COWEN AND COMPANY

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Industry Outlook

Investors Are From Mars, The FDA Is From Venus

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I.V. Remodulin Has Helped Take Majority Share From Flolan

Like Flolan, i.v. Remodulin is delivered through an indwelling central venous catheter. However, i.v. Remodulin shares many of s.c. Remodulin advantages such as longer half-life and easier reconstitution. Our consultants continue to view Flolan as the gold standard of therapy, particularly for acutely and severely ill PAH patients. However, they also view Remodulin's convenience profile as attractive, and some are transitioning patients from i.v. Flolan to i.v. Remodulin. A rapid-switch study evaluating conversion from i.v. Flolan to Remodulin in the outpatient setting was presented at the American Thoracic Society meeting in May 2006 and provides some additional incentive to switch.

Successful completion of the subpart H study evaluating transition from Flolan to s.c. Remodulin has allowed United Therapeutics to broaden the Remodulin label to specifically include an indication for diminishing the rate of clinical deterioration in patients requiring transition from Flolan. In an 8-week, randomized, double-blind, placebo-controlled, multicenter study, patients on Flolan were switched to placebo or Remodulin. 93% (13 of 14) of Remodulin patients versus 13% (1 of 8) of placebo patients transitioned from Flolan successfully (p=0.0002).

As of Q3:10, the infused Remodulin franchise was on a roughly $440MM/year run rate, while Flolan achieved 2009 sales of 189MM GBP (approx $300MM). Therefore, Remodulin has supplanted Flolan as the preferred infused prostanoid. We believe Remodulin will continue to claim steady market share from Flolan as clinician experience grows, despite the availability of a low-priced generic. We estimate Remodulin revenue (s.c. plus i.v.) of $413MM, $440MM, $440MM, $445MM, $450MM and $455MM in 2010-15, respectively.

Consultants Hesitant To Use New Epoprostenols

A generic epoprostenol from Teva was approved by the FDA on April 23, 2008. Actelion markets a thermostable formulation of epoprostenol called Veletri. It was approved in mid-2008 in the U.S. for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.

Our consultants have been hesitant to use either. The note that IV epoprostenol is extremely difficult to dose correctly. If it is misdosed in a patient, or if treatment is interrupted, patients' disease can worsen quickly, possibly causing the death of the patient. Therefore the physicians must have both confidence in the supplier of the epoprostenol, as well as sufficient data on how it should be dosed. Today, neither of the newer epoprostenols have both.

Teva's production of epoprostenol was halted, interrupting its supply. This has caused the physicians to lose faith in Teva as a supplier, and has caused the physicians to abandon it.

Although Actelion's thermostable formulation of epoprostenol could be easier to use than Flolan, the consultants want to see more data before adopting it. They note that to date there are no switch studies, and so it is unknown if the differences in formulation could have an effect on the dosing, safety, or efficacy. They await good, rigorously collected switch data before adopting it. Actelion is conducting such a study, with data expected during H2:2011.

Flolan Sales

Flolan (GSK) Sales (GBP MM)											
	Q1:08A	Q2:08A	Q3:08A	Q4:08A	2008A	Q1:09A	Q2:09A	Q3:09A	Q4:09A	2009A	Q1:10A
U.S.	10	9	10	14	43	13	11	9	14	47	9
Worldwide	34	38	41	47	160	46	47	44	52	189	43

Source: GSK

Tyvaso's Phase III TRIUMPH Trial Lives Up To Its Name

United Therapeutics developed a formulation of Remodulin called Tyvaso that is delivered four times (one minute per inhalation) daily via a portable nebulizer. In late 2007, United Therapeutics reported positive data from a 12-week, randomized, double-blind, placebo-controlled, multi-center Phase III study (TRIUMPH) in patients with NYHA Class III and IV PAH.

The TRIUMPH (TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension) study was a randomized, double-blind, placebo-controlled trial of Tyvaso in patients with severe pulmonary hypertension. The trial closed enrollment in July 2007, with 235 patients. Patients were enrolled who had NYHA Class III or Class IV pulmonary hypertension. They could be on a stable dose of 125 mg bid bosentan or any stable dose of sildenafil for at least three months prior to the study start. Patients were to have an unencouraged six-minute walk test of between 200 and 450 meters at screening. Exclusion criteria included pregnancy, having changed or discontinued any PAH medication in three months prior to enrollment, and having received any investigational drug within 30 days of the start of the study. Patients were randomized 1:1 to either placebo or Tyvaso given four times per day via the Optineb nebulizer. Dropouts were accounted for using a last observation carry-forward method (LOCF), and any patients who died during the trial period were assigned a six-minute walk distance of 0 meters.

Full data from the study were presented at the American Thoracic Society annual meeting in May 2008. The trial succeeded in meeting its primary efficacy endpoint demonstrating an improvement in placebo-adjusted median 6MW distance of approximately 20 meters ($p<0.0006$, Hodges-Lehmann estimate and non-parametric analysis of covariance in accordance with the trial's pre-specified statistical analysis plan). Mean baseline walk distance in the trial was approximately 350 meters. The trough exposure (defined as a minimum of four hours after inhalation of Tyvaso, for treatment change in 6MW distance at week 12 relative to baseline) was also significantly improved, with an increase in median 6MW distance of 14 meters ($p<0.01$). Additionally, the 6MW distance at week 6 relative to baseline was significantly improved, with an increase in median 6MW distance of approximately 19 meters ($p<0.0005$). The trial failed to meet its secondary endpoints, including change in Borg Dyspnea Scale rating (shortness of breath test), NYHA functional class, time to clinical worsening (as defined by death, transplant, atrial septostomy, hospitalization due to PAH, or initiation of another approved PAH therapy), and the 6MW distance at treatment day 1. Two measures of quality of life, the global score and the physical score, were statistically significantly improved with Tyvaso treatment.

Interestingly, the effect in the primary endpoint seemed to be driven by patients on background Tracleer. Patients on background Tracleer had a median improvement in 6MWD of 25m, while those on sildenafil had a median improvement of only 9m. The