**United's entrenched position in the PAH market faces upcoming competition.**



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**Investment Thesis** 05/12/2016

United Therapeutics' product lifecycle management and entrenched position in the pulmonary arterial hypertension space give the firm a unique advantage, but we expect near-term patent losses and increased branded competition to weigh on returns. The firm is a market leader in two of the three main drug classes: prostacyclin analogs, phosphodiesterase type 5 inhibitors, and endothelin receptor antagonists.

United dominates the prostacyclin market with its treprostinil franchise, which includes Remodulin (subcutaneous and intravenous injection), Tyvaso (inhaled), and recently launched Orenitram (oral). The most severe patients typically receive infused prostacyclin, which is titrated upward until the patient dies or receives new lungs. Earlier-stage patients can start on one or more ERA/PDE-5 oral therapies, like United's oral PDE-5 drug Adcirca, which offer the most convenient dosing and are less invasive. We expect favorable efficacy data from Gilead/Glaxo's combo trial with Letairis/Volibris (ERA) to boost Adcirca sales.

However, patents on United's three largest drugs--Remodulin, Tyvaso, and Adcirca--will expire in 2017-18, exposing 90% of revenue to potential generic competition. In addition, rival Actelion recently launched Uptravi (oral selexipag), which boasts strong efficacy and is likely to capture Orenitram and Tyvaso patients if United cannot counter with new data, expected in 2017. We believe the extreme dose sensitivity of many Remodulin patients and unique drug device patent on Tyvaso will slow generic erosion of sales, but the ramp of competition produces a large risk for United.

United's pipeline will be key for PAH patient retention in upcoming years. While the company has successfully pushed new drugs and delivery methods to market, it is no stranger to approval process stumbles. Orenitram initially faced Food and Drug Administration rejection, and more recently so did United/Medtronic's implantable treprostinil pump, delaying market entry until at least 2017. Following burgeoning success with Unituxin (neuroblastoma), United is looking to expand in the pediatric oncology market, which we believe would diversify revenues and support its moat.

**Economic Moat** 05/12/2016

Due to the extreme dose sensitivity of PAH patients on prostacyclin therapy and the company’s innovation in drug delivery, we believe United will retain a significant portion of the most severe PAH patients despite generic and branded competition, which forms the basis of our narrow economic moat rating. While there is no argument that United is now a major player in both the prostacyclin and PDE-5 drug classes, patents on its three largest drugs--Remodulin, Tyvaso (prostacyclins), and Adcirca (PDE-5 inhibitor)--will expire in 2017-18, exposing 90% of the firm's revenue to potential generic competition.

However, we think generic erosion on Remodulin (infused treprostinil) and Tyvaso (inhaled treprostinil) sales will be muted compared with a typical patent loss scenario. Patients on Remodulin are typically among the sickest and are very sensitive to dose changes. If prostacyclin treatment is abruptly stopped, patients risk severe rebound effects. Remodulin’s thermostable formulation and longer half-life gives patients a larger buffer time to reach a hospital and renew therapy than Actelion’s Veletri (epoprostenol sodium). Primarily due to this advantage, United has captured an overwhelming majority of the injectable prostacyclin segment. While generic drugs are deemed to have the bioequivalent strength of branded drugs, they are not exact replicas in strength. Physicians will likely want to see longer records to ensure that transitioning patients will not harm treatment trajectory, as was the case when GlaxoSmithKline’s Flolan (infused epoprostenol) went generic. If it is approved, we believe United and Medtronic’s implantable pump would further help retain Remodulin patients. Meanwhile, Tyvaso has a unique drug/device combination patent, which means generic companies will need to gain FDA approval on both the nebulizer and drug proposed, which complicates bringing generics to market.

We anticipate that United will be able to protect a large share of the sickest patients, who face limited options before lung transplantation, from branded competition. Actelion, which leads the ERA market and also competes directly with United in prostacyclin treatments, remains a threat, and recently launched Uptravi, its oral prostacyclin drug backed by the largest PAH study to date with strong efficacy data. However, Uptravi’s clinical trial results showed high rates of patients discontinuing the drug (14% compared with 7% in placebo), and despite the drug’s improvement over placebo endpoints, 27% of patients saw their disease progress. Even if patients switch to Uptravi in the short term, a good portion will eventually require alternative treatments without a dosage ceiling and are likely to be captured by United’s treprostinil therapies, which can be dialed up in sync with disease progression. Because the cost of United’s treprostinil drugs increase with dosage, revenues per patient can be upward of $150,000 per year during later stages of the disease. Tyvaso (inhaled treprostinil) also has a clear dosing advantage over Actelion’s Ventavis, which requires more frequent and longer administration sessions, and remains the lead player in the nebulized prostacyclin space with a market share more than 90%.

Strong sales and margins have kept the company’s balance sheet flush with cash, and high returns on invested capital have historically left a large buffer over the company’s cost of capital. Given the severity of the disease and need for increased therapy as the patient ultimately worsens, prostacyclin drugs typically cost more than $100,000 per year. Since PDE-5 inhibitors--including United’s Adcirca (tadalafil)--are also prescribed for erectile dysfunction, they are priced much lower, closer to the cost associated with the ED indication. We would consider a downgrade of our narrow economic moat rating as time progresses closer to increased generic uptake, without the addition of large and viable late-stage pipeline candidates to offset the erosion to revenue. A moat upgrade would require more product diversification into non-PAH areas coupled with greater patent protection.

