6 to 11 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures for treprostinil on day 1 (A) and day 13 (B)

(A)

Parameter	Cohort 1 (n = 9)	Cohort 2 (n = 7)	Cohort 3 (n = 4)
Treprostinil Dose	**1.0 mg**	**1.0 mg**	**2.0 mg**
C_{max} (ng/mL)	0.99 (60.7%)	0.85 (24.2%)	1.54 (49.7%)
T_{max} (hr)[†]	4.00	3.07	3.00
$AUC_{0\text{-}36h}$ (hr*ng/mL)	3.83 (62.9%)	3.86 (35.6%)	7.20 (48.5%)
AUC_{inf} (hr*ng/mL)	3.88 (62.1%)	4.01 (36.5%)	7.30 (48.4%)

(B)

Parameter	Cohort 1 (n = 9)	Cohort 2 (n = 7)	Cohort 3 (n = 4)
Treprostinil Dose	**1.0 mg**	**2.0 mg**	**3.0 mg**
C_{max} (ng/mL)	0.87 (40.3%)	1.66 (46.7%)	1.63 (23.4%)
T_{max} (hr)[†]	4.0	4.0	3.5
$AUC_{0\text{-}12h}$ (hr*ng/mL)	4.07 (37.9%)	8.12 (33.4%)	8.79 (29.7%)

Table 2: Summary of treatment emergent adverse events by treatment cohort

COHORT	Study Drug*2	
	UT-15C SR (n=9 per cohort)	**Placebo** (n=3 per cohort)
1	7 (78%) [24]	1 (33%) [1]
2	8 (89%) [65]	3 (100%) [5]
3	9 (100%) [50]	1 (33%) [2]
TOTAL	24 (89%) [139]	5 (56%) [8]

*Numbers displayed are number of subjects (% subject) [number of adverse events]

Concentration-time profile

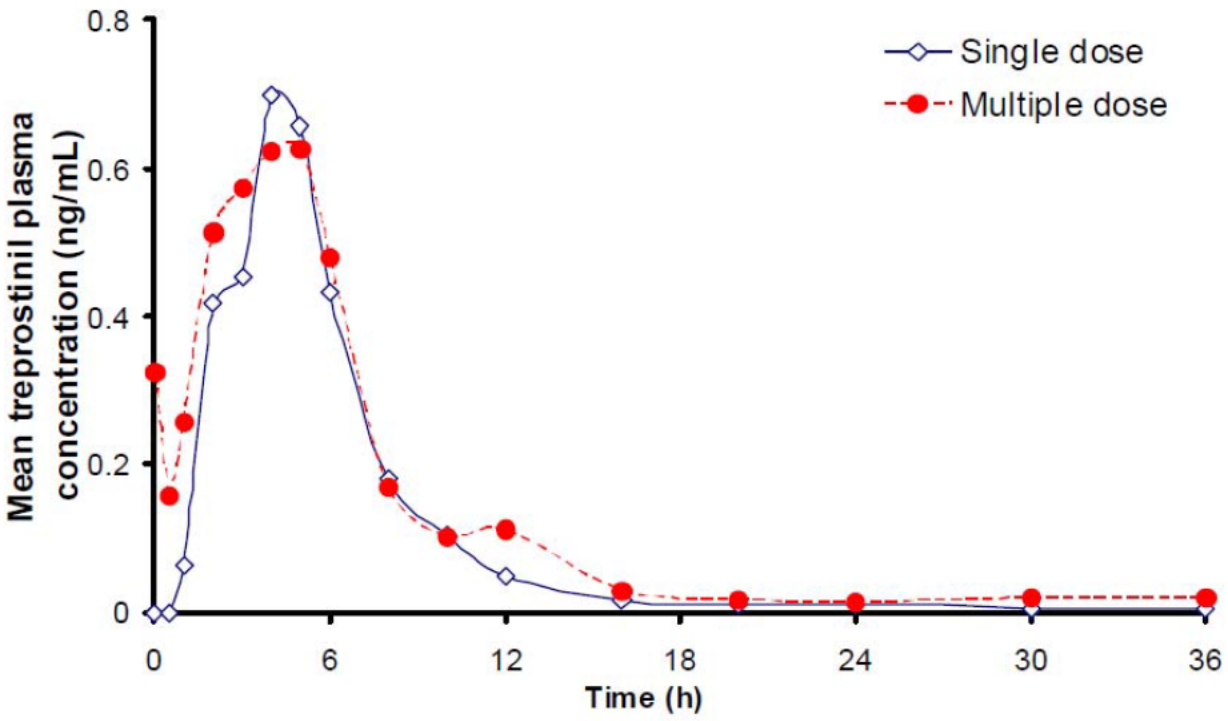


Figure 1: Mean treprostinil plasma concentration-time profile following multiple doses of 1 mg treprostinil diolamine administered BID in healthy volunteers on days 1 and 13.

CONCLUSION

- The concentration-time course of treprostinil is highly variable across individual which prevents a reliable estimation of the elimination half-life and other pharmacokinetic parameters.
- The pharmacokinetic profiles and the measures are similar between day 1 and 13 in cohort 1 following repeat dosing of 1 mg TDE ER, suggesting very minimal accumulation with a BID regimen.
- Since, there is no significant accumulation between day 1 and 13 in cohort 1, an estimate of within subject variability can be obtained. Based on this study (n=8), the root mean square error (RMSE; which provides a fair estimate of within-subject variability) is 31% and 25% for C_{max} and AUC, respectively.
- The number of treatment related adverse events increased with increase in exposure to treprostinil (Table 2).

ER prototype selection and the effect of a high fat meal

Study report: TDE-PH-103	**Study period:** 04/22/2005 - 05/01/2005	EDR Link

TITLE

A safety, tolerability and pharmacokinetic study comparing three 12 h sustained release tablet prototypes of UT-15C (treprostinil diolamine) administered to healthy adult volunteers in the fasted and fed states

OBJECTIVE

The objective of the study was to compare the pharmacokinetic performance of the three extended release prototypes in fed and fasted state and to select an appropriate dosage form for further clinical development.

STUDY DESIGN

Open-label, single center, three-cohort, two-period, crossover pharmacokinetic study in healthy volunteers.

Cohort 1 (N=10): Formulation A ((b) (4) – Single-dose, fed *vs* fasted
Cohort 2 (N=10): Formulation B (b) (4) – Single-dose, fed *vs* fasted
Cohort 3 (N=10): Formulation C (b) (4) – Single-dose, fed *vs* fasted
Dose = 1 mg

Formulations A and B were developed by (b) (4) where the core composition was altered to achieve different release rates. Formulation C was manufactured by (b) (4) and the release is mediated by an osmotic mechanism through a laser drilled hole. All the formulations were administered both in fed and fasted state to evaluate if concentrations were sustained during the inter-dosing interval of 12 h.

PK Sampling

In each dosing cohort, blood samples were to be obtained at 0 (pre-dose), and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13, 14, 16, 20 and 24 h post-drug administration.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 30 adult male and female healthy volunteers were enrolled in the study with 10 subjects per cohort. All 30 subjects completed this study.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 2560
QCs (pg/mL)	30, 960, 1600
Accuracy/Bias	-5.3 to -3.7 %
Precision	4.4 to 13.7 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil when administered as three different sustained release prototypes

Parameter	COHORT [redacted] (b) (4)					
	Fasted (n=10)	Fed (n=10)	Fasted (n=10)	Fed (n=10)	Fasted (n=10)	Fed (n=10)
T_{lag} (hr)[a]	0.13	0.42	0.25	0.5	0.13	0.25
C_{max} (ng/mL)	1.843 (51.7%)	2.21 (78.9%)	0.926 (64.8%)	0.975 (22.4%)	0.862 (52.6%)	0.931 (39.4%)
T_{max} (hr)[a]	2.03	4.00	2.5	9.0	3.5	6.0
$T_{1/2}$ (hr)	3.37 (76.0%)[b,c]	1.42 (27.9%)[b,c]	9.12 (60.9%)[b]	4.44 (112.5%)[b]	5.28 (68.9%)	3.14 (99.5%)
λ_z (/hr)	0.306 (55.5%)[c]	0.519 (23.5%)	0.113 (63.9%)	0.361 (91.9%)	0.188 (54.2%)	0.387 (58.9%)
AUC_{0-24h} (ng*hr/mL)	5.293 (53.0%)	6.044 (37.6%)	3.206 (44.8%)	4.105 (21.3%)	3.899 (50.4%)[b]	5.444 (20.9%)[b]
AUC_t (ng*hr/mL)	5.279 (53.1%)	6.011 (37.5%)	3.195 (45.1%)	4.091 (21.4%)	3.895 (50.5%)	5.419 (20.8%)
AUC_{inf} (ng*hr/mL)	4.975 (53.5%)[c]	6.058 (37.4%)	3.398 (40.1%)	4.556 (27.0%)	4.028 (48.9%)[b]	5.5 (20.7%)[b]
CL/F (mL/hr/kg)	3641 (55.6%)[c]	2524 (24.7%)	4889 (48.0%)	3282 (33.3%)	4071 (51.2%)	2490 (18.5%)
V_z/F (mL/kg)	22509 (124.9%)[c]	5240 (41.7%)	73155 (100.6%)	17427 (86.7%)	35568 (124.5%)	11419 (97.6%)

[a] Median is reported for T_{max} and T_{lag}.
[b] Significantly different results for the two treatments (α=0.05). [ANOVA was performed on C_{max}, AUC_{inf}, AUC_{0-24h} and $T_{1/2}$.]
[c] n = 9

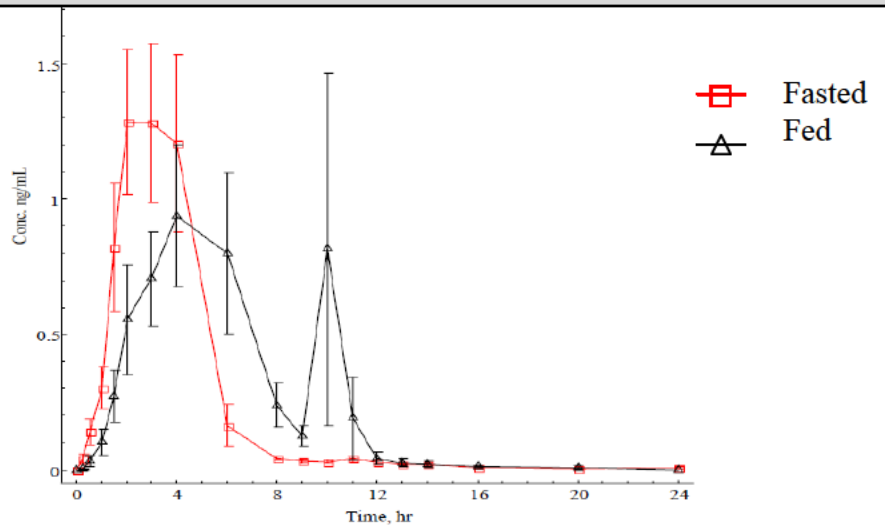
Table 2: Effect of food on the pharmacokinetic measures of treprostinil across three different sustained release prototypes

Cohort	Parameter	Least Squares Geometric Means		Ratio of Means	90% Confidence Interval[a]
(b) (4)		Fasted (n=10)	Fed (n= 10)		
	C_{max} (ng/mL)	1.63	1.77	1.09	0.73, 1.62
	AUC_{inf} (ng*hr/mL)[b]	4.23	5.33	1.26	0.87, 1.83
	AUC_{0-24h} (ng*hr/mL)	4.58	5.71	1.25	0.89, 1.76
(b) (4)		Fasted (n=10)	Fed (n=10)		
	C_{max} (ng/mL)	0.78	0.95	1.22	0.85, 1.76
	AUC_{inf} (ng*hr/mL)	3.13	4.42	1.41	1.04, 1.92
	AUC_{0-24h} (ng*hr/mL)	2.87	4.02	1.40	1.04, 1.88
(b) (4)		Fasted (n=10)	Fed (n=10)		
	C_{max} (ng/mL)	0.77	0.87	1.13	0.87, 1.48
	AUC_{inf} (ng*hr/mL)	3.61	5.39	1.49	1.17, 1.90
	AUC_{0-24h} (ng*hr/mL)	3.45	5.33	1.55	1.20, 1.99

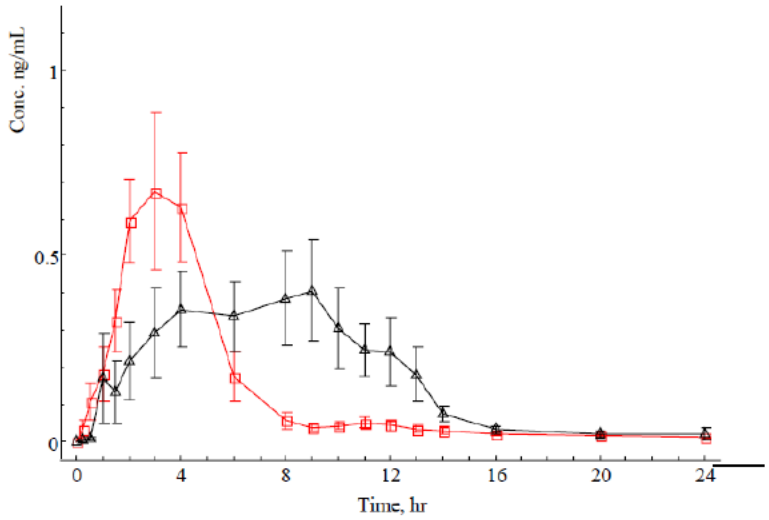
[a] The 90% confidence intervals were outside the reference ranges (0.70-1.43 for C_{max} and 0.80-1.25 for AUC_{inf}) that indicate bioequivalence.
[b] n=9

Concentration-time profile

(b) (4)



(b) (4)



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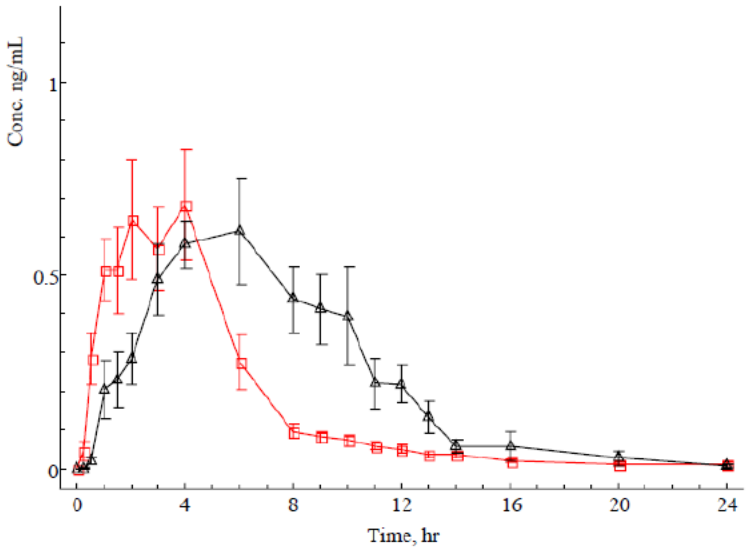


Figure 1: Mean treprostinil plasma concentration-time profile following 1 mg single-dose treprostinil diolamine administered as three different extended release prototypes in fed *vs* fasted states.

