# United Therapeutics faces bleak future for oral Remodulin approval with disappointing PAH results, lack of physician enthusiasm

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Overall efficacy from oral drug described as underwhelming despite one positive study

Plans to file for approval with Freedom C2 failure perplex physicians; two positive studies believed to be FDA-preferred

Physicians not inclined to use oral Remodulin in clinic with current drugs demonstrating better efficacy

United Therapeutics' (NASDAQ:UTHR) oral Remodulin (treprostinil) faces a bleak future, experts said. The company still plans to file for FDA approval for the pulmonary arterial hypertension (PAH) treatment indication, despite its recent failure in the pivotal Phase III Freedom-C2 study.

The failed combination therapy study (oral Remodulin combined with other first line PAH therapies) was described by physicians as the pivotal study which would likely mirror its realistic treatment setting.

Oral Remodulin, a prostacyclin analogue, reached positive results in an earlier monotherapy study (Freedom-M), which the firm will submit as the basis for its approval application; however, experts have described all the data for this drug as "underwhelming" and an approval would therefore be surprising, they added.

United Therapeutics declined to comment for this article.

A United press release said the company will go ahead with an NDA filing in 1H12 and believes that the positive Freedom-M study should support the application in treatment-naïve patients. The release said treprostinil's already-approved status for use in PAH by subcutaneous, intravenous and inhaled routes of administration should

support the filing.

While United hasn't disclosed its correspondence with the FDA and the exact NDA filing requirements for oral Remodulin, experts previously told this news service they expected the FDA to only accept two positive trials for approval of the drug given its troubled history.

Before FREEDOM-C2, United conducted another combination trial (FREEDOM-C) for oral Remodulin with other first line PAH therapies. A high side effect profile linked to dosing saw a high drop-out rate contributing to an ultimate trial failure. United revised the dosing for its monotherapy trial (FREEDOM-M) and started a new combination trial (FREEDOM-C2). FREEDOM-M reported positive results in June with a mean six-minute-walk distance (6MWD) improvement of 23m (p=0.0125), while the C2 trial failed to reach statistical significance on its 6MWD primary endpoint with a median improvement of 10m (p=0.089). Both studies missed secondary endpoints.

The results of the C2 trial were "totally underwhelming," said Dr Harrison Farber, director, Pulmonary Hypertension Center, Boston University, who added he was surprised the company was going ahead with the FDA filing. Even though FREEDOM-M was statistically significant, "it wasn't very impressive," and efficacy was "marginal at best," he said.

Following the data release, there isn't much enthusiasm about the drug regardless of its fate, added Dr Peter Engel, medical director, Pulmonary Hypertension Program, Heart & Vascular Center, The Christ Hospital, Cincinnati. Even if the drug did get approved, Farber said he doubted any experienced physician would use it in practice.

The data is not strong enough to even think about giving this drug to treatment naïve patients as a first line option, said Farber. The drug itself takes time to dose, and it is not worth wasting any time with the efficacy demonstrated in the trials as a result, Engel added.

The data released is inferior to the data achieved by drugs already used as first line therapies, said Engel. Current standard first-line therapies include PDE5 inhibitors such as Pfizer's (NYSE:PFE) Revatio and United Therapeutics' Adcirca as well as ERAs (endothelial receptor agonists) such as Actelion's (VTX:ATLN) Tracleer and Gilead's (NASDAQ:GILD) Leitaris.

In addition, Farber expressed concern that less experienced physicians might prescribe this drug (swayed by an attractive oral route) as an alternative to IV Remodulin, which would not be best practice as IV Remodulin has established efficacy for more severe patients.

The safety of the drug was superior in the C2 trial compared to the failed C trial, said Engel, so the firm appears to have worked out the dosing, he added. There was still a notable difference in side effects (headache, diarrhea, nausea) between study drug and placebo and patients who dropped out of the trial can't tolerate it at all, said Farber. Eleven percent of patients dropped out of the C2 study due to adverse events and considering this is just a 16-week trial, that is a high number for an incredibly short period of time, Farber added.

One C2 study investigator said the C2 results were "unimpressive" and although the M study was positive, the magnitude of change in the 6MWD was still "a little disappointing." He said the only saving grace for an approval would be leniency considering the molecule is already approved in other modes of delivery. He said he was uncertain of this outcome materialising. A second investigator agreed that a lot of physicians were disappointed with the walk distance achieved in Freedom M.

With the way trials are being conducted now, this trial design is somewhat inferior with an easier endpoint to hit and the drug still didn't deliver attractive results, said Farber. The second investigator noted the 6MWD endpoint has been used for 15 years and a more modern morbidity/mortality endpoint in the form of an "event driven" trial (similar to Actelion's ongoing trials for macitentan and selexipag) would have given more confidence on the drug's efficacy.

Engel noted that if the drug wasn't able to prove itself in the 6MWD trial (requiring a lower bar for efficacy) then this gives little hope for its success in an event-driven study. However the first investigator said a longer event-driven trial might be worthwhile, as the problem with oral Remodulin is getting the dose up high enough to start seeing efficacy -- which can be somewhat limited by shorter trials.

While efficacy results did not reach statistical significance in C2, the company could still submit the C2 trial to show improved safety of the drug, Farber said, but he questioned why a company would submit data to show that the drug didn't work. Experts noted that despite improved safety in the C2 trial, the oral route of treprostinil was still accompanied by higher tolerability risks compared with other modes of delivery.

United Therapeutics has a market cap of USD 2.6bn.

by Surani Fernando in London