

Update on the Development of Oral Prostacyclin Analogs for the Treatment of PAH



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The first reports in 1982 utilizing intravenous (IV) epoprostenol infusion to treat pulmonary arterial hypertension (PAH) reported profound acute and chronic benefits for patients with a historically progressive and deadly disease.^{1,2} The pivotal registration trial published in 1996 confirmed epoprostenol's short-term efficacy in a very ill cohort of PAH patients: 8/40 patients randomized to conventional therapy died during 12 weeks of observation.³ Although there was no placebo and the subjects in this trial were not blinded to treatment, epoprostenol-treated patients had better exercise capacity, hemodynamics, and survival. The lack of a blinded control group was a theoretical limitation in this study, but subsequent long-term, open-label investigations have substantiated the efficacy of epoprostenol.^{4,5}

The efficacy of epoprostenol comes with a substantial burden for the patient and caregivers. The drug must be mixed daily and chilled continuously with ice packs; this is especially challenging for patients who live in arid climates. The CADD Legacy pump required for epoprostenol administration is large enough to be inconvenient during daily living. In addition, the drug's short elimination half-life (~4 minutes) creates a potential risk for abrupt hemodynamic effects should therapy be interrupted. Finally, a chronically indwelling IV catheter carries the burden of daily care and places patients at risk for bacteremia and septic shock.⁶ Patients with chronic IV catheters can also develop venous thrombosis and vascular stenosis.

To attenuate some of epoprostenol's limitations, investigators studied the thermostable prostacyclin analogue, treprostinil.⁷ Chemical properties of treprostinil include stability in neutral pH solution at room temperature and a 4-hour elimination half-life. These properties simplify mixing (none), obviate the need for refrigeration of the pump, decrease possible risk of adverse effects (AEs) from abrupt discontinuation, and enable a subcutaneous (SC) delivery with a small infusion device. Unfortunately, the placebo-controlled trial was disappointing, with an overall 16 m improvement in exercise tolerance (6-minute walk) and modest hemodynamic benefits during 12 weeks of study.⁷ The trial's key limitations included low dose achieved and infusion site pain. The

maximum protocol-specified dose for the pivotal trial (22 ng/kg/min) was modest by current standards, but the median dose actually attained was lower (9 ng/kg/min). Infusion sites were painful for actively treated patients (85% treprostinil, 27% placebo); the pain was severe enough to require narcotics in 32% of patients, and 8% ultimately stopped therapy because of intolerable pain with infusion site changes every 3 days.

Additional data for efficacy and tolerability of treprostinil have since emerged. A post-hoc analysis of the dosing quartiles for the placebo-controlled pivotal trials strongly suggested a dose-response relationship in the blinded studies.⁷ Subsequent open-label trials suggested better efficacy at doses between 40-60 ng/kg/min in treatment-naïve patients or in those previously stable on epoprostenol.⁸⁻¹⁰ European investigators found reasonable tolerance for SC delivery when patients changed infusion sites less frequently (once every 2-4 weeks).¹¹ Long-term results were favorable among the large cohort (859 patients) who received open-label SC treprostinil as part of the initial registration trials with a 71% survival (Kaplan-Meier estimate) at 3 years.¹² Finally, a small but double-blind and placebo-controlled trial showed that aggressively dosed SC treprostinil prevented clinical worsening when stable patients were weaned from IV epoprostenol.¹³