CONCLUSION

- [redacted] did not sustain the plasma concentrations of treprostinil during the inter-dosing interval in either fasted or fed state. Therefore, the sponsor ruled out this dosage from further clinical development.
- [redacted] and [redacted] formulation did reasonably well to sustain the plasma concentration of treprostinil during the inter-dosing interval of 12 h. Both formulations when administered in a fed state reduced the inter-subject variability from 50% to 20%. Moreover, the [redacted] formulation showed improved bioavailability when compared to [redacted] and hence was chosen as the desired dosage form for further clinical development.
- A high fat meal increased the systemic exposure to treprostinil by 50%. Due to a higher relative bioavailability and lower inter-subject variability, all clinical pharmacology studies and the pivotal efficacy trials were carried out by administering treprostinil diolamine with a standard meal.

Effect of meal with varying caloric and fat content

Study report: TDE-PH-115	**Study period:** 10/03/2009 - 11/01/2009	EDR Link

TITLE

Effect of different meal types on the pharmacokinetics of a single 1 mg oral dose of UT-15C (treprostinil diolamine) ER tablets in healthy volunteers

OBJECTIVE

To compare the effects of different meal compositions including a 500 calorie balanced meal (Meal A), a 250 calorie balanced meal (Meal B), a 250 calorie high fat meal (Meal C), or a 250 calorie liquid meal replacement supplement (Ensure®; Meal D) on the pharmacokinetics of treprostinil following a single oral dose of 1 mg UT-15C ER tablet in healthy subjects.

STUDY DESIGN

Open-label, single center, four-treatment, four-period, four-sequence, crossover pharmacokinetic study in healthy volunteers.

Meal A (WB500): 500 calorie balanced meal (55% carbohydrate, 30% F, 15% protein)
Meal B (WB250): 250 calorie balanced meal (55% carbohydrate, 30% F, 15% protein)
Meal C (HF250): 250 calorie high fat meal (30% carbohydrate, 50% F, 20% protein)
Meal D (Ensure®): 250 calorie liquid meal supplement (54% carbohydrate, 30% fat, 16% protein)
Dose = 1 mg

PK Sampling

In each dose period, blood samples for PK assessments were carried out at 0 (pre-dose), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32 and 36 h post-dose.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 32 adult male and female healthy volunteers were enrolled in the study. Thirty subjects completed this study.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-2.7 to 0.5 %
Precision	2.7 to 4.9 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil when administered together with four different meal types

Meal Type	Statistics	C_{max} (pg/mL)	t_{max} (hr)	$AUC_{(0-24)}$ (hr*pg/mL)	$AUC_{(0-t)}$ (hr*pg/mL)	$AUC_{(0-inf)}$ (hr*pg/mL)	t½ (hr)
A (WB500) n=31	GeoMean	818	na	3379	3391	3502	3.26
	CVb%	54.5	na	54.2	55.7	55.2	67.1
	Median	840	4.0	3785	3853	3956	3.12
	Min	326	1.0	915.0	884.4	916.2	1.08
	Max	1860	16	8406	8656	8792	9.80
B (WB250) n=31	GeoMean	715	na	2927	2932	3033	3.57
	CVb%	54.6	na	44.5	45.4	43.8	54.2
	Median	677	4.0	2952	3041	3090	4.02
	Min	310	2.0	1368	1368	1434	0.65
	Max	2180	10	8551	8551	8576	9.97
C (HF250) n=30	GeoMean	691	na	3208	3217	3296	3.39
	CVb%	39.9	na	45.1	46.5	45.6	53.0
	Median	626	4.0	3237	3161	3257	3.99
	Min	390	0.5	1208	1163	1227	1.04
	Max	1890	6.0	7773	7773	7813	6.50
D (Ensure®) n=30	GeoMean	720	na	3060	3075	3157	3.23
	CVb%	31.0	na	31.8	33.1	32.4	46.6
	Median	699	3.1	3162	3191	3271	3.55
	Min	366	2.0	1615	1594	1616	1.19
	Max	1210	5.1	6257	6257	6327	7.35

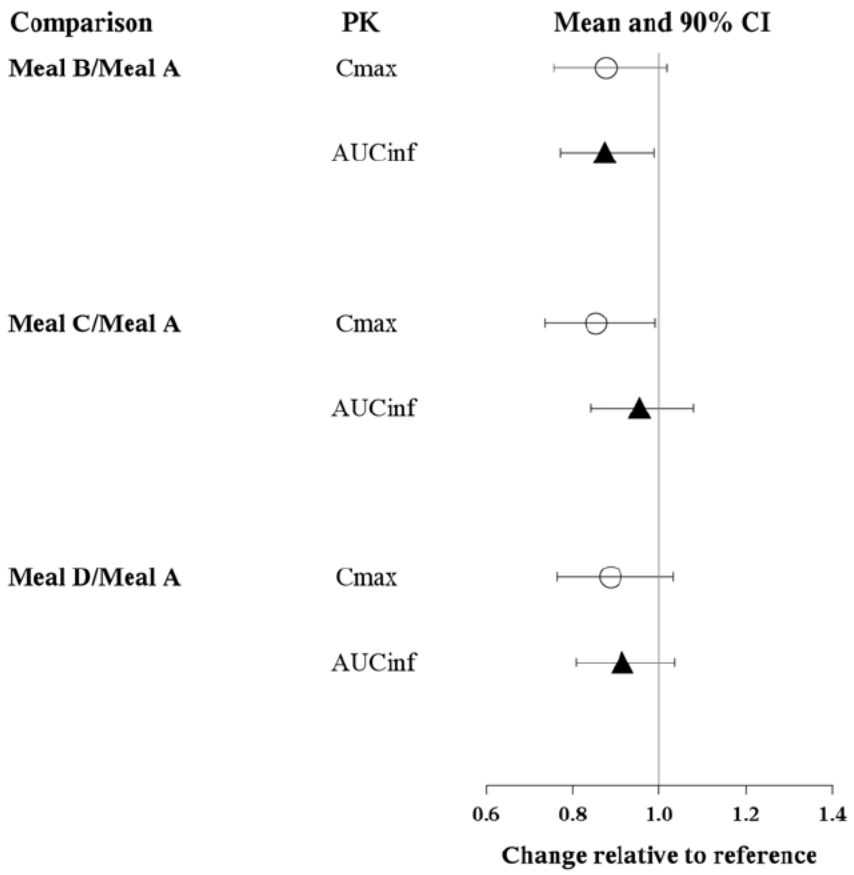


Figure 1: Effect of four different meal types on the pharmacokinetic measures of treprostinil

Concentration-time profile

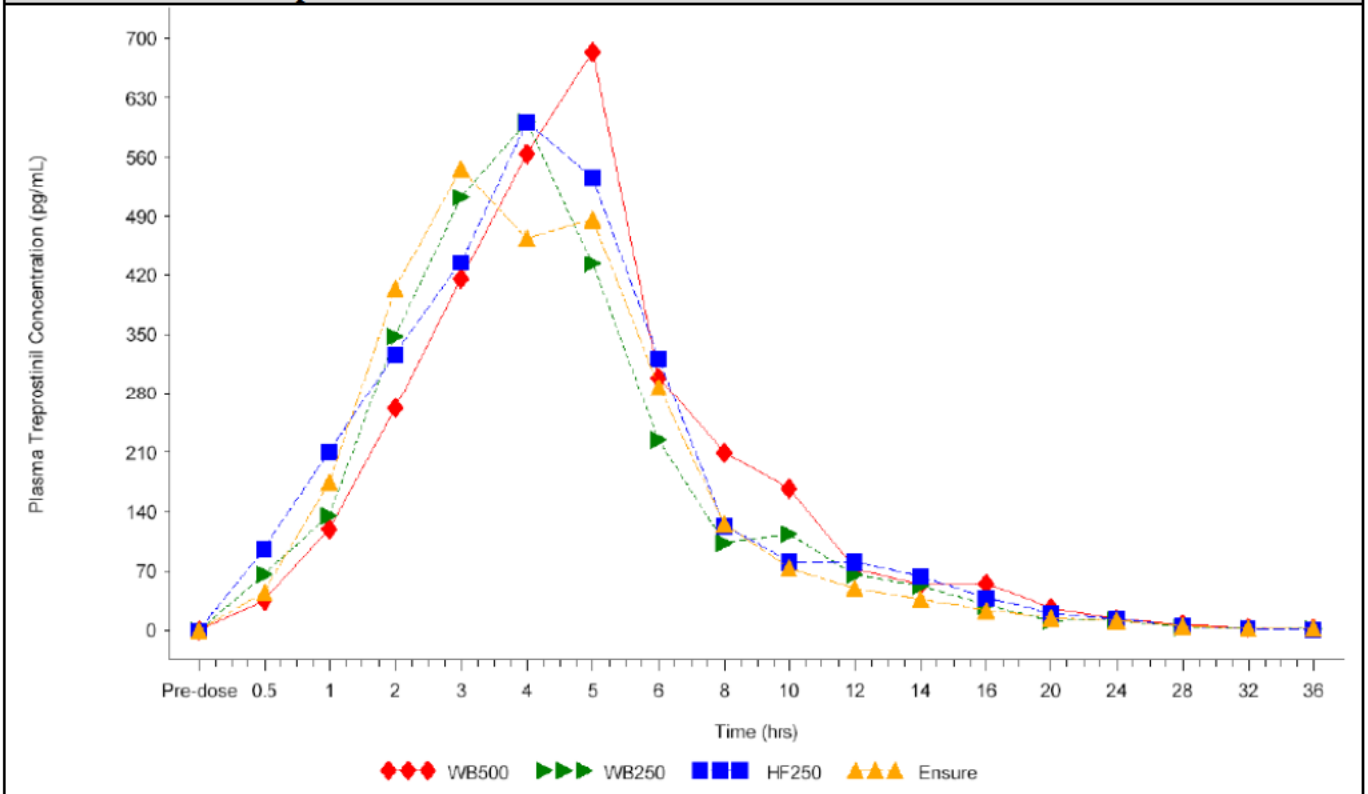


Figure 2: Mean treprostinil plasma concentration-time profile following 1 mg single-dose treprostinil diolamine administered with four different meal types.

CONCLUSION

- As seen earlier, when administered with a high fat meal (study TDE-PH-103) systemic exposure to treprostinil increased by 50%,
- However, there is no impact in the systemic exposure to treprostinil when TDE ER tablet is administered with meals varying in caloric and fat content, suggesting a meal alone affects the exposure irrespective of the caloric and fat content.
- All clinical pharmacology and pivotal efficacy trials were carried out in a fed state with a standardized meal at breakfast and dinner (approx. 500 calories).

Effect of renal impairment

Study report: TDE-PH-120	**Study period:** 07/13/2010 - 09/24/2010	EDR Link

TITLE

An evaluation of the pharmacokinetics and safety of a single-dose of UT-15C (treprostinil diolamine) ER in subjects with renal impairment

OBJECTIVE

To evaluate the impact of renal impairment on the pharmacokinetics of treprostinil.

STUDY DESIGN

Open-label, single center, single-dose, two-period, two-sequence crossover study in ESRD patients compared to healthy controls.

Cohort: *ESRD patients*

	Period 1	Period 2
Seq. 1	TDE ER 1 mg 4 h prior to dialysis	TDE ER 1 mg immediately following dialysis
Seq. 2	TDE ER 1 mg immediately following dialysis	TDE ER 1 mg 4 h prior to dialysis

A 14-day wash-out separates both the periods

Cohort: *Healthy subjects*
A single-dose of TDE ER 1 mg.

PK Sampling

Blood samples for pharmacokinetic analysis were obtained at the following time points: 0 (pre-dose), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 36, 42 and 48 hr post dose. A 60-hr sample was collected for the ESRD group.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

N = 8, healthy subjects with normal renal function (CrCl > 80 mL/min).
N = 8, ESRD patients on dialysis.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-5.0 to -2.0 %
Precision	2.8 to 5.5 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil when administered in healthy subjects and ESRD patients

Subject Cohort Treatment	Statistics	C_{max} (pg/mL)	t_{max}* (hr)	$AUC_{(0-t)}$ (hr*pg/mL)	$AUC_{(0-inf)}$ (hr*pg/mL)	$t_{½}$ (hr)
ESRD Post Dialysis (N = 8)	GeoMean	732	na	3162	3224	2.36
	CVb%	56.3	na	46.0	45.3	54.7
	Mean	822	5.0	3440	3499	2.62
	CV%	50.3	na	44.0	43.4	44.2
	Median	680	4.5	3191	3240	2.35
	Min	310	2.0	1901	1919	0.89
	Max	1430	10	5930	5986	4.29
ESRD 4 Hours Before Dialysis (N = 8)	GeoMean	492	na	2487	2546	1.88
	CVb%	54.8	na	87.8	84.9	60.7
	Mean	551	4.3	3118	3162	2.13
	CV%	51.0	na	66.1	65.1	52.0
	Median	551	4.0	3110	3152	2.05
	Min	248	1.0	865	918	0.78
	Max	1110	8.0	6817	6853	4.19
Healthy Normal Renal Function (N = 8)	GeoMean	686	na	4103	4180	3.18
	CVb%	23.9	na	57.1	55.9	56.2
	Mean	702	6.1	4648	4713	3.56
	CV%	21.9	na	54.2	53.2	47.9
	Median	730	5.5	3713	3802	3.54
	Min	456	3.0	2120	2190	1.51
	Max	862	10	8647	8719	6.00

*values are median for t_{max}. na = not applicable.