[**Valuation**](http://quicktake.morningstar.com/StockNet/StockValuation.aspx?Country=USA&Symbol=UTHR&culture=en-US) 05/12/2016

Our $116 fair value estimate incorporates modest generic declines for Remodulin and Tyvaso starting in 2017 and 2018, respectively, partially offset by incremental value added from pipeline candidates. We model peak Remodulin and Tyvaso sales at nearly $600 million and $500 million, respectively, before patent expiration. We have tempered expectations for Orenitram, as competition with Uptravi is likely to weigh on sales, and forecast roughly $400 million of annual revenue by 2020. Adcirca is an easily replicable small molecule--we believe the drug faces sharp deterioration with the entry of generic competition in 2017. Unituxin has already captured most of the U.S. pediatric neuroblastoma patients through its clinical trials, and we anticipate the addition of EU patients will create total sales around $100 million. We place a high 85% probability on the approval of United’s ex-vivo lung perfusion system since it is already commercialized in Canada. While United’s partner, Medtronic, struggled getting its implantable pump approved by the FDA, its approval (50% probability) would significantly improve United’s ability to retain IV patients after patent loss, as the device offers more convenient drug administration and less risk of infection. Our forecasts lead to low-single-digit revenue growth up to 2018 when generic drugs penetrate the PAH market, after which growth turns slightly negative. Adjusted gross margins (excluding share-based compensation) increased to an all-time high at nearly 96% of revenue in 2015, thanks to the end of Remodulin royalty payments. We expect these levels to persist until 2018, when anticipated generic decline will leave revenue more exposed to royalty-paying products and pressure gross margins down to 90%. We model adjusted research and development expenses steadily increasing from 9% of sales as the firm invests in its pipeline to offset upcoming patent losses. We believe selling, general, and administrative expense will ramp up with product launches, but will be offset by the decline in resources needed to penetrate U.S. PAH prescribers, where United already has well-established relationships. We would consider raising our fair value estimate if Orenitram’s Freedom-EV results (anticipated in 2017) show superiority over Uptravi or if the Remodulin implantable pump looks more likely to enter the market and retain patients. Our assumptions culminate in 39% returns on invested capital in 2020 with a 9% cost of equity.

**Risk** 05/12/2016

United is dependent on slow generic erosion once its key drugs Remodulin and Tyvaso lose patent protection. While there are compelling reasons for why generic infused and inhaled treprostinil will encounter slow uptake, higher-than-anticipated generic competition would have a major impact on sales and cost of goods sold, as United no longer pays royalties on Remodulin and Tyvaso. United is trying to manage the lifecycle of its treprostinil franchise through product and device improvements. However, the FDA recently rejected partner Medtronic’s implantable pump for Remodulin, and United’s phase II development of esuberaprost in combination with Tyvaso has a shaky past. Esuberaprost is reformulated version of beraprost, which failed to gain FDA approval as a monotherapy in the early 2000s.

Actelion’s oral prostacyclin analog Uptravi may also steal market share from United’s Orenitram and Tyvaso. Uptravi’s Griphon trial is the largest and longest PAH trial conducted to date, demonstrating a 40% reduction in morbidity/mortality over the placebo group. While Griphon was not a head-to-head comparison against Orenitram, which showed small improvement in the six-minute walk distance, physicians may find Uptravi’s clinical benefit and large dataset more compelling. This would steal earlier-stage patients away from Orenitram and Tyvaso, whose growth has already slowed with the entrance of oral prostacyclin drugs. Results from the Freedom-EV trial evaluating Orenitram’s impact on mortality/morbidity end points are expected in 2017.

As with all biotech companies, United’s future rests on the productivity and success of its pipeline. Failure to gain timely FDA approval for product enhancements or new drugs will leave the company with little to defend itself against competitors. In addition, as the treatment paradigm for PAH shifts to combination therapy, payers may be less willing to pay high prices for a single drug, increasing reimbursement risk in upcoming years.

**Management** 05/12/2016

We award United’s management a Standard stewardship rating. The firm has struggled with FDA approval for some of its products, but we believe its focused expertise and patient acquisition strategy bodes well for shareholders. Chairman and CEO Martine Rothblatt founded company in 1996 after her daughter was diagnosed with PAH, which provides the firm with a strong incentive to continuously develop innovative treatments. Prior to United, Rothblatt worked as a telecommunications lawyer before starting Sirius Satellite Radio, which later merged to form Sirius XM Radio. The rest of the management team has a deep history with the firm and industry. COO Michael Benkowitz, who previously led the firm’s administrative functions since 2011, recently took over for former United veteran David Zaccardelli. United’s 10-member board consists of seven independent members, which we look upon favorably.

With almost nonexistent debt and strong cash flow, United is primed to make bolt-on product acquisitions. The firm hired a director of business development in 2015. Management has displayed discipline in waiting for the right opportunity--early-stage rare-disease products focused on the pulmonary, cardiology and pediatric oncology markets--which we think jibes well with investor interests. Stumbles with the FDA, however, lower our confidence in management’s execution. Orenitram was rejected by the FDA multiple times before gaining a surprise approval, while Tyvaso also encountered approval delays. In more recent years, United has bought back shares and is anticipated to do so in the near term, which will provide additional value to shareholders. Investors should also take note of management’s visionary long-term strategy. Although we believe some of United’s long-term projects, which include xenotransplantation and drone delivery of organs, may be able to reap large benefits in the future, we would like to see the firm continue to balance its long-term and risky endeavors with more near-term and viable developments.

**Overview**

Profile:

United Therapeutics specializes in drug development for pulmonary arterial hypertension, a rare and progressive disease marked by abnormally high blood pressure in the arteries of the lungs. The firm is a market leader in two of the three primary drugs classes used to treat PAH. Nearly all of its sales are generated within the U.S. United also markets a pediatric oncology drug.

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**Morningstar's Take**

**UTHR**

* Analyst

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| Price 05-13-2016  | Fair Value Estimate | Uncertainty   |
| 111.48 USD | 116 USD | High |