In spite of an impressive efficacy profile, the difficult delivery system has limited early, routine use of these parenteral prostanoids, especially in patients with less severe symptoms. Any pump-based system makes swimming and competitive sports challenging; even bathing and sleeping are problematic. The costs for parenteral drugs are also extreme for the health care system.¹⁴ Iloprost, an inhaled prostanoid, has been demonstrated effective in treatment-naïve PAH patients.¹⁵ In the pivotal European trial, investigators enrolled 203 patients with NYHA class III/IV symptoms; this trial differed from others by enrolling patients with chronic thromboembolic pulmonary hypertension (57/203, ~25%) as well as more traditional WHO Group 1 patients. Actively treated patients utilized inhaled iloprost a mean of 7.5 times daily (90% of patients received 5 mcg/inhalation), and they were more likely to achieve the combined efficacy endpoint: 10% increase in 6MW distance *and* an improvement in NYHA functional class. Iloprost patients had a placebo-corrected improvement of 36 m in the 6MW distance at 12 weeks (59 m in those with idiopathic PAH [IPAH]). Hemodynamics were studied in all patients; iloprost protected against deterioration but actively treated patients did not

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experience improvement in baseline (pre-treatment) hemodynamics after 12 weeks of inhaled therapy. Both the Mahler dyspnea index and a quality of life measure were better in actively treated patients. Cough, flushing, and jaw pain were more likely in iloprost-treated patients.

Thus, inhaled iloprost is a reasonable alternative to IV or SC catheters, but the trial measured efficacy with an average 7 treatments daily, each lasting 7-12 minutes. An inhaled formulation of treprostinil with QID dosing has been reported but has not yet been FDA-approved¹⁶ [*Editor's note*: Dr Chakinala's article contains considerable details about the study of inhaled treprostinil].

Because all available prostanoids have cumbersome delivery systems, development of an oral prostanoid has been of great interest. The initial oral prostanoid (beraprost sodium) was studied first in Japan. In 1994, the Japanese regulatory authority approved beraprost for PAH because patient cohorts treated with open-label drugs improved as compared to historical controls. However, formal studies in the US and Europe were both disappointing, and the drug was never approved on either continent.^{17, 18} Subsequently, a novel salt of treprostinil was developed (treprostinil diethanolamine, UT-15C), and the results of the first trial were initially reported in May 2009.¹⁹ While this trial did not achieve primary efficacy endpoints, a number of factors potentially limiting adequate evaluation of this agent have been suggested and a second trial has started.

In this article, I will summarize the 2 published beraprost trials and the recently presented results with oral treprostinil. I will analyze the similarities and differences between the drugs and their respective data sets and provide the reader with a current progress report in the development of oral prostacyclin agents.

Beraprost

Beraprost sodium is made in 20 mcg "immediate release" tablets and is stable at gastric pH. The active enantiomer is rapidly absorbed and eliminated with a 30- to 50-minute half-life.²⁰ Preliminary pharmacokinetic (PK) analyses in healthy humans did not reveal drug accumulation at doses between 20-60 mcg when the drug was given TID for 3 days.²⁰ Headache and flushing were noted after each dose in 2/3 of patients given the drug over the aforementioned 3 days. European and North American trials were undertaken and are summarized and discussed below.

The ALPHABET Trial

ALPHABET was a European multicenter, randomized trial comparing beraprost sodium administered QID with placebo in 130 patients over 12 weeks.¹⁷ The primary efficacy endpoint was placebo-corrected improvement in 6MW; hemodynamics and functional class were also studied as secondary endpoints. Investigators recruited patients with WHO/NYHA functional class II and III symptoms, and the drug dose was titrated up weekly over the 12-week study period to a maximum dose of 120 mcg QID. Placebo patients achieved 110 mcg QID, and the median dose achieved in the active group was 80 mcg QID. Actively treated patients experienced substantial prostacyclin-like AEs during the titration phase, but these tended to improve during the maintenance phase (once patients had experienced dose-limiting side effects, further up-titration was not attempted). Six patients (9%) in the actively treated group withdrew prematurely because of AEs while only 3% (n=2) of placebo patients dropped out. The 6MW distance improved by 25 m overall and by 46 m in the subset of patients with IPAH. Hemodynamics and functional class were un-

changed in the actively treated patients. Time to clinical worsening was not evaluated in this study.