Table 2: Impact of renal impairment and dialysis on the pharmacokinetics of treprostinil

	Geometric mean ratio	
	ESRD (dosing post-dialysis) *vs* Healthy	ESRD (dosing pre-dialysis) *vs* Healthy
C_{max}	1.07	0.72
AUC_{0-inf}	0.77	0.61

Concentration-time profile

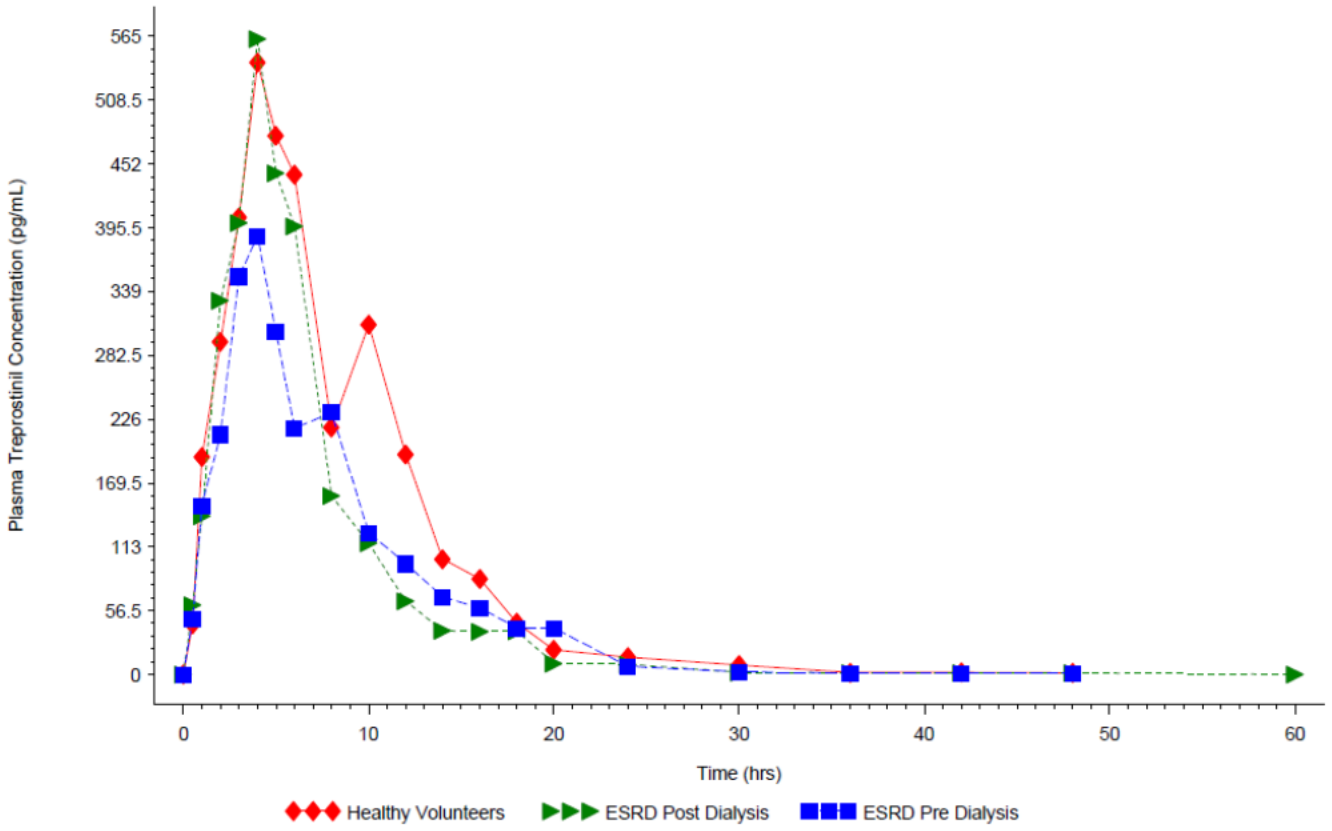


Figure 1: Mean treprostinil plasma concentration-time profile following 1 mg single-dose treprostinil diolamine administered in healthy volunteers and in ESRD patients prior and post-dialysis.

CONCLUSION

- There is no significant impact of renal impairment on the pharmacokinetics of treprostinil as seen by comparison of PK metrics between healthy volunteers and ESRD post-dialysis group.
- Comparison of PK profiles between ESRD patients post-dialysis and pre-dialysis shows a minor impact of hemodialysis. There is approximately 20% decrease in systemic exposure due to dialysis in ESRD patients.
- The results corroborate with the mass balance study results which shows less than 2% of the parent drug i.e., treprostinil eliminated unchanged in urine, which suggests a minor pathway for the renal elimination of treprostinil.

Effect of hepatic impairment

Study report: TDE-PH-112	**Study period:** 12/11/2008 - 08/06/2009	EDR Link

TITLE

An evaluation of the pharmacokinetics and safety of a single-dose of UT-15C (treprostinil diolamine) ER in subjects with hepatic impairment compared with healthy volunteers.

OBJECTIVE

To evaluate the impact of hepatic impairment on the pharmacokinetics of treprostinil.

STUDY DESIGN

Open-label, single-dose, four cohort sequential pharmacokinetic study in subjects with hepatic impairment compared to healthy controls.

Cohort 1: *Mild hepatic impairment (Child-Pugh class A)*
Cohort 2: *Moderate hepatic impairment (Child-Pugh class B)*
Cohort 3: *Severe hepatic impairment (Child-Pugh class C)*
Cohort 4: *Healthy volunteers*

During enrollment of subjects with severe hepatic impairment (cohort 3), a safety analysis was conducted for every two subjects prior to enrollment of the next two subjects. If, at any time during these safety reviews, it was determined by the study sponsor that it was unsafe to continue enrollment, the sponsor was to stop enrollment per protocol-defined stopping criteria.

Dose: A single-dose of TDE ER 1 mg.

PK Sampling

Blood samples for pharmacokinetic analysis were obtained at the following time points: 0 (pre-dose), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42 and 48 h post-dose. An additional 60 h sample was collected for the hepatic impairment group.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for hepatic impaired group to healthy volunteer group ratio is constructed.

Population

A total of up to 32 subjects were to be dosed (up to eight subjects per cohort). Only 30 subjects completed the study per protocol. Dosing in subjects with severe hepatic impairment was prematurely stopped for safety concerns after dosing 6 of the 8 potential subjects.

RESULTS

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	2.1 to 7.4 %
Precision	2.0 to 7.3 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil when administered in healthy subjects and hepatic impaired subjects

Parameters	Arithmetic Mean (CV%)			
	Cohort 1: Mild Hepatic Impairment	Cohort 2: Moderate Hepatic Impairment	Cohort 3: Severe Hepatic Impairment	Cohort 4: Healthy Subjects
N	8	8	6	8
AUC_{0-24} (pg•h/mL)	4637 (48.7)	10272 (61.8)	16062 (33.3)	2100 (59.3)
AUC_{0-48} (pg•h/mL)	5057 (47.2)	10773 (59.6)	18104 (36.9)	2167 (62.1)
AUC_{0-t} (pg•h/mL)	5127 (47.4)	10810 (59.3)	18166 (36.8)	2155 (62.4)
$AUC_{0-\infty}$ (pg•h/mL)	5045 (49.9)[b]	11661 (61.4)[b]	18213 (36.7)	2412 (63.0)[b]
C_{max} (pg/mL)	777 (26.2)	1981 (57.9)	2358 (36.9)	495 (33.6)
CL/F (L/h)	242 (45.7)[b]	134 (78.4)[b]	63.1 (44.7)	558 (59.4)[b]
$t_{1/2}$ (h)	9.64 (73.8)[b]	6.72 (35.7)[b]	6.50 (58.7)	4.95 (73.8)[b]
t_{max}[a] (h)	5.00 (3.00 - 10.00)	5.00 (2.00 - 10.00)	5.00 (5.00 - 24.00)	3.50 (1.00 - 6.00)
V_z/F (L)	3112 (49.2)[b]	1471 (96.2)[b]	582 (67.8)	3235 (56.7)[b]

[a] =median (min - max) , [b] n=6

Table 2: Impact of hepatic impairment on the pharmacokinetics of treprostinil

	Fold increase		
	Mild HI *vs* Healthy	Moderate HI *vs* Healthy	Severe HI *vs* Healthy
C_{max}	1.6	3.6	4.7
AUC_{0-inf}	2.2	4.6	8.2

Concentration-time profile

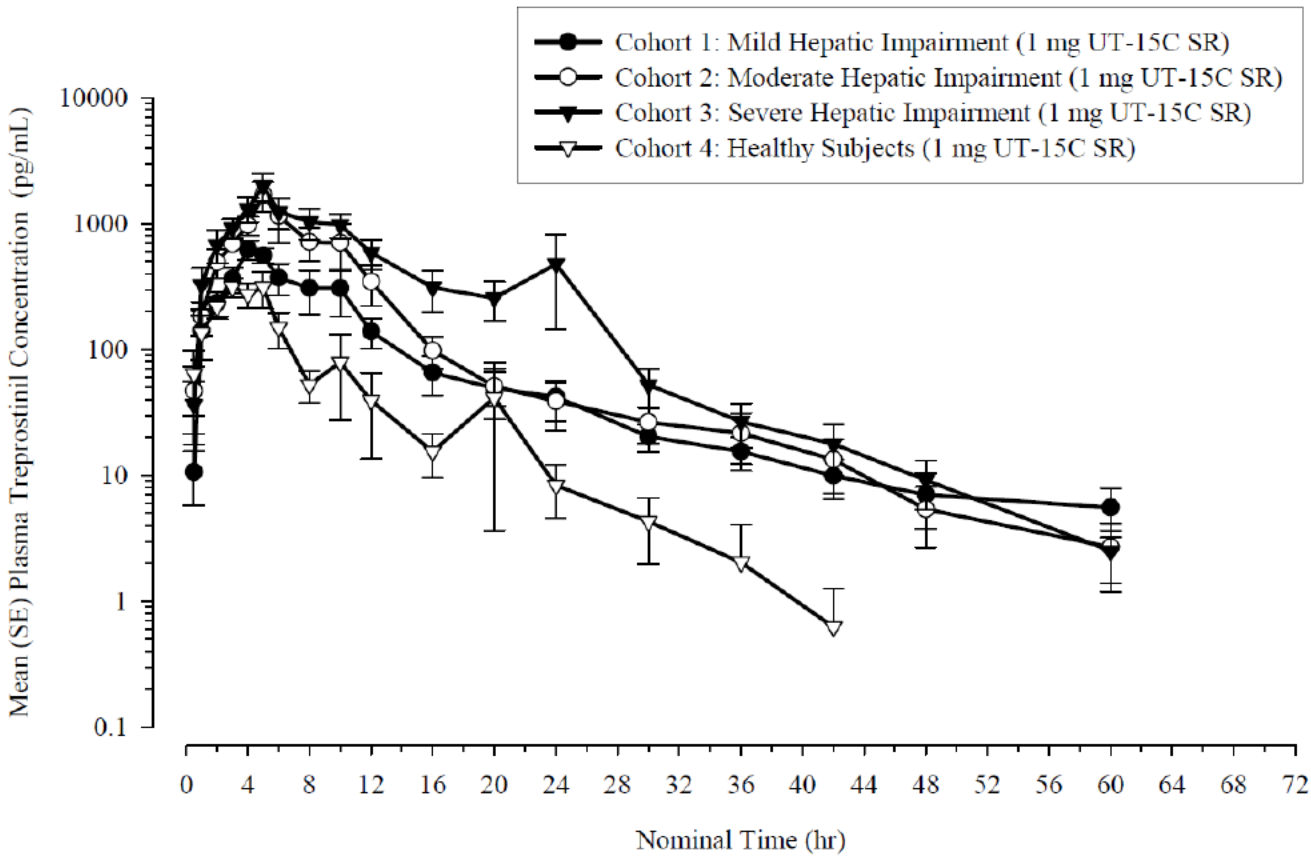


Figure 1: Mean treprostinil plasma concentration-time profile following 1 mg single-dose treprostinil diolamine administered in healthy volunteers and in hepatic impaired subjects.

CONCLUSION

- From the mass balance study, it is known that treprostinil is extensively metabolized by the liver with a significant first pass-effect. Therefore, increase in both C_{max} and AUC are expected in hepatic impaired subjects (as seen in Table 2) when compared to healthy controls.
- Increase in peak concentration i.e., C_{max}, as observed in hepatic impaired subjects suggests that the hepatic first-pass effect is significantly compromised. This decrease in first-pass effect, in general, is due to the lack of metabolic enzymes in subjects with hepatic insufficiency. However, for drugs which are taken up into the liver by active processes, such as via OATP1B1 and OATP1B3, a reduced uptake into the liver could also contribute to the decrease in first-pass effect.
- Increase in systemic exposure i.e., AUC, as observed in hepatic impaired subjects in this study is a combination of increase in peak concentration (driven by decrease in first-pass effect) and a decrease in systemic clearance. A decrease in systemic clearance cannot be clearly discerned from this study, since the half-life of treprostinil cannot be precisely estimated due to multiple peaks in the plasma concentration-time profile.
- Given the observed increase in C_{max} and AUC for varying degrees of hepatic impairment, a dose-adjustment is needed in patients with mild hepatic impairment to account for a 2-fold increase in exposure when compared to healthy subjects. Due to unavailability of a 4-fold lower strength, use of treprostinil should be avoided in patients with moderate hepatic impairment. The use of treprostinil in patients with severe hepatic impairment must be contraindicated.

DDI -- Bosentan

Study report: TDE-PH-105	**Study period:** 01/13/2006 - 02/08/2006	EDR Link

TITLE

An evaluation of the steady state pharmacokinetics of UT-15C ER (treprostinil diolamine) with Tracleer® (bosentan) following oral co-administration in healthy adult volunteers

RATIONALE

Treprostinil is metabolized by CYP2C8 (major) and 2C9 (minor). Bosentan is an inducer of CYP2C9.

STUDY DESIGN

Open-label, single center, three-period, three-sequence, crossover pharmacokinetic study in healthy volunteers.

	Period 1	Period 2	Period 3
Seq. 1	TDE ER 1 mg BID for 4.5 d	Tracleer® 125 mg BID for 4.5 d	TDE ER 1 mg BID + Tracleer® 125 mg BID for 4.5 d
Seq. 2	Tracleer® 125 mg BID for 4.5 d	TDE ER 1 mg BID + Tracleer® 125 mg BID for 4.5 d	TDE ER 1 mg BID for 4.5 d
Seq. 3	TDE ER 1 mg BID + Tracleer® 125 mg BID for 4.5 d	TDE ER 1 mg BID for 4.5 d	Tracleer® 125 mg BID for 4.5 d

A 5-day wash-out separated the treatment periods.

PK Sampling

On the final day of each of the three treatment periods, blood samples will be obtained at the following time points: 0 (just prior to final morning dose), and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, and 48 h.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 24 adult male and female healthy volunteers were enrolled in the study. Twenty two subjects completed the study. One subject discontinued due to protocol violation and another subject withdrew consent.

