Evaluate Vantage

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Ultragenyx bounces back, but painful questions remain

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Not putting all your eggs in one basket has clear benefits, as Ultragenyx showed yesterday. The group bounced back from the disappointment of a recent phase II failure with triheptanoin, reporting positive pivotal data for a separate asset, burosumab, in adults with X-linked hypophosphataemia.

However, somewhat lost in the market's initial euphoria was a surprising miss on an important secondary endpoint measuring pain in the burosumab trial. The group had stressed the project's significant effect on pain reduction in a previous study, and what to make of the miss will now be down to the US FDA.

In a call with investors Ultragenyx executives said they would file for US approval later this year. The project's submission has already been accepted by the European Medicines Agency.

Impressive primary

A miss on pain – one of three key secondary efficacy measures – should not immediately detract from burosumab's impressive effect on a clinical primary endpoint, proportion of patients achieving serum phosphorus levels above the lower limit of normal versus placebo.

The phase III trial, in 134 adults, showed 94% of patients taking burosumab achieving this endpoint, significantly greater than the 8% of those on placebo ($p<0.0001$). The rare disease is a form of rickets characterised by low blood levels of phosphorus unresponsive to vitamin D, hence the FDA's insistence on proving burosumab's effect on this hard clinical endpoint.

However, pain, as measured by the Brief Pain Inventory at 24 weeks, was improved only numerically, without hitting statistical significance. Of two other key secondaries, stiffness improvement was hit with significance, while physical function was not, all after accounting for the statistical penalty for multiple looks at the data.

True, pain endpoints are notoriously hard to hit, and it might be that 24 weeks is too short a time for this benefit to play out. Alternatively, by the time these patients reach adulthood the resulting bone deformity, and concomitant pain, might already be irreversible.

Yet in a previous trial burosumab did show an improvement in the Brief Pain Inventory over baseline at 24 and 48 weeks ($p=0.037$), and Ultragenyx had emphasised this in light of reduction in bone pain being a key aim of X-linked hypophosphataemia treatment. Indeed, the pivotal trial had begun with pain improvement as the primary endpoint.

Ultragenyx was initially up 20% in yesterday's post-market, though by the time it opened this morning the stock had faded to a 5% increase. The shares remain below the $88 level they touched ahead of the triheptanoin disappointment in March (*Ultragenyx looks ahead after triheptanoin failure, March 23, 2017*).

Most valuable asset

While the company has two additional late-stage rare disease assets it is burosumab that is now its most valuable project, with an NPV of $1.1bn, as calculated from *EvaluatePharma's* consensus of sellside forecasts.

Burosumab is expected to sell $905m in 2022, with $574m accruing to its originator, Kyowa Hakko Kirin, and the rest to Ultragenyx under the groups' 2013 co-development/co-promotion deal.

Ultragenyx was unwilling to speculate how many endpoints it thought needed to be hit to ensure approval, but stressed that, based on overall numerical improvement across all key measures, the trial "demonstrated clinical benefit".

There do not appear to be any other R&D assets in development specifically for X-linked hypophosphataemia, and for now investors have to hope that this and the pivotal data are enough to convince the FDA.

Project	Detail	Trial ID
Burosumab (KRN23)	134 aduts with X-linked hypophosphataemia	NCT02526160

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