The North American Beraprost Trial

This randomized, placebo-controlled trial was slightly smaller (116 patients) but longer than the ALPHABET trial.¹⁸ The protocol enrolled patients with NYHA/WHO class II and III symptoms and aimed for a higher beraprost dose (200 mcg QID) during 12 months of blinded treatment. The inclusion criteria did not specify 6MW distance, and interestingly patients had a higher average 6MW (>430 m) than any of the other monotherapy trials to date [*Editor's note*: See summary table of patient populations in Dr Chakinala's article, this issue]. The investigators specified a composite incidence of disease progression as the primary endpoint and studied peak oxygen consumption (measured by cardiopulmonary exercise testing, CPET) in every patient repeatedly during the study; hemodynamics were studied in 60% of the overall patient group.

The European trial for PAH (above) and a trial evaluating beraprost therapy for intermittent claudication were both in progress when the North American trial was launched. The claudication data revealed no benefit for beraprost. Because of this, the North American PAH trial was terminated due to concerns for lack of efficacy when all patients had completed 9 months; at that point, most (>90%) had completed 12 months.

At 3 and 6 months, the placebo-corrected 6MW distance was improved (<30 m for treatment-naïve patients). However, no mean improvement was apparent at month 12. The primary disease progression endpoint (cumulative incidence of death, epoprostenol rescue, or a 25% reduction in peak oxygen consumption [VO_2]) was statistically better at 6 months but not at 9 or 12 months. Peak VO_2 measured during CPET did not show statistical improvement during the trial. Finally, there were no significant improvements (nor even trends) in hemodynamics at 12 months. Dosing during this trial was less than initial protocol goals (110 mcg QID in actively treated patients and 120 QID in placebo patients at 12 months). Doses at 3 months were smaller (70 mcg QID active, 80 QID placebo) and increased slowly over the 12 months. Investigators cited headache, flushing, jaw pain, and dizziness as dose-limiting AEs.

Because the results contrasted starkly with the known efficacy of infusion prostanoid therapy, one can consider aspects of the drug's profile and speculate about the limitations of the beraprost preparation studied. One potential explanation for the results is that patients were exposed to the drug for too short an overall time period during the day. QID dosing coupled with a rapid elimination half-life (between 30 and 50 minutes) predicts that potential exposure to meaningful drug levels may have been as short as 6-8 hours each day. A related problem is that prostacyclin-type AEs may have been more prominent with beraprost's rapid release and higher peak levels (which occurred QID); those AEs may have limited attempts to increase the dose to more effective levels.

For comparison, the BREATHE-1 data with oral bosentan showed a placebo-corrected 35 m benefit at 16 weeks with fewer AEs.²¹ Studied at about the same time as the beraprost trials, actively treated BREATHE-1 patients also achieved secondary endpoints: a delay in time to clinical worsening and modest hemodynamic benefits. Particularly with bosentan as a safe and well-tolerated oral therapy, the risk:benefit for beraprost was marginal. After the North American beraprost study, there were no further attempts to develop immediate release beraprost. There are cur-