RESULTS

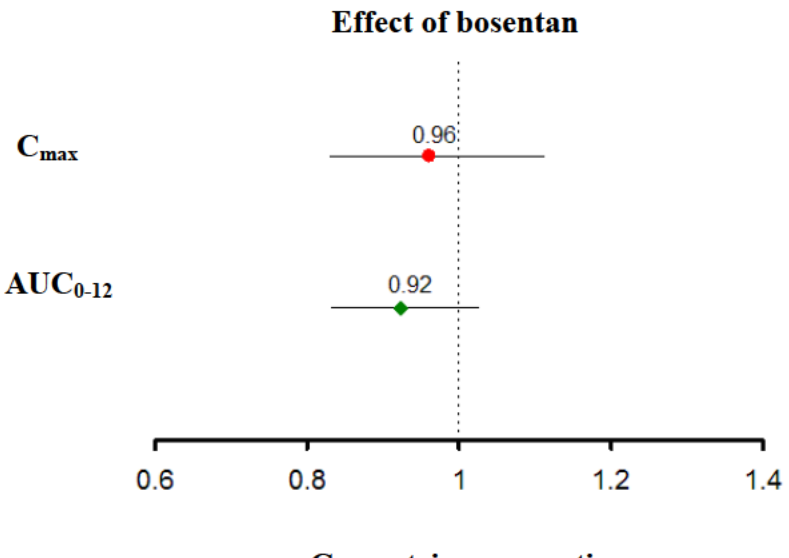


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. Data is represented as geometric mean ratio of test to reference with 90% CI around the point estimate.

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5120
QCs (pg/mL)	30, 1920, 3840
Accuracy/Bias	-0.7 to 2.1 %
Precision	3.8 to 5.4 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER**	**TDE ER + Bosentan**
C_{max} (ng/mL)	0.790 (34)	0.784 (45)
T_{max} (h)†	3.0	3.0
AUC_{0-12} (h*ng/mL)	3.84 (30)	3.56 (32)

† *Median*

Concentration-time profile

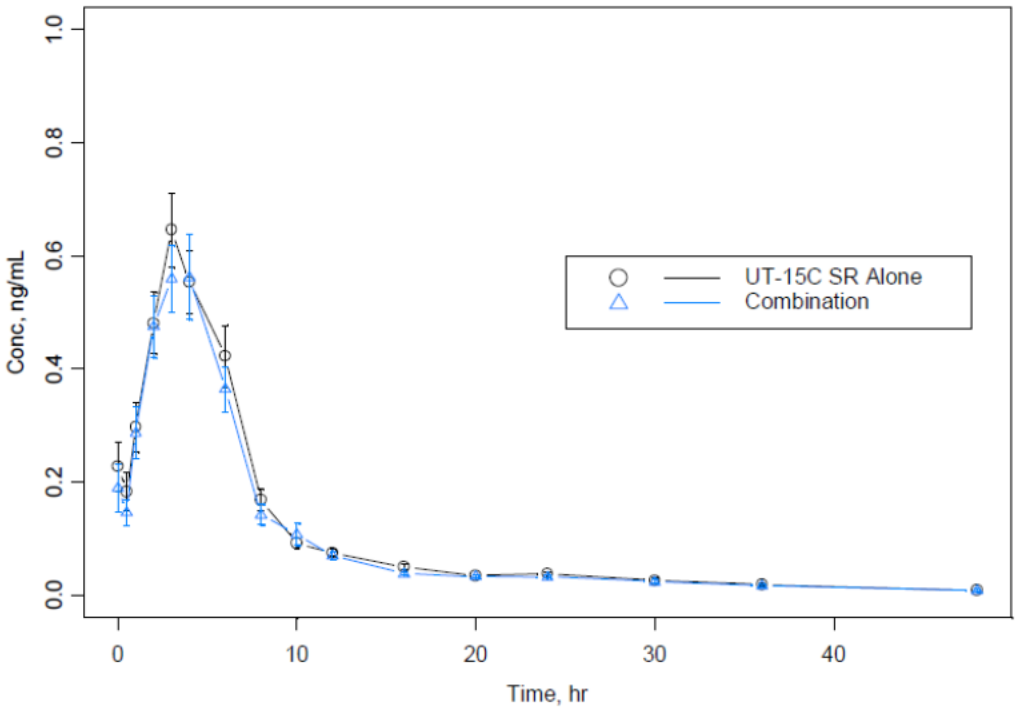


Figure 2: Mean treprostinil plasma concentration-time profile following multiple dose administration of 1 mg TDE ER tablet BID alone and with co-administration of Tracleer®.

CONCLUSION

- Bosentan, an inducer of CYP2C9, did not significantly affect the systemic exposure to treprostinil. No dose-adjustment is required when co-administered with Tracleer®.
- This study also quantified the systemic exposure of bosentan and its active metabolite, Ro 48-5033 (data not shown). The plasma levels of both bosentan and Ro 48-5033 were not affected when co-administered with treprostinil diolamine.

DDI -- Sildenafil

Study report: TDE-PH-106	**Study period:** 01/27/2006 - 03/13/2006	EDR Link

TITLE

An evaluation of the steady state pharmacokinetics of UT-15C ER (treprostinil diolamine) and Revatio™ (sildenafil citrate) following oral co-administration in healthy adult volunteers

RATIONALE

Treprostinil is metabolized by CYP2C8 (major) and 2C9 (minor). Sildenafil is a weak inhibitor of CYP2C9.

STUDY DESIGN

Open-label, single center, three-period, three-sequence, crossover pharmacokinetic study in healthy volunteers.

	Period 1	Period 2	Period 3
Seq. 1	TDE ER 1 mg BID for 4.5 d	Revatio™ 20 mg TID for 4.5 d	TDE ER 1 mg BID + Revatio™ 20 mg TID for 4.5 d
Seq. 2	Revatio™ 20 mg TID for 4.5 d	TDE ER 1 mg BID + Revatio™ 20 mg TID for 4.5 d	TDE ER 1 mg BID for 4.5 d
Seq. 3	TDE ER 1 mg BID + Revatio™ 20 mg TID for 4.5 d	TDE ER 1 mg BID for 4.5 d	Revatio™ 20 mg TID for 4.5 d

A 5-day wash-out separated the treatment periods.

PK Sampling

On the final day of each of the three treatment periods, blood samples will be obtained at the following time points: 0 (just prior to final morning dose), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, and 48 h.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 18 adult male and female healthy volunteers were enrolled in the study. Seventeen subjects completed the study and one subject withdrew consent prior to period 3.

RESULTS

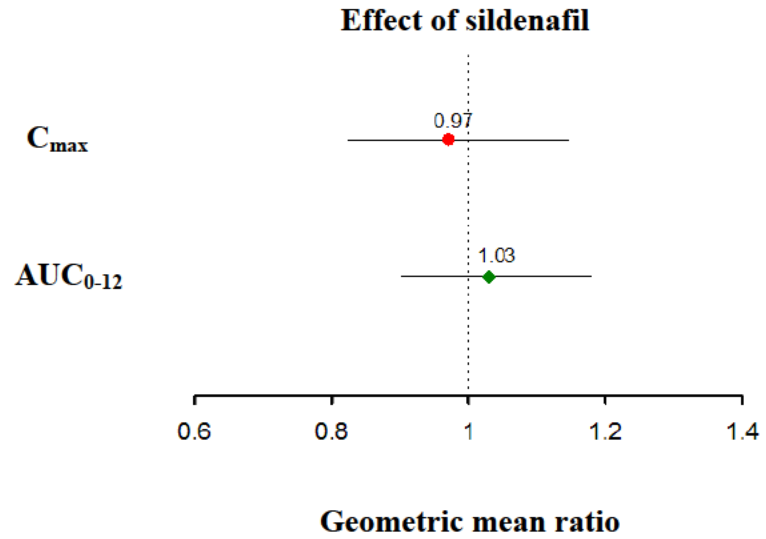


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. Data is represented as geometric mean ratio of test to reference with 90% CI around the point estimate.

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5120
QCs (pg/mL)	30, 1920, 3840
Accuracy/Bias	-3.0 to -0.5 %
Precision	4.0 to 6.5 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER**	**TDE ER + Sildenafil**
C_{max} (ng/mL)	0.776 (33)	0.756 (39)
T_{max} (h)†	3.0	4.0
AUC_{0-12} (h*ng/mL)	3.66 (37)	3.73 (33)

† *Median*

Concentration-time profile

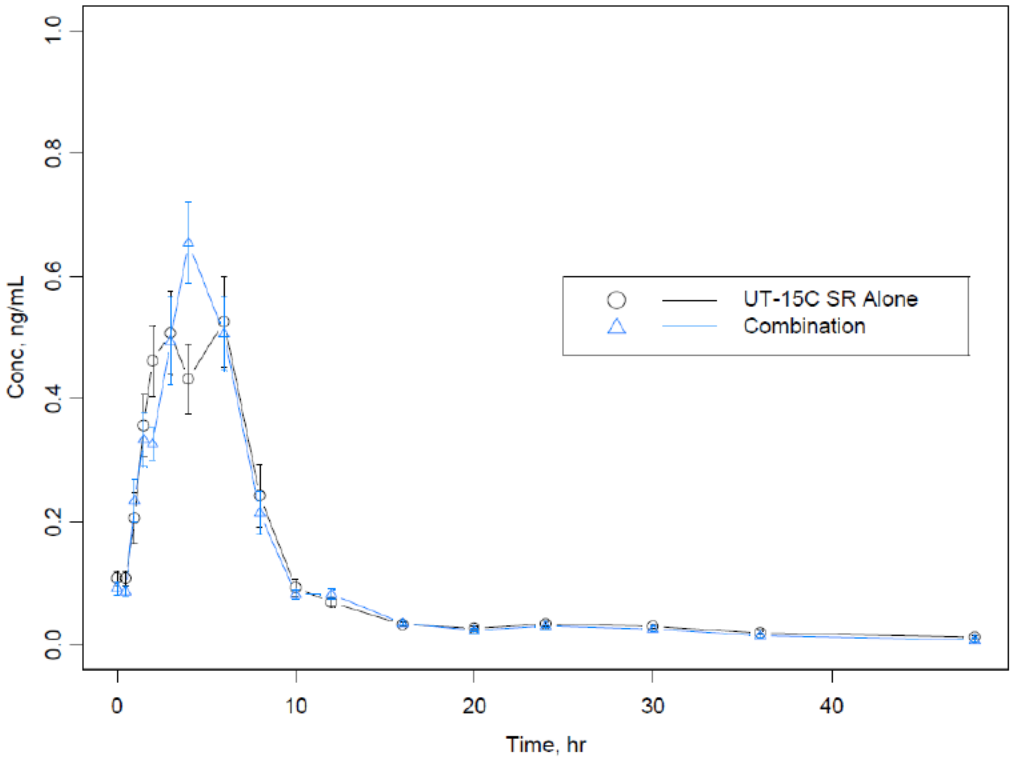


Figure 2: Mean treprostinil plasma concentration-time profile following multiple dose administration of 1 mg TDE ER tablet BID alone and with co-administration of Revatio™.

CONCLUSION

- Sildenafil, a weak inhibitor of CYP2C9, did not affect the systemic exposure to treprostinil, since, metabolism via CYP2C9 is a minor pathway for treprostinil.
- This study also quantified the systemic exposure of sildenafil and its active metabolite, N-desmethylsildenafil (data not shown). The plasma levels of both sildenafil and N-desmethylsildenafil were not affected when co-administered with treprostinil diolamine.

DDI -- Rifampin

Study report: TDE-PH-109	**Study period:** 02/09/2008 - 02/21/2008	EDR Link

TITLE

An evaluation of single oral dose UT-15C ER (treprostinil diolamine) pharmacokinetics following repeated dosing with prototypical cytochrome P450 2C8 and 2C9 enzyme inducer rifampin in healthy adult volunteers

RATIONALE

Treprostinil is metabolized by CYP2C8 (major) and 2C9 (minor). Rifampin is an inducer of CYP2C8 and 2C9.

STUDY DESIGN

Open-label, single center, two-treatment, single-sequence, crossover pharmacokinetic study in healthy volunteers.

	Period 1	Period 2
Seq. 1	Day 1: TDE ER 1 mg (SD)	Days 3-12: Rifampin 600 mg QD Day 11: TDE ER 1 mg (SD)

Both periods are separated by a wash-out of 10 days.

PK Sampling

On each of the TDE ER dosing day in Periods 1 and 2, serial pharmacokinetic samples were collected from all subjects at 0 (pre-dose), and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 21, 24, 28, 32, 36, and 48 h post TDE ER dosing

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 20 adult male and female healthy volunteers were enrolled in the study. All 20 subjects completed the study per protocol.

RESULTS

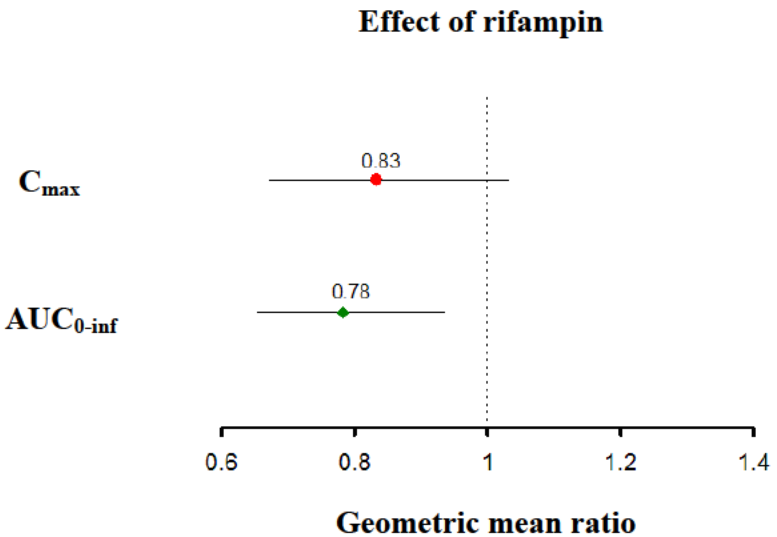


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. Data is represented as geometric mean ratio of test to reference with 90% CI around the point estimate.

