Uniqure’s accelerated approval hopes take a hit

Despite showing arguable signals of efficacy Uniqure’s Huntington’s disease gene therapy has some fundamental problems.

Uniqure’s Huntington’s disease gene therapy AMT-130 might be one of biotech’s most valuable unpartnered assets, but its track record of disappointments suggests why big groups remain uninterested. Today brought further pain, as confusing biomarker data that could imperil AMT-130’s accelerated approval chances wiped 45% off Uniqure’s share price.

The findings came from an update of a phase 1/2 US study that also called into doubt AMT-130’s mechanism, with contradictory findings about patients’ levels of mutant huntingtin protein (mHTT). Uniqure presented numerous analyses of patients’ functioning, but these look positive only against historical controls and not the trial’s own sham surgery cohort.

This all came from the latest update of a study whose first results were marked by a confusing safety picture and lack of clarity about efficacy. Uniqure’s stock later fell when the trial was paused after high AMT-130 doses caused severe adverse reaction in three patients.

Red flags

Still, when efficacy data have been released they have shown promise – until now.

Today’s update comprises 26 Huntington’s disease patients, with up to two years’ follow-up. Six are in a low-dose AMT-130 group, 10 in a high-dose, and 10 in a sham surgery cohort. Uniqure has previously disclosed data only from the low-dose cohort.

The first red flag today came from analyses of mHTT levels, which were reduced with the low dose – albeit not by much versus baseline – but which actually rose with the high dose. AMT-130 aims to knock down mHTT, so failure to show an effect on this basic measure might call into question the gene therapy’s mechanism.

On an analyst call Uniqure blamed the findings on the inherent limitations of the assay used to measure mHTT levels in the cerebrospinal fluid. Management called the assay “challenging and variable”, and said it was unclear whether what was seen was a real biological effect or an artefact of this assay.
The second concern is over levels of neurofilament light chain (NFL), which is a marker of neuronal injury and whose reduction was controversially used to back the accelerated approval of Biogen’s ALS drug Qalsody.

Uniqure said it has been encouraged to see NFL declining below baseline. However, it has only seen this with the low AMT-130 dose. Paradoxically, high-dose AMT-130 yielded NFL levels above baseline, though these data came from slightly shorter follow-up.

Uniqure blamed the high-dose result on the confounding effect of patients who had suffered the earlier disclosed severe adverse events. It is clear that AMT-130 dosing, which necessitates drilling into the skull and infusion into deep brain structures, is associated with NFL spikes and, given that Roche/Ionis’s failed Huntington’s project tominersen saw NFL increases in phase 1/2, it is at least positive that these seem to resolve.

Though investors disagree, Uniqure insisted that its study update was positive, and to support this view it cited numerous measures of Huntington’s patients’ function, including total motor score, total functional capacity, Stroop Word test, and SDMT and cUHDRS scores.
However, here too any effect of AMT-130 is not obvious. Most of these measures are seen improving from baseline, some to a surprising degree; but this trial is notable for including a sham surgery group, and unfortunately any improvement versus this control cohort is hard to discern, leaving Uniqure dependent on a favourable comparison versus historical controls.

While discussions on a regulatory path forward have yet to take place, it is clear that an accelerated approval plan has been thrown into disarray. The big risk now is that Uniqure pushes into phase 3 in hundreds of patients when in reality it might need to go back to the drawing board.