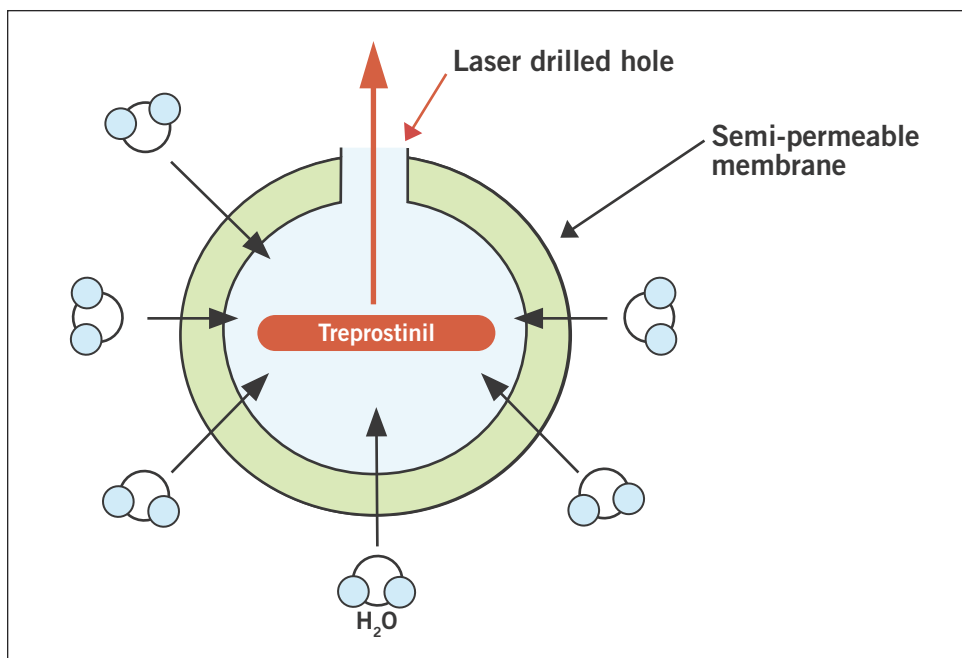


Figure 1: Schematic illustration of UT-15C (oral treprostinil diethanolamine) controlled release tablets. The treprostinil-coated dextrose powder is pressed into a solid tablet and coated by a membrane permeant only to water. In the GI tract, water leaches through the membrane and dissolves the salt; the drug is then slowly released through the single laser-drilled hole.

rently Phase II trials enrolling patients to study a sustained release version of beraprost, which may mitigate some of the problems encountered with immediate release beraprost.

Treprostinil diethanolamine

The oral prostacyclin analog treprostinil diethanolamine (UT-15C) was synthesized specifically to address the perceived shortcomings of beraprost sodium. A solid tablet with the diethanolamine salt is coated with a semi-permeant membrane that lets water in but does not allow the drug to escape (**Figure 1**). The osmotic tablet is then pierced by a laser. In the GI tract, water leaches through the membrane and dissolves the salt; the drug is then slowly released through the single hole. Preclinical data suggested that UT-15C had a terminal half-life of approximately 4.5 hours and achieved blood levels with a broad and sustained plateau of serum drug concentration, which more closely approximated continuous parenteral dosing with treprostinil. This important distinction was in contrast to the short half-life and rapid rise to and fall from peak serum concentrations produced by beraprost; these different characteristics suggested a better tolerance and the potential to deliver efficacy comparable to a parenteral delivery route. PK data from normal volunteers supported a twice-daily dosing regimen when tablets were taken with a 500-calorie meal (including 20 g of fat). These important properties and potential benefits formed the basis of the preclinical and early Phase III trials of UT-15C for the treatment of PAH that are discussed below.

The placebo-controlled FREEDOM trials studied BID dosing for patients with PAH. PK data from a cohort of 74 patients treated with UT-15C during the open-label extension phase was presented in 2009.²² The data support a BID dosing regimen for most patients, and it appears that there is a linear correlation between UT-15C dose and total prostanoid exposure (area under the curve, $r^2=0.7$). At a dose of 3.5 mg BID ($n=8$ patients), UT-15C produced clinically relevant serum treprostinil levels (see **Figure 2** legend for detailed explanation) at every time point between 2

and 8 hours after the dose. There was a smooth rise and fall in serum levels over the whole 12-hour epoch (**Figure 2**).²² A handful of patients chronically dosed with 10-16 mg BID tolerated *peak* serum treprostinil levels equivalent to those measured with the parenteral drug at doses greater than 100 ng/kg/min.²³

Phase III placebo-controlled trials with oral treprostinil have been partially completed. These trials included multiple sub-studies but in general studied oral treprostinil as either initial (FREEDOM-M) or add-on therapy (FREEDOM-C). Initial clinical data are available only from the combination portion of the FREEDOM trials so far with continuing enrollment in the treatment-naïve study.