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-2.7 to 0.3 %
Precision	7.0 to 9.6 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER**	**TDE ER + Rifampin**
C_{max} (ng/mL)	0.548 (45)	0.486 (51)
T_{max} (h)†	4.0	4.0
$AUC_{0\text{-}last}$ (h*ng/mL)	2.72 (48)	2.12 (70)
$AUC_{0\text{-}\infty}$ (h*ng/mL)	2.58 (39)	2.34 (68)

† *Median*

Concentration-time profile

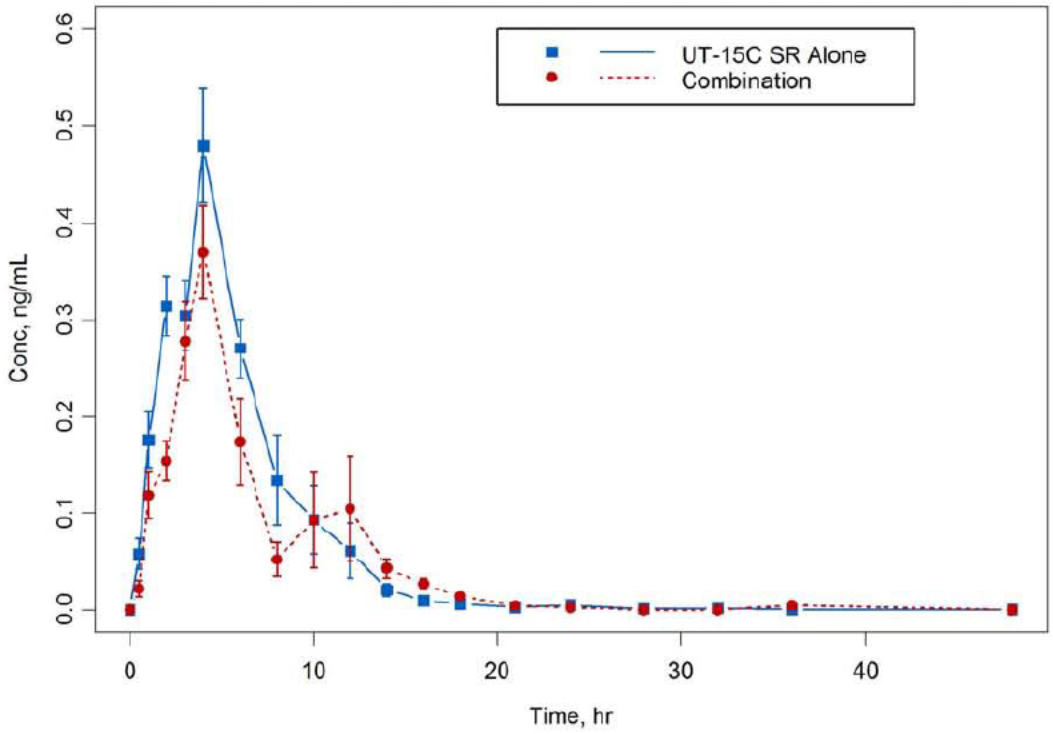


Figure 2: Mean treprostinil plasma concentration-time profile following single oral administration of 1 mg TDE ER tablet alone and following co-administration with rifampin 600 mg QD

CONCLUSION

- No dose-adjustment is required to account for the 20% decrease in exposure when co-administered with rifampin, a CYP2C8 and 2C9 inducer, since treprostinil will be titrated to tolerability.

DDI -- Gemfibrozil and Fluconazole

Study report: TDE-PH-110	**Study period:** 02/21/2008 - 03/13/2008	EDR Link

TITLE

An evaluation of single oral dose UT-15C ER (treprostinil diolamine) pharmacokinetics following repeated dosing with oral prototypical cytochrome P450 2C8 (gemfibrozil) and 2C9 (fluconazole) inhibitors in healthy adult volunteers

RATIONALE

Treprostinil is metabolized by CYP2C8 (major) and 2C9 (minor). Gemfibrozil and fluconazole are strong inhibitors of CYP2C8 and 2C9, respectively.

STUDY DESIGN

Open-label, single center, randomized, two-cohort, two-period, two-sequence, crossover, pharmacokinetic study in healthy volunteers

Cohort 1: *Gemfibrozil*

	Period 1	**Period 2**
Seq. 1	Days 1-4: Gemfibrozil 600 mg BID Day 3: TDE ER 1 mg (SD)	Day 14: TDE ER 1 mg (SD)
Seq. 2	Day 3: TDE ER 1 mg (SD)	Days 12-15: Gemfibrozil 600 mg BID Day 14: TDE ER 1 mg (SD)

Cohort 2: *Fluconazole*

	Period 1	**Period 2**
Seq. 1	Day 1: Fluconazole 400 mg QD Days 2-7: Fluconazole 200 mg QD Day 6: TDE ER 1 mg (SD)	Day 20: TDE ER 1 mg (SD)
Seq. 2	Day 6: TDE ER 1 mg (SD)	Day 15: Fluconazole 400 mg QD Days 16-21: Fluconazole 200 mg QD Day 20: TDE ER 1 mg (SD)

Both periods are separated by a wash-out of 7 days.

PK Sampling

On each of the TDE ER dosing day in Periods 1 and 2, serial pharmacokinetic samples were collected from all subjects at 0 (pre-dose), and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 21, 24, 28, 32, 36, and 48 h post TDE ER dosing

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 40 (2 cohorts of 20 subjects; 10 per sequence) adult male and female healthy volunteers were enrolled in the study. All 20 subjects in both cohorts completed the study per protocol.

RESULTS

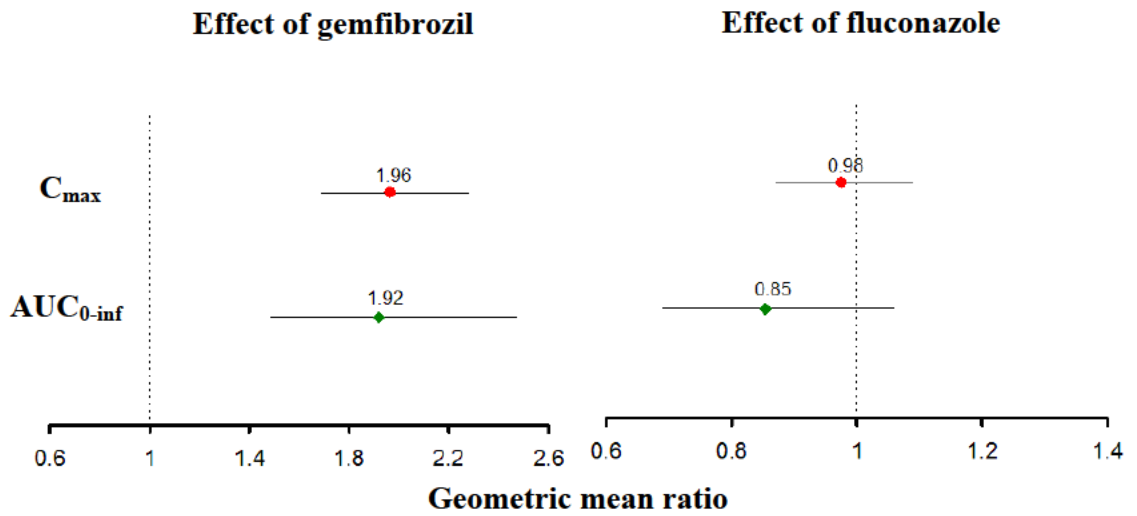


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. Data is represented as geometric mean ratio of test to reference with 90% CI around the point estimate.

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-5.0 to -2.1 %
Precision	6.6 to 8.6 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

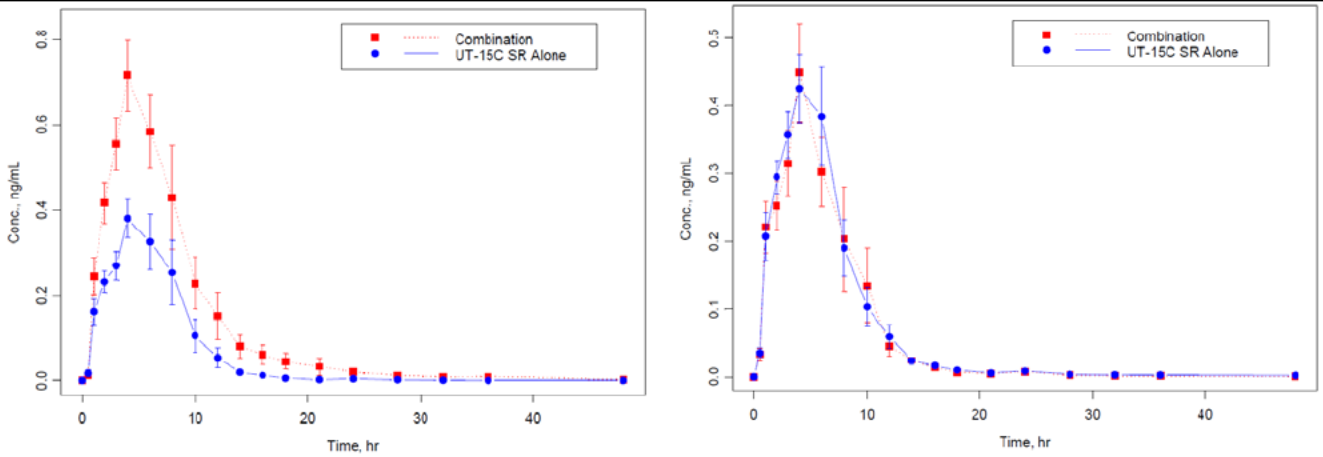
PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER**	**TDE ER + Gemfibrozil**
C_{max} (ng/mL)	0.562 (45)	1.062 (38)
T_{max} (h)†	4.0	4.0
AUC_{0-last} (h*ng/mL)	5.70 (46)	2.76 (56)
$AUC_{0-\infty}$ (h*ng/mL)	5.37 (54)	2.75 (45)

† *Median*

Concentration-time profile



With gemfibrozil **With fluconazole**

Figure 2: Mean treprostinil plasma concentration-time profile following single oral administration of 1 mg TDE ER tablet alone and following co-administration with (A) gemfibrozil, 600 mg BID and (B) fluconazole, 200 mg QD

CONCLUSION

- Systemic exposure to treprostinil was increased by 2-fold when co-administered with gemfibrozil, a CYP2C8 and OATP1B1 inhibitor. Given that the systemic exposure to treprostinil was decreased by only 20% when co-administered with rifampin, a CYP2C8 inducer, it can be hypothesized that inhibition of both CYP2C8 and OATP1B1 could contribute to the 2-fold increase in systemic exposure when co-administered with gemfibrozil.
- Due to a 2-fold increase when co-administered with gemfibrozil, treprostinil when co-administered with CYP2C8 inhibitors, should be started at a lower dose of 0.125 mg and titrated in steps of 0.125 every 3-4 days.
- Systemic exposure to treprostinil was not affected when co-administered with a strong CYP2C9 inhibitor, fluconazole, suggesting that metabolism via CYP2C9 is minimal.

DDI -- Esomeprazole

Study report: TDE-PH-116	**Study period:** 10/01/2009 - 10/09/2009	EDR Link

TITLE

An evaluation of single dose UT-15 ER (treprostinil diolamine) pharmacokinetics following repeated dosing with the proton pump inhibitor esomeprazole in healthy adult volunteers

RATIONALE

Treprostinil is a weakly acidic drug. When co-administered with proton pump inhibitors, there is a potential for PPIs to cause an increase in the solubility of a weakly acidic drug such as treprostinil which could result in higher systemic exposures.

STUDY DESIGN

Open-label, single center, two-period, single-sequence, crossover pharmacokinetic study in healthy volunteers.

	Period 1	Period 2
Seq. 1	Day 1: TDE ER 1 mg (SD)	Days 3-9: Esomeprazole 40 mg 1 h prior to breakfast Day 8: TDE ER 1 mg (SD)

PK Sampling

On days 1 and 8, blood samples will be obtained at the following time points: 0 (prior to dosing), and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32 and 36 h.

Statistical method

ANOVA model on log transformed parameters C_{max} and AUC. LS mean and the 90% CI for test to reference ratio is constructed.

Population

Healthy subjects.
N = 30 adult male and female healthy volunteers were enrolled in the study. All 30 subjects completed this study.

RESULTS

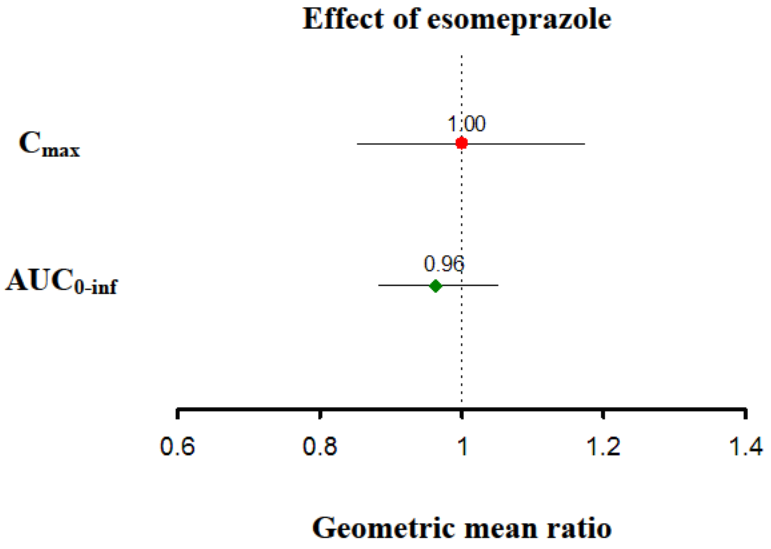


Figure 1: Results of the statistical analysis. X-axis represents the geometric mean ratios. Data is represented as geometric mean ratio of test to reference with 90% CI around the point estimate.

Bioanalysis assay method

The performance of the assay method during study sample analysis is summarized in the table below:

	Treprostinil
Method	**UPLC-MS/MS**
LLOQ (pg/mL)	10
Range (pg/mL)	10 to 5000
QCs (pg/mL)	30, 600, 3750
Accuracy/Bias	-2.7 to 0.5 %
Precision	2.7 to 4.9 %

Reviewer's comment: The analytical assay method is acceptable since the accuracy and precision for QC samples are within the acceptable limits of ±15% as specified in 'Guidance for Industry: Bioanalytical Method Validation.'

