Evaluate Vantage

December 18, 2019

As Nash shifts again, the focus remains on Genfit's big readout

Jacob Plieth

Genfit investors, who early next year will see the Resolve-It study yield data, digest further developments in the Nash space.

The once red-hot therapy area of Nash is mired in clinical setbacks, and this week it added two more disappointments: today Boehringer Ingelheim canned one of its many deals in this space, two days after Gilead revealed that its multi-project Atlas study had failed.

True, the Gilead setback was not a great surprise, and there was a separate positive development as Poxel today claimed an early clinical Nash win. But the riskiest bet of all remains Genfit, whose future hangs in the balance as its crucial pivotal study of elafibranor is due to yield results early next year.

Though some of Genfit's most bullish retail followers remain convinced of success in the Resolve-It trial, the industry's numerous Nash failures have contributed to the French group's stock declining 30% year to date (*Cymabay is out, but for Genfit the band plays on, November 26, 2019*).

Fear of interactions

The latest of these is Boehringer's AOC3 inhibitor BI 1467335, which the German group today discontinued in Nash owing to the risk of drug-drug interactions.

This decision was taken in spite of an ostensibly positive phase IIa trial, and was based on "assessment of another recently completed phase I study", Boehringer said. The group had licensed BI 1467335 from Pharmaxis for $30m up front in 2015, as part of a push into Nash that also saw it sign alliances with Yuhan, Dicerna and Mina.

It is unlikely that Boehringer's enthusiasm for the space burns as brightly as it did a few years ago. The same can be said about Gilead, another company that had tried to buy its way into Nash, but which at its latest quarterly update barely mentioned this therapy area at all.

It seems that Gilead's new chief executive, Daniel O'Day, does not share the commitment to Nash of his predecessor, especially given this year's failure of Gilead's Ask1 inhibitor selonsertib.

If this was a sign that the Atlas study was likely to fail then such fears were confirmed on Monday; Gilead said none of the three combinations tested in Atlas hit the primary endpoint, proportion of patients achieving ≥1-stage improvement in fibrosis without worsening of Nash.

The trial was exploring combinations of selonsertib, the ACC inhibitor firsocostat and cilofexor, an FXR agonist. Echoing earlier findings the most promising readings emerged from the arm testing firsocostat plus cilofexor; patients in this cohort demonstrated significant improvements in various fibrosis measures and liver function.

Whether Gilead considers these signals strong enough to justify further work is unclear, and safety is something to consider. The regimen caused as 28.2% rate of mild to moderate pruritus while 3.9% of patients experienced a big jump in triglyceride levels.

This is a known issue with ACC inhibitors – Pfizer's candidate in this class, PF-05221304, caused 10% of patients to experience hypertriglyceridemia, it was revealed at AASLD, taking the shine off a dramatic impact on liver fat.

Developers are adding fenofibrates to these combinations to ameliorate this off-target effect, and this is probably where Gilead's focus now turns. Last month the company added a Vascepa plus firsocostat plus cilofexor arm to a separate phase II study, another cohort of which includes fenofibrate with the same combination; results are due later in 2020.

Early win?

Against such a backdrop any positive developments are welcome, and one was provided today when the French group Poxel said PXL065 showed an acceptable pharmacokinetic profile in phase I. This led it to decide that a 36-week phase II study in biopsy-proven Nash should start next year.

However, PXL065 is merely a deuterium-stabilised stereoisomer of Takeda's ill-fated diabetes treatment, Actos. The toxicity of such PPAR agonist glitazone drugs has led to contraindications, and for now all Poxel can do is point to a dog study backing PXL065's improved safety over Actos.

The detail will be of interest to Genfit, whose elafibranor is also a PPAR – though targeting the alpha and delta subunits eliminates the risk of serious toxicity, the group's fans argue. Either way, the debate should be settled with the imminent readout of Resolve-It.

Just last week yet another contender, Intercept, revealed that its Nash project Ocaliva would likely face a US advisory panel on April 22, delaying a regulatory decision beyond the March 26 PDUFA date that priority review had brought it.

Ocaliva is widely expected to receive a grilling, so even if the chances of a Nash drug seeing the light of day are diminishing the space can hardly be called dull.