The placebo-controlled FREEDOM-C trial was designed to assess the added benefit of UT-15C in combination with an endothelin-receptor antagonist (ETR-A), a phosphodiesterase-5 inhibitor (PDE-I), or both. The enrollment criteria were broad including those with NYHA/WHO class II-IV symptoms and walk distances between

150-450 m. Inclusion criteria allowing class II patients and those on 2 background therapies is much broader than many previous combination therapy investigations, which have typically excluded these populations. The primary endpoint was a change in 6MW at 16 weeks, and the study was powered with a 90% ability to observe a 35 m walk improvement in a cohort of 300 patients.

A total of 354 patients were randomized in a 1:1 fashion to placebo or UT-15C. At 16 weeks, the median placebo-corrected treatment effect in the UT-15C patients was 11 m ($P=0.07$).¹⁹ The placebo patients were remarkably stable with a 5 m median improvement in 6MW over the 16-week period. There was no delay in clinical worsening for treated patients compared to placebo but there were few clinical worsening events in the placebo group (12, 7%). There were no changes in functional class, and the full data set will soon be submitted for publication.

Although initial results overall may appear disappointing, there are several points worth noting which support continued development of this agent. There was a substantial rate of withdrawal due to AEs. Fourteen percent of actively treated patients stopped therapy because of drug-related AEs (all prostacyclin like; compare with 5% dropouts in the placebo group). One-third of patients (58 of 174) randomized to active treatment either dropped out or never achieved a dose of UT-15C greater than 1 mg BID.

One explanation for this dropout might be excess dosing leading to drug intolerance from predictable prostacyclin side effects. At least 2 pieces of data from the trial suggest that this may be the case. Dropouts due to AEs were especially problematic early in this study. The 1 mg tablets initially utilized caused an intolerable degree of headache, flushing, and nausea in many patients. Extrapolating from the PK data above, the 1 mg tablets available for dose titration would be expected to produce peak serum levels comparable to 10-15 ng/kg/min of infused treprostinil—a dose which experience suggests may not be well tolerated in an acute administration. Smaller tablets introduced later in the trial (0.5 mg and 0.25 mg tablets) seemed to be better tolerated, and there