PK summary statistics

Table 1: Summary of pharmacokinetic measures and parameters for treprostinil

	Arithmetic mean (% CV)	
PK metric	**TDE ER**	**TDE ER + Bosentan**
C_{max} (ng/mL)	0.968 (61)	0.912 (42)
T_{max} (h)†	5.0	5.0
$AUC_{0\text{-}inf}$ (h*ng/mL)	4.44 (38)	4.24 (38)

† *Median*

Concentration-time profile

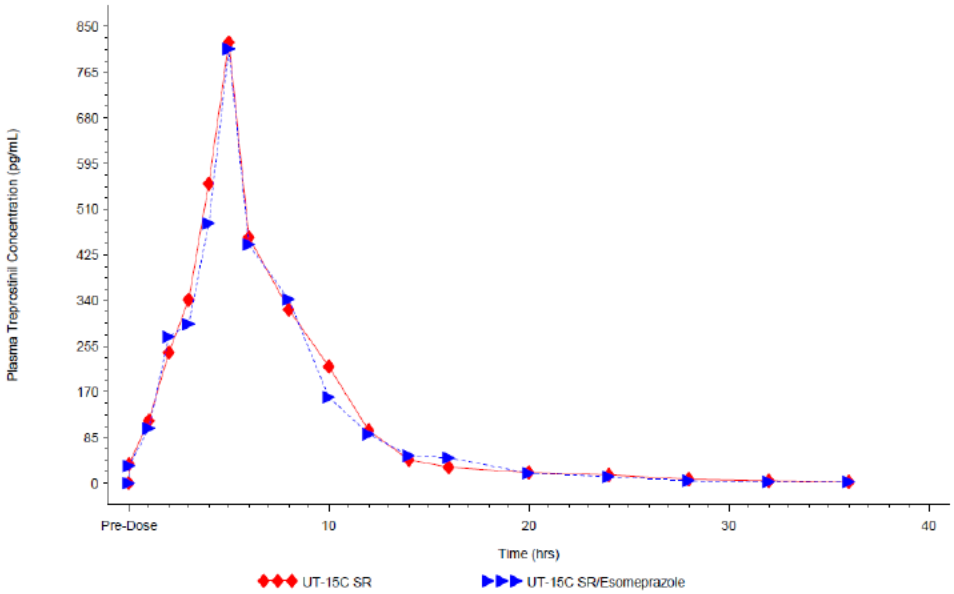


Figure 2: Mean treprostinil plasma concentration-time profile following single-dose administration of 1 mg TDE ER tablet alone and with co-administration of esomeprazole.

CONCLUSION

- There is no significant change in the systemic exposure of treprostinil when co-administered with esomeprazole which warrants a dose-adjustment.

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key question.

1.1.1 Is there an exposure-response relationship for efficacy?

Based on the reviewer's analysis, an exposure-response relationship for exercise capacity i.e., 6-minute walk distance (6MWD) was observed. The phase 3 trials of treprostinil incorporated a titration to tolerability design. The relationship between the last dose normalized to body weight and the corresponding percent change from baseline in 6MWD was explored. In study TDE-PH-302, a trend for dose-dependent increase in the percent change from baseline in 6MWD (corresponding to peak treprostinil exposures) at week 12 was observed as a function of the last dose normalized to body weight as shown in Figure 1. The relationship is constructed using data from patients who completed the study and is not confounded with imputation methodologies used to account for drop-outs in the trial. A similar relationship was also observed between last dose normalized to body weight and percent change in baseline in 6MWD at week 11 (corresponding to trough treprostinil exposures) as shown in Figure 2.

Figure 1. Relationship between last dose normalized to body weight and corresponding percent change from baseline in 6MWD at week 12 corresponding to peak treprostinil plasma concentrations from study TDE-PH-302 in completers. [N = 246; active=160, placebo=86]. A positive slope for the relationship was observed [Mean and 95% CI: 123 (41.8 – 204) as percent change from baseline-per-mg/kg of treprostinil].

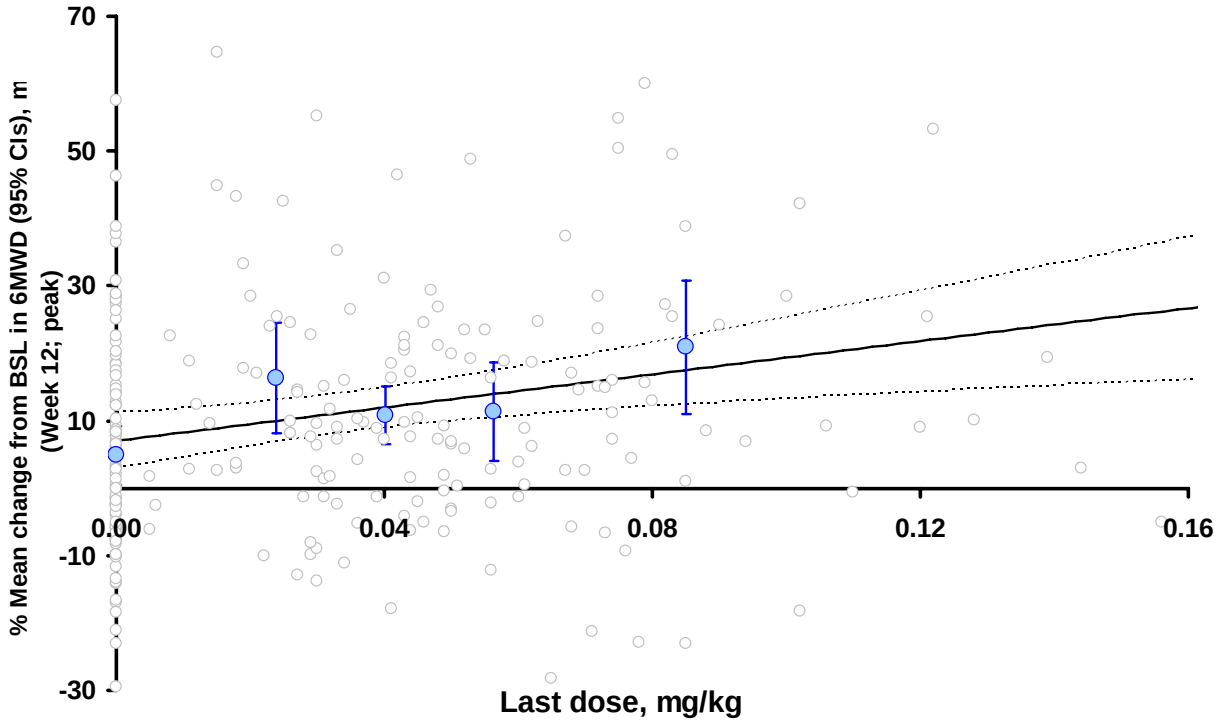
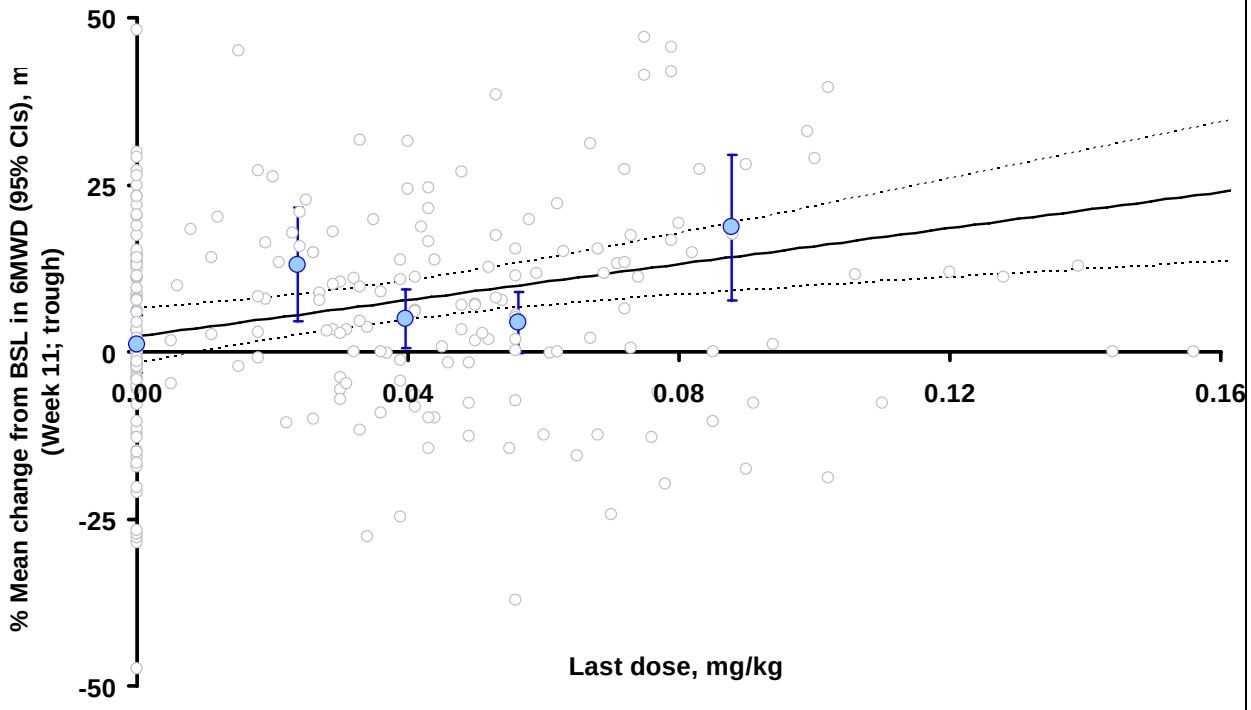


Figure 2. Relationship between last dose normalized to body weight and corresponding percent change from baseline in 6MWD at week 11 corresponding to trough treprostinil plasma concentration from study TDE-PH-302 in completers. [N = 243; active=159, placebo=84]. A positive slope for the relationship was observed [Mean and 95% CI: 135 (54.8 – 215) as percent change from baseline-per-mg/kg of treprostinil].



Note: Individual patient data is represented by the gray open circles. The blue closed circles and error bars represent the corresponding mean and 95% CIs of percent change from baseline in 6MWD for each median dose quartile. The solid line represents the linear fit modeled through the entire dataset with 95% CIs represented by dotted lines. Y-axis is truncated to provide an optimum view to aid understand this relationship.

Assuming a linear relationship, similar dose-dependent trend for the relationship between 6MWD at week 16 corresponding to peak treprostinil exposures as a function of the last dose normalized to body weight was also observed for studies TDE-PH-301 (Figure 3) and TDE-PH-308 (Figure 4) in completers where treprostinil was evaluated in the background of other oral PAH therapies. A non-zero slope for the relationship is shown in as mean and 95% CI.

Figure 3. Relationship between last dose normalized to body weight and corresponding percent change from baseline in 6MWD at week 16 corresponding to peak treprostinil plasma concentrations from study TDE-PH-301 in completers. [N = 246; active=118, placebo=128]. A positive slope for the relationship was observed [Mean and 95% CI: 98.5 (32.7 – 164) as percent change from baseline-per-mg/kg of treprostinil].

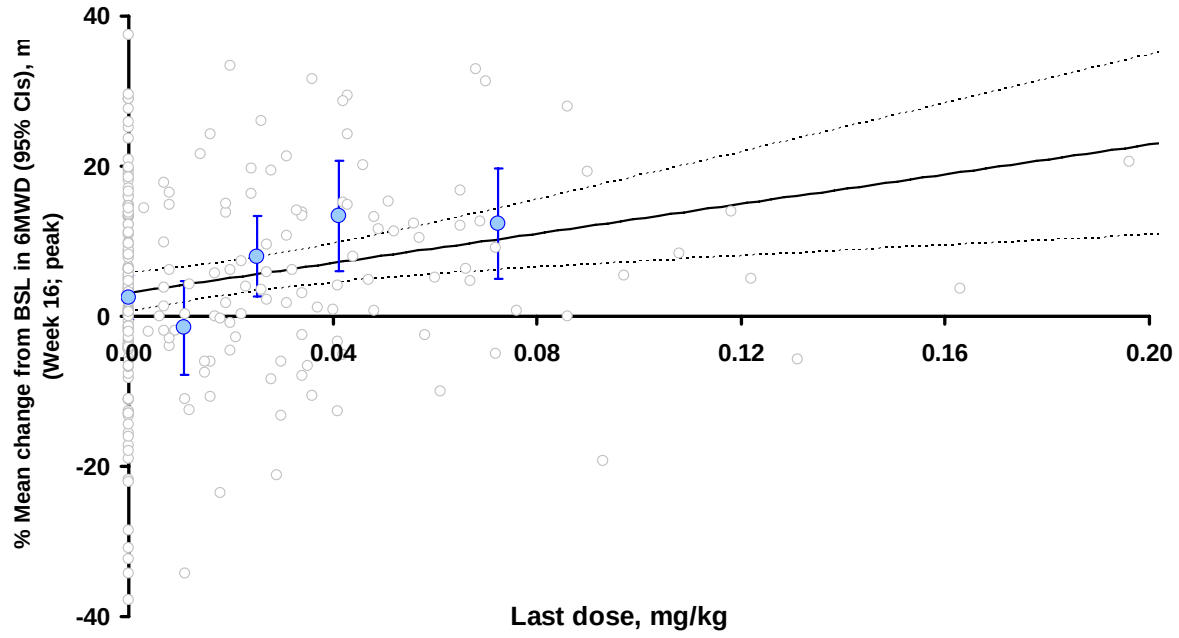
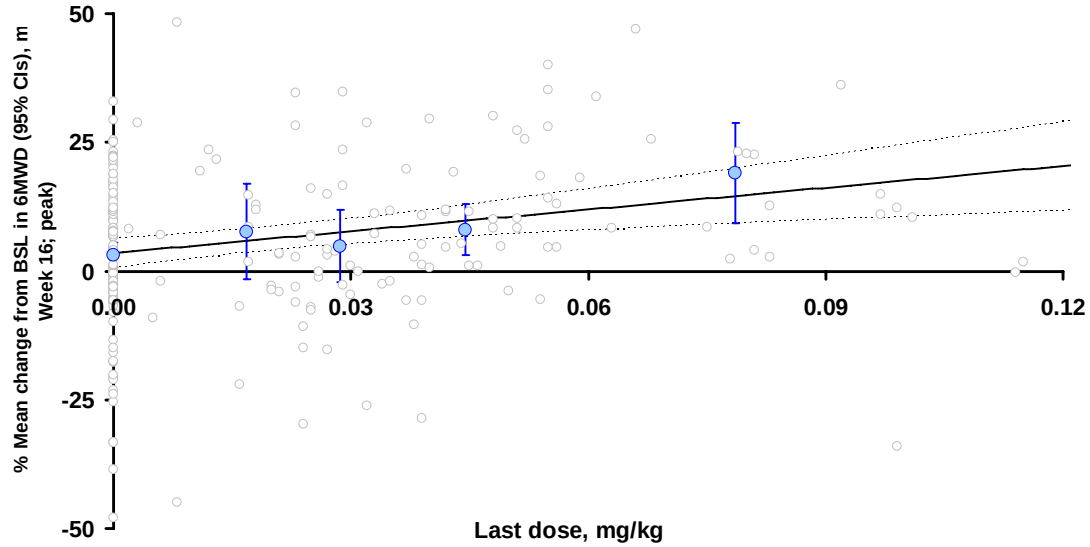


Figure 4. Relationship between last dose normalized to body weight and corresponding percent change from baseline in 6MWD at week 16 corresponding to peak treprostinil plasma concentrations from study TDE-PH-308 in completers. [N = 249; active=120, placebo=129]. A positive slope for the relationship was observed [Mean and 95% CI: 141 (58.0 – 224) as percent change from baseline-per-mg/kg of treprostinil].



