Evaluate Vantage

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JP Morgan conference - MannKind takes a deep breath and prepares to file

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Having this week unveiled positive data from the last phase III trial of Afresa, a rapid-acting inhaled insulin product, showing bioequivalence of its commercial inhaler device to the one used in clinical trials, Alfred Mann, the founder and chief executive of MannKind, is gearing up to file an NDA for Afresa in the next two to three weeks.

Speaking to EP Vantage at the JP Morgan Healthcare conference, Mr Mann said the prospect of the drug actually getting approval has reignited much needed partnering discussions, with interest from both big and medium-sized pharma, as well as biotech companies. Given the potential for regulatory delays and a requirement to run extensive post-marketing studies, plus the need for a significant marketing effort to overcome likely patient and doctor scepticism, any partner will need deep pockets.

Partnership potential

“We were in discussions when Pfizer put out its big announcement and we decided it was the wrong environment so we stopped,” Mr Mann said. “We thought that maybe after approval they might start again, but what has happened is that there is growing interest in the product and they want to move quite quickly.”

However, any deal struck now would probably come with multiple strings attached, with the bulk of the deal value only being released with FDA approval and achieving pre-determined sales milestones. As such, despite current interest, it seems more likely that interested parties will wait until approval, when the full conditions of authorisation and therefore Afresa’s commercial potential, will become clearer.

Labour of love

Developing Afresa is a project that has consumed over nine years of Mr Mann’s life and to date almost $1bn of his own money. As such, it is not surprising that with this amount of personal investment in the product he is bullish about approval and commercial success.

This optimism flies in the face of the fact that the first approved inhaled insulin, Exubera, was withdrawn in late 2007 due to a lack of sales (*Nektar left gasping over Pfizer's Exubera decision, October 18, 2007*).

Safety first

Expressing his confidence in FDA endorsement of Afresa, Mr Mann emphatically states: “No question in my mind, we’ve done over 40 trials in 5,000 people without a single safety signal at any point, except one reported case of cancer in a smoker, and given the sample size you would statistically expect more than one cancer case.”

While Mr Mann is certain that Afresa itself does not cause cancer, one thing he is less sure about is if any form of inhaled insulin exacerbates the condition: “You cannot say that it does not accelerate lung cancer, it is possible.”

It is this uncertainty about the longer term effects of inhaled insulin that might make the path to approval harder than Mr Mann expects. While the group has two years of good safety data, the FDA has the right to demand post marketing studies that could go on for years, a move that might deter some potential partners.

Commercial opportunity

Approval is not the only hurdle the product faces. Potentially more significant is uptake. The well publicised, if not conclusively proven, link between Exubera and cancer (*Exubera scare winds MannKind, April 9, 2008*) could deter potential users of Afresa, despite its safety record and efficacy above conventional insulin injections.

It was these doubts about the commercial opportunity in inhaled insulin that led Novo Nordisk last January to

abandon AERx, despite the product reaching phase III without any safety signals. In March of last year, Eli Lilly also stopped developing its AIR Inhaled Insulin with Alkermes, leaving MannKind the last man standing (*MannKind - last gasp for inhaled insulin, March 10, 2008*).

Focus on the benefits

The failures of other treatments, however, has not left Mr Mann in any doubt that the benefits he sees in Afresa will make it successful.“Exubera was a very inconvenient way to deliver insulin, with no clinical advantage at a high cost with some function risk; we have none of that,” he says.

Afresa has indeed so far avoided the lung function worries that were associated with Exubera. A phase III study at the end of December showed that patients who had been using the product for two years did not have statistically different lung function to those in the placebo group.

Mr Mann also believes that the formulation has overcome the problems with hypoglycaemia, a condition when blood sugar levels fall to low after taking insulin. With Afresa the risk of hypoglycaemia only occurs if patients have eaten less than 100 calories, a highly unusually scenario given that it is administered at meal times.

Additionally, the studies have revealed less weight gain in patients taking Afresa than those receiving injectable insulin, a fact that the group has been keen to talk up.

True faith

Partnering aside, one thing that is certain is that the closer Afresa has come to approval the more MannKind’s shares have recovered. In the last six months shares have risen by just over 40% to $3.75, showing that some in the market have faith in the product’s potential to be approved. Nevertheless, MannKind’s shares are still a long way from the $20.88 they traded at in 2006 when there were others still in the field and hopes were high that inhaled insulin would revolutionise the lifestyle of diabetic patients.

MannKind’s faith was further demonstrated this month when the group paid $2.5m for rights to SemBioSys Genetics' plant-produced recombinant human insulin for use in Afresa.

At the moment the insulin for Afresa is supplied by a subsidiary of Schering-Plough. However, following Schering-Plough’s acquisition of Organon, there have been concerns at MannKind about Schering-Plough’s long term commitment to producing insulin, hence the deal with SemBioSys for an alternative source of insulin, potentially at a lower cost.

Eggs in one basket

MannKind really does not have any alternative other than to believe in Afresa. The treatment is the group’s only advanced product and accounts for all of its potential value, which is a mighty looking $2.33bn, according to EvaluatePharma's NPV Analyzer. The sum dwarfs MannKind’s market cap of $374m. Sales of the drug are expected to hit $679m by 2014, according to consensus forecasts, but individual forecasts differ wildly between analysts who believe in the product and those who are more sceptical.

One person, however, who has never wavered about the product is Mr Mann. “I would not have put $919m into the company if I did not believe in it,” he says simply. With filing now only days way, time will tell whether Mr Mann’s investment and unwavering faith will be repaid.