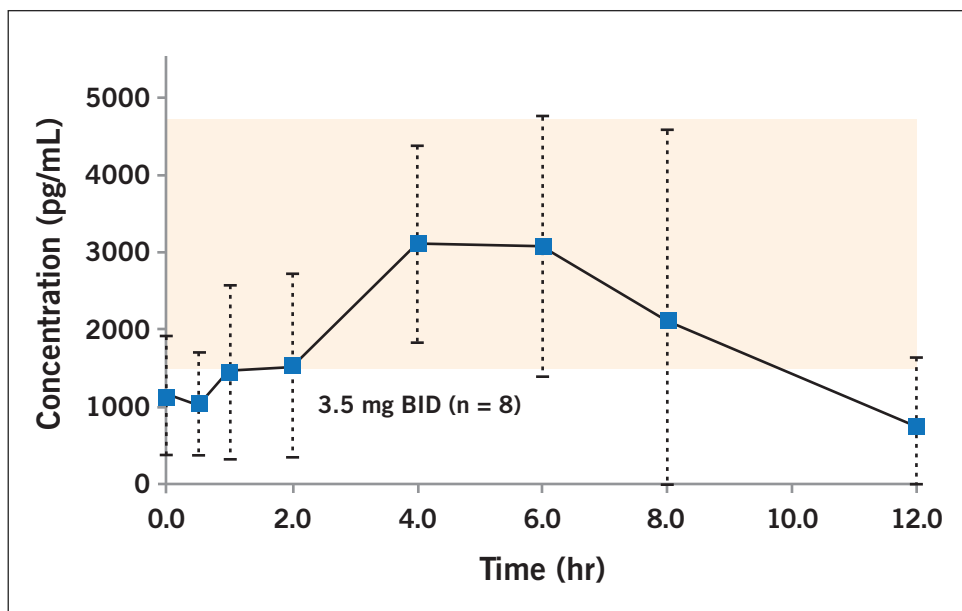


Figure 2: Average concentration-time profile for 8 PAH patients chronically dosed with oral UT-15C at 3.5 mg BID. Serum treprostinil levels were drawn at the designated time points following a dose of UT-15C and measured by liquid chromatography-mass spectroscopy at a central facility. To help put these numbers in perspective, the shaded area illustrates serum treprostinil levels measured from a large cohort of PAH patients on parenteral treprostinil dosed between 10-30 ng/kg/min.²⁹ In other words, UT-15C produced peak serum treprostinil levels that would be similar to those obtained with parenteral treprostinil at ~20 ng/kg/min. For each time point between 2 and 8 hours, these UT-15C patients had treprostinil levels at or greater than those expected for a patient on 10 ng/kg/min of parenteral drug. Data shown as mean \pm standard deviation.

were fewer dropouts related to AEs as the trial proceeded.¹⁹

A second observation is apparent from a post-hoc analysis of 6MW according to maximum dose achieved. As noted above, exactly 1/3 of treated patients either dropped out or never achieved a dose >1 mg BID. For the $\sim 1/3$ who achieved doses of 3.5 mg BID (or greater), the median placebo-corrected 6MW improvement was 34 m. To put that dose of UT-15C in context, the average serum treprostinil levels shown in Figure 2 for 8 patients on 3.5 mg BID correspond to serum levels that have been measured in PAH patients on parenteral treprostinil at doses between 10-30 ng/kg/min. At doses of 3.5 mg BID or greater, UT-15C produced a 34 m 6MW benefit even though 44% of those patients were already on 2 background therapies. This could be a relevant improvement when one considers the more modest benefits (19-25 m) measured in other combination trials in which there was only a single background therapy.^{16, 24-26}

The above post-hoc observations leave room for optimism, especially because of the greater flexibility in dose titration (smaller tablets), and a follow-up trial has already been launched in June 2009 (FREEDOM-C2). This 16-week trial will have inclusion criteria nearly identical to the initial study except that enrollment walks will be shorter (between 150-400 m). The dosing will be increased in blind fashion using 0.25 mg tablets and attempting to achieve doses between 3.5-5.0 mg before the 15th week of the study. The primary endpoint remains the estimated median improvement in 6MW. It will probably take 2 years to enroll the necessary 300 patients (power analysis identical to the initial FREEDOM-C). Hopefully this trial will provide a meaningful evaluation of the merits and risks associated with adding oral UT-15C to background PAH therapy in a broadly defined cohort of PAH patients.

Conclusion

Evaluation of the collective data for epoprostenol and treprostinil suggests that parenteral prostacyclins can be very effective in limiting disease progression. There is no doubt that parenteral epoprostenol provides impressive short- and long-term benefits for PAH patients with advanced disease. A growing body of published evidence suggests efficacious results when parenteral treprostinil is dosed aggressively, and the SC dosing option allows some clinicians to consider this earlier in the treatment algorithm for their patients (SC treprostinil is FDA-labeled for use in class II patients). Nonetheless, any parenteral infusion system remains a substantial impediment to prostacyclin treatment for many patients, especially those with more modest symptoms. Thus, an oral prostanoid that offers a substantial fraction of our patients the efficacy previously found only with a cumbersome infusion could represent an important “next step” in PAH therapy. At this point, we have much to learn (refined understanding of the drug’s use and perhaps better drugs) to realize fully the elusive promise of a highly effective oral prostacyclin

agent. We remain far from the goal but the future looks promising for better efficacy and better quality of life in PAH with 3 drugs in the pipeline: an oral prostacyclin receptor agonist (Actelion, “NS-304”^{27, 28} soon to begin Phase II), beraprost-MR (Phase II), and UT-15C (Phase III). [Editor’s note: Many of the study concepts, limitations, and discussions will be carried forward into the roundtable section of this issue for further critical examination.]

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