2 REVIEWER'S ANALYSIS

2.1 Background

Trials: In the current submission, three controlled clinical trials have been performed to demonstrate the effectiveness and safety of treprostinil in patients with pulmonary arterial hypertension (PAH) following twice-daily administration of oral extended release tablets of treprostinil diolamine (Table 1). In study TDE-PH-302, the effectiveness of treprostinil as a front-line therapy was evaluated. Studies TDE-PH-301 and -308 evaluated the use of treprostinil as an add-on therapy to other approved oral therapies.
Dosing scheme: All the trials incorporated a titration to tolerability design. Studies TDE-PH-302 and -301 had a starting dose of 1 mg BID during initial enrollment, but was later reduced to 0.5 mg BID and subsequently to 0.25 mg BID due to tolerability concerns. However, the trial TDE-PH-308 was originally initiated at a starting dose of 0.25 mg BID. In all trials, the titration increment was 0.25 mg BID every 3-4 days as tolerated. If 0.25 mg dose increments were not tolerated, an increment of 0.125 mg was employed.
Exposure: Samples for evaluating the pharmacokinetics of treprostinil were not collected in Phase 3 trials. Hence, a concentration-response analysis was not feasible for this submission. But, dose-response relationship was explored with the 'dose' metric being analyzed as (a) last stabilized dose normalized to body weight (last dose/kg) and (b) cumulative dose.
Response: The efficacy measures included in the clinical development program are widely used and accepted as clinically meaningful indices for patients with PAH. In studies TDE-PH-301, -302 and -308, the primary efficacy endpoint was change in 6MWD (6MWD) from baseline to the end of the study i.e., week 12 for study TDE-PH-302 and week 16 for study TDE-PH-301 and -308.

Table 1. List and design features of clinical studies supporting this application

Study No.	Description	N	Dose	Duration
TDE-PH-302	Randomized, multi-center, placebo-controlled study in subjects with PAH NOT receiving approved background therapy	349	0.25-1 mg BID starting dose with dose increasing over time	12 Weeks
TDE-PH-301	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background Therapy	354	0.25-1 mg BID starting dose with dose increasing over time	16 Weeks
TDE-PH-308	Randomized, multi-center, placebo-controlled study in subjects with PAH on approved background Therapy	310	0.25 mg BID starting dose with dose increasing over time	16 Weeks

2.2 Objective

The objective was to explore the (a) last stabilized dose *vs* percent change from baseline 6MWD, and (b) cumulative dose *vs* percent change from baseline 6MWD relationship in support of the efficacy of treprostinil across the three clinical trials.

2.3 Methodology

A. Last dose/kg *vs* percent change from baseline 6MWD:
The relationship between last stabilized dose normalized to body weight and the corresponding percent change from baseline in 6MWD was explored using a univariate linear regression model. As the trials employed a titration to tolerability design, the last stabilized dose was deemed a relevant metric for this exploration. To bring the independent variable on a continuous scale, the last dose was further normalized to the body weight of the patient. For the response metric, percent change from baseline in 6MWD at the end of the study was considered more robust than the absolute change from baseline, since, the former takes into account baseline 6MWD. The relationship was constructed using the data from patients who completed the study, since a completer analysis is not confounded with imputation methodologies used to account for missing data in the trial. Completers of the study with corresponding peak 6MWD at week 12 represent about 70% and 75% of the total randomized patients in the treatment and placebo arms, respectively. However, it is important to note that the analysis presented cannot rule out time dependent effects and an interaction between tolerability and the ability to exercise.

B. Cumulative dose *vs* percent change from baseline 6MWD:
One of the drawbacks of evaluating the relationship between last stabilized dose normalized to body weight and corresponding percent change from baseline in 6MWD is that it ignores the time-course of dose titration. It is possible for patients to have the same last stabilized dose but differing in the duration at that dose. In order to further evaluate the exposure-response relationship, percent change from baseline in 6MWD as a function of cumulative treprostinil dose was constructed in all randomized patients i.e., the intent-to-treat (ITT) population as a sensitivity analysis. The relationship was investigated using a univariate linear regression model. The last observed 6MWD data was used in patients who dropped out during the trial with their cumulative doses truncated until the day of the last observed response data. For patients who dropped prior to week 4, baseline 6MWD data was carried forward with a cumulative dose set to 'zero'.

2.3.1 Data

A. Last dose/kg *vs* percent change from baseline 6MWD:

TDE-PH-302: 'WALKTEST.xpt' and 'MPL.xpt' were merged to get the master analysis data set (Table 2). This file was further reduced to a smaller analysis data set which contained the 6MWD data at week 11 (corresponding to trough treprostinil plasma concentration) and at week 12 (corresponding to peak treprostinil plasma concentrations) in patients who completed the trial. This dataset contained a total of 246 patients; active=160 and placebo=86 for peak 6MWD data at week 12 and a total of 243 patients; active=159 and placebo=84 for trough 6MWD data at week 11.
TDE-PH-301: 'WALKTEST.xpt' and 'MPL.xpt' were merged to get the master analysis data set (Table 2). This file was further reduced to a smaller analysis data set which contained the 6MWD data at week 16 (corresponding to peak treprostinil plasma concentration) in patients

who completed the trial. This dataset contained a total of 246 patients; active=118 and placebo=128.

TDE-PH-308: 'PEAKWT.xpt' and 'MPL.xpt' were merged to get the master analysis data set (Table 2). This file was further reduced to a smaller analysis data set which contained the 6MWD data at week 16 (corresponding to peak treprostinil plasma concentration) in patients who completed the trial. This dataset contained a total of 249 patients; active=120 and placebo=129.

B. Cumulative dose *vs* percent change from baseline 6MWD:

TDE-PH-302: 'DOSING.xpt' was used to calculate the cumulative dose exposed by a patient during the time of stay in the trial (Table 2). The calculated cumulative dose was then merged along with 'WALKTEST.xpt' and 'MPL.xpt' to get the master analysis data set. This file was further reduced to a smaller analysis data set which contained the 6MWD data at week 12 (irrespective of peak/trough treprostinil plasma concentration) with corresponding cumulative dose until the end of the study and the last observed 6MWD data in patients who dropped out during the trial with their cumulative doses truncated until the day of the last observed response data. For patients who dropped prior to week 4, baseline 6MWD data was carried forward with a cumulative dose set to 'zero'. This dataset contained a total of 349 patients, active=233 and placebo=116.

Table 2. Data sets used for exposure-response analysis

Study Number	Name	Link to EDR
TDE-PH-302	DOSING.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-302\analysis\legacy\datasets\dosing.xpt
	MPL.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-302\analysis\legacy\datasets\mpl.xpt
	WALKTEST.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-302\analysis\legacy\datasets\walktest.xpt
TDE-PH-301	MPL.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-301\analysis\legacy\datasets\mpl.xpt
	WALKTEST.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-301\analysis\legacy\datasets\walktest.xpt
TDE-PH-308	MPL.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-308\analysis\legacy\datasets\mpl.xpt
	PEAKWT.xpt	\\Cdsesub1\evsprod\NDA203496\0000\m5\datasets\tde-ph-308\analysis\legacy\datasets\peakwt.xpt

2.3.2 Software

Data sorting: JMP
Linear regression: Graphpad Prism
Graphical plots: Excel

2.4 Results

Results of the univariate linear regression analysis showed that there was a trend for dose-dependent increase in the percent change from baseline in 6MWD corresponding to the peak and trough treprostinil exposures at week 12 and 11, respectively, in TDE-PH-302 and at week 16 in TDE-PH-301 and -308, corresponding to peak treprostinil exposures, all as a function of last dose normalized to body weight. The relationships were derived upon anchoring the placebo response. A significant non-zero slope for the relationships was obtained assuming a linear trend as shown in Table 3. Assuming a linear relationship seemed reasonable based on the residual plots as shown in Figure 6. The slope for the relationship denoted percent change from baseline in 6MWD per 1 mg/kg dose. Based on the results, it can be concluded that:

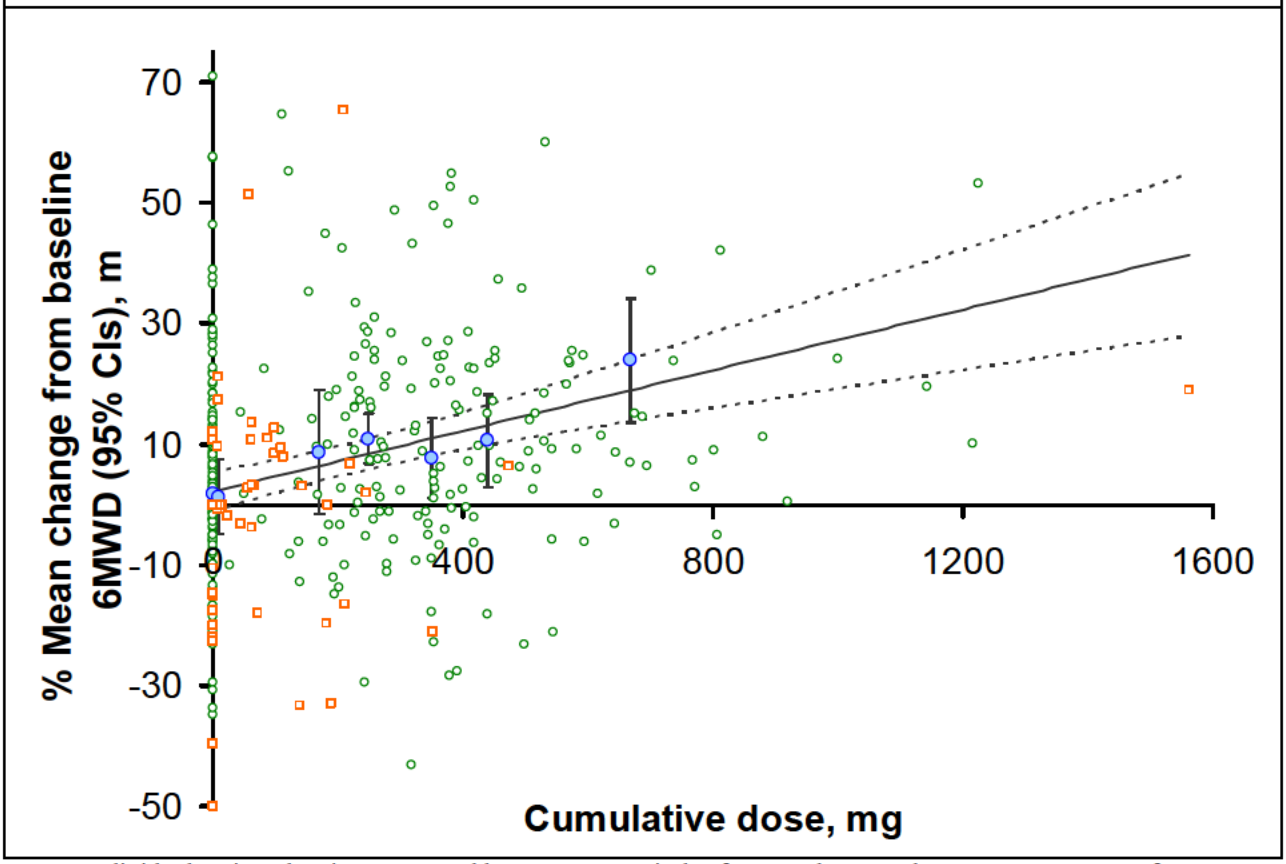
- A significant relationship exists regardless of the analysis corresponding to peak (week 12) or trough (week 11) treprostinil concentration in TDE-PH-302, which is suggestive of the fact that the effect or the ability to exercise is preserved during the entire inter-dosing interval.

- A significant relationship exists in TDE-PH-301 and -308, where treprostinil was evaluated as an add-on in the background of other oral PAH therapies. Moreover, when treprostinil exposure was evaluated as 'cumulative doses' (accounting for titrations and data imputations for drop-outs during the trial) against the percent change from baseline 6MWD in all randomized patients in TDE-PH-302 (ITT population), there was a significant non-zero slope for the relationship upon anchoring to placebo response suggestive of a trend for dose-dependent increase in percent change from baseline 6MWD as a function of cumulative treprostinil dose (Figure 5). For this relationship, the slope represented 2.5% change from baseline in 6MWD per 100 mg cumulative treprostinil dose. In addition, it was observed that the non-completers with lower cumulative exposures had correspondingly lower percent change from baseline 6MWD.

Table 3. Slope and y-intercept with 95% confidence intervals for describing the relationship between last dose normalized to body weight and corresponding percent change from baseline in 6MWD for treprostinil across different trials.

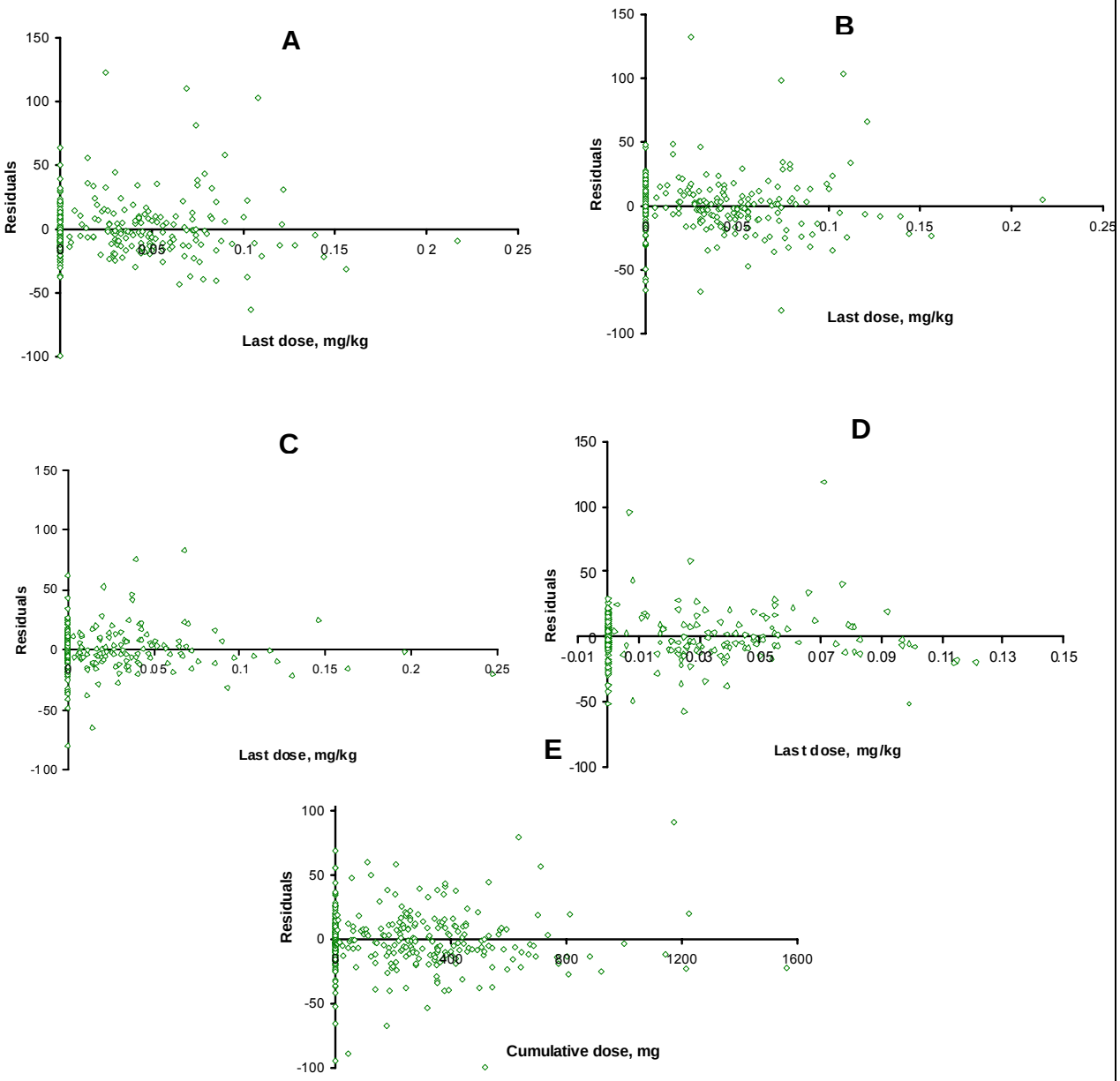
	TDE_PH-302 Week 12, Peak	TDE-PH-302 Week 12, Trough	TDE-PH-301 Week 16, Peak	TDE-PH-308 Week 16, Peak
Slope (95% CIs)	123 (41.8, 204)	135 (54.8, 215)	98.5 (32.7, 164)	141 (58.0, 224)
Intercept (95% CIs)	7.03 (2.92, 11.2)	2.34 (-1.70, 6.39)	3.16 (0.534, 5.78)	3.50 (0.641, 6.35)

Figure 5. Relationship between cumulative treprostinil dose and corresponding percent change from baseline from study TDE-PH-302 in all randomized patients (ITT population). [N = 349; active=233, placebo=116]. A positive slope for the relationship was observed [Mean and 95% CIs: 2.50 (1.50 – 3.50) as percent change from baseline-per-100 mg of cumulative treprostinil dose].



Note: Individual patient data is represented by green open circles for completers and orange open squares for non-completers. The blue closed circles and error bars represent the corresponding mean and 95% CIs of percent change from baseline in 6MWD for each median dose quartile. The solid line represents the linear fit modeled through the entire dataset with 95% CIs represented by dotted lines. Y-axis is truncated to provide an optimum view to aid understand this relationship.

Figure 6. Plot of residuals from linear regression (A) TDE-PH-302, week 12 peak, (B) TDE-PH-302, week 11 trough, (C) TDE-PH-301, week 16 peak, (D) TDE-PH-308, week 16 peak, and (E) TDE-PH-302, ITT.



2.5 Conclusion

A trend for dose-dependent increase in percent change from baseline 6MWD as a function of last dose normalized to body weight and as cumulative dose is observed. The relationship is significant during the entire dosing interval in a monotherapy setting, while at least at time corresponding to peak treprostinil systemic exposure in an adjunct setting.

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/s/

SUDHARSHAN HARIHARAN
10/27/2012

SATJIT S BRAR
10/27/2012

RAJANIKANTH MADABUSHI
10/28/2012

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 203496	**Reviewer:** Akm Khairuzzaman, Ph.D.	
Submission Date:	Dec 27, 2011		
Division:	Division of Cardiovascular and Renal Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	United Therapeutics Corp		
Trade Name:	(b) (4) (proposed)	**Date Assigned:**	09/02/2011
Established Name:	Treprostinil diethanolamine	**Date of Review:**	08/28/2012
Indication:	Pulmonary Arterial Hypertension	**Type of Submission:** 505(b)(1) NDA	
Formulation/strengths	Sustained Release Tablets, 0.125, 0.25, (b) (4) 1 and 2.5 mg		
Route of Administration	Oral		

SYNOPSIS:

This is an e-CTD 505(b)(1) NDA for a sustained release tablets (osmotic pump system) containing treprostinil diethanolamine (UT-15C), a chemically stable tricyclic analog of prostacyclin (PGI2) for the treatment of Pulmonary Arterial Hypertension (PAH). Treprostinil diethanolamine is a salt, the base of which is the approved drug products namely: Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution. Both these drug products are also manufactured by the same applicant, United Therapeutics Inc. The proposed drug product, (b) (4) is a sustained release tablet (osmotic pump delivery) formulation in (b) (4) different strengths namely: 0.125, 0.25, (b) (4) 1 and 2.5 mg as treprostinil base. The target drug release kinetic rate from the tablets is expected to be a zero or pseudo zero order over a period of 12 hours with about 80-90% release. The CQA of this product includes dissolution. The applicant has developed an in-vitro / in-vivo correlation (IVIVC) (using WinNonlin) to mathematically correlate the pharmacokinetic parameters (C_{max}, AUC) with in-vitro dissolution data. The applicant has also claimed that the drug is a BCS (b) (4) compound based on the solubility and caco-2 permeability study.

COMMENTS

1. There is a potential for alcohol-induced dose dumping. Applicant is addressing these issues by labeling.
2. The IVIVC is not acceptable. Applicant agreed not to use this to support their dissolution limit and revised the dissolution limit as per the agency's recommendation (se details in the review).
3. Extended release designation is acceptable.

RECOMMENDATION

This NDA is **recommended for approval** from the Biopharmaceutics perspective. Currently there are no pending issues from biopharmaceutics point of view.

Akm Khairuzzaman, Ph.D.	**John Duan, PhD.**
Biopharmaceutics Reviewer, ONDQA	Biopharmaceutics Reviewer, ONDQA

BIOPHARMACEUTICS ASSESSMENT

Physico-chemical Characteristics of the Drug:

Solubility: The intrinsic solubility of treprostinil is about 6 μ g/mL and the Log P is about 3. Therefore, diethanolamine was selected as the counterion to treprostinil to form a salt based on solubility, melting temperature, and hygroscopicity. By enhancing the solubility of the API through salt formation, treprostinil diethanolamine avoids dissolution rate-limited absorption and can be delivered orally with sustained-release technology. Applicant reported the equilibrium solubility of treprostinil diethanolamine salt to be greater than 800 mg/mL in water at 25°C and thus has selected this salt for further development. Based on these findings, the reviewer's analysis on the dose solubility in the gastrointestinal tract are as follows:

All strengths namely: 0.125 mg 0.25 mg, (b) (4) 1 mg and 2.5 mg (as treprostinil base) should be highly soluble in the gastric and intestinal medium.

Permeability: Applicant has conducted a permeability study on Caco-2 cells. Data showed that treprostinil diethanolamine has moderate permeability across intestinal membranes and an apparent permeability of 3.07 X 10^6 cm/sec was reported across Caco-2 cells.

Reviewers Comment: *Applicant has proposed that this drug could be classified as a BCS* (b) (4) *drug. However, based on the in vivo and in vitro data the reviewer believes that this drug could be designated as BCS class III.*

PK characteristics: Treprostinil C_{max} increased dose proportionally and treprostinil AUC(0-inf) and AUC(0-t) increased nearly dose proportionally over the dose range of 0.5 to 2.5 mg.

The reviewer's analyses on the formulation development : ***Acceptable.***

The formulation development of [redacted] used several prototypes that were used in clinical trials to select the target *in vivo* profile. Dissolution was defined as a CQA.

Three different prototype formulations were tested in vivo [redacted] Further tuning in formulation and process development led to the following final formulation composition of this product:

Table 1. Formulation composition of the drug product

Component	Reference to Quality Standard	Function	Amount per tablet (mg)				
			0.125 mg	0.25 mg	[redacted]	1 mg	2.5 mg
Treprostinil diethanolamine	In-House Standard	Active Pharmaceutical Ingredient	[redacted]				
Xylitol [redacted]	NF, EP	[redacted]					
[redacted] (Maltodextrin)	NF, EP						
Sodium Lauryl Sulfate	NF, EP, JP						
Magnesium Stearate	NF, EP						
Cellulose Acetate	NF, EP						
Triethyl Citrate	NF, EP						
[redacted]							
Polyvinyl alcohol*	USP, EP, JP						
Titanium Dioxide*	USP, EP, JP						
[redacted]*	NF, EP, JP						
Talc*	n/a						
FD&C Blue #2 / [redacted]	NF, JP						
Iron Oxide Yellow*	NF, JP						
Iron Oxide Red*	NF, JP						
Total				**214.0**		**214.0**	**214.0**

All strengths of are [redacted]

Proposed Dissolution Method & How the method was developed: ***Not acceptable***

The proposed method is as follows:

Apparatus	:	[redacted]
Dissolution medium	:	
Dissolution volume	:	
Speed	:	

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(b) (4)

Reviewer's evaluation: (b) (4)

Based on all these observations, the reviewer believes that there is a high potential for alcohol dose dumping and in vivo study is recommended or appropriate instruction should be included in the labeling.

Question to the applicant: *There is a potential for alcohol-induced dose dumping. Appropriate instruction should be included in the labeling.*

Applicant's response: *A statement that this product should not be taken with alcohol has been added to the enclosed labeling.*

Reviewer's Final Evaluation: ACCEPTABLE.

SUSTAINED RELEASE DESIGNATION: ***Acceptable***.
Treprostinil is available in the market in other dosage form such as Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution. As per the **CFR 21, 320.25 (f) (iii) the applicant should meet the following requirement: *"The drug product's steady state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application".*** *However, it is to be noted that both the product available in the market is very different (injectable and inhalation products) compared to this solid oral formulation and therefore the following peak-to-trough PK comparison is made (by the applicant) between this sustained release product and an oral solution which is not available in the market.*

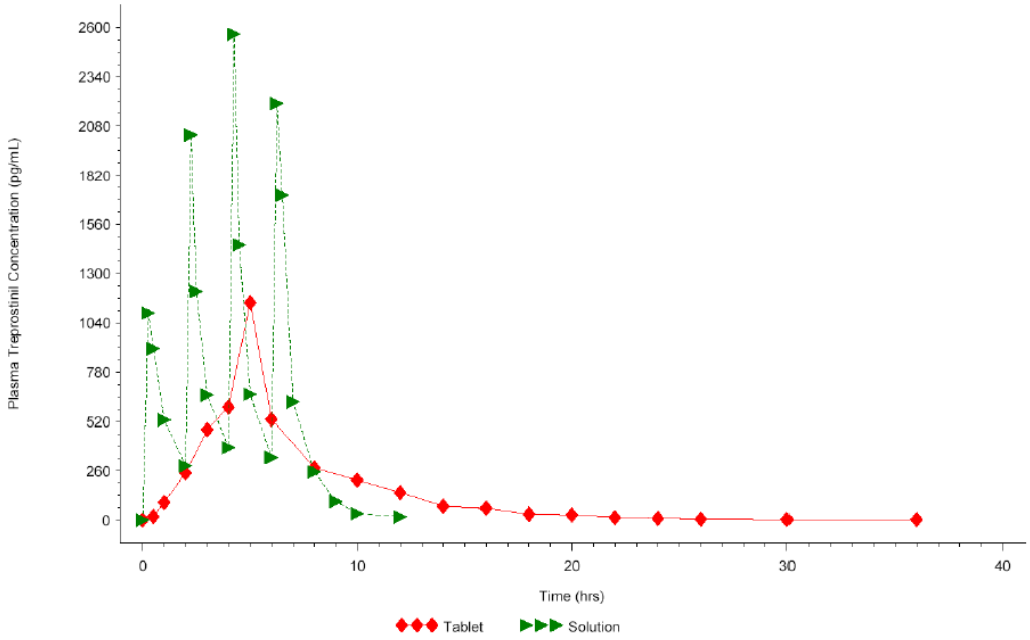

Fig. 19. Peak-to-trough PK comparison between the solid oral sustained release formulation vs. oral solution of Treprostinil.

Reviewer's evaluation*: Although there is no marketed immediate release solid oral dosage form for this drug, a direct comparison for the drug plasma fluctuation index cannot be measured. However, based on the in vitro drug release characteristics, the design of drug product formulation (an osmotic pump drug delivery system) and the above comparison, the formulation can be designated as a sustained release formulation.* ***Acceptable****.*

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/s/

AKM KHAIRUZZAMAN
08/28/2012
Recommended for approval from Biopharmaceutics point of view

JOHN Z DUAN
08/30/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**203496**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**I**	**Generic Name**	**Treprostinil diethanolamine**
Medical Division	**DCRP**	**Drug Class**	**Prostacyclin analog**
OCP Reviewer(s)	**Sudharshan Hariharan**	**Indication(s)**	**Treatment of pulmonary arterial hypertension (PAH)**
OCP Team Leader	**Raj Madabushi**	**Dosage Form**	**Sustained release tablet**
Pharmacometrics Reviewer	**Satjit Brar**	**Dosing Regimen**	**Twice daily**
Date of Submission	**12/27/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**08/27/2012**	**Sponsor**	**United Therapeutics**
Medical Division Due Date	**09/27/2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**10/27/2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	
I. Clinical Pharmacology				
Mass balance:	**X**	**1**	**1**	
Isozyme characterization:	**X**	**1**	**1**	
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**	**1**	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**	**1**	
multiple dose:	**X**	**1**	**1**	
Patients-				
single dose:				
multiple dose:	**X**	**1**	**1**	
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**	**1**	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**5**	**5**	
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**	**1**	
hepatic impairment:	**X**	**1**	**1**	
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**	**1**	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**	**1**	
Relative bioavailability -				
solution as reference:	**X**	**1**	**1**	
alternate formulation as reference:	**X**	**1**	**1**	
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**	**1**	
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**	**2**	
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies			**22**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)						
	Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X				
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X		
	Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X				
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X		
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X		
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X				
	General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Please submit the analysis dataset used to generate the dose- and concentration-response information and plots in section 1.2.5.1 within the "Summary of Clinical Pharmacology Studies". All analysis codes or control streams, output listings and scripts used to generate plots should be provided. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

2. Please conduct a dissolution study to evaluate alcohol induced dose-dumping from the drug product. Please furnish the results at the earliest during the review cycle of this NDA.

Sudharshan Hariharan 02/08/2012

Reviewing Clinical Pharmacologist Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Raj Madabushi	02/08/2012
Team Leader/Supervisor	Date

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/s/

SUDHARSHAN HARIHARAN
02/08/2012

RAJANIKANTH MADABUSHI
02/09/2012