Evaluate Vantage

February 19, 2019

Inventiva’s fibrosis flop hits Nash hopes

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A stumble for Inventiva’s lanifibranor in a rare fibrotic disease could bode ill for its prospects in Nash, and for those of other PPAR agonists.

The failure of Inventiva’s lanifibranor in a phase II systemic sclerosis study should not necessarily be taken as a predictor of its performance in a crucial ongoing Nash trial, but it will not have built confidence.

The phase IIb Native trial of lanifibranor, a pan-PPAR agonist, in Nash is not set to report until 2020. But nearer-term tests of this mechanism are approaching, with big readouts due from Genfit and Cymabay Therapeutics this year.

Shares of Inventiva, which climbed 34% last week in anticipation of the systemic sclerosis readout, fell 46% today after yesterday’s post-market announcement.

Hopes for the most advanced PPAR in Nash, Genfit’s elafibranor, are already low after the failure of thephase II Golden trial (*Behind the management smokescreen, Genfit study is still a fail, March 27, 2015*). Meanwhile, Cymabay claims to have the best-in-class PPAR agonist in seladelpar.

Selected PPAR agonists in development				
Project	**Company**	**Pharma class**	**Lead indication(s)**	**Note**
Phase III				
Elafibranor	Genfit	PPAR alpha & delta agonist	Nash	Topline data from Resolve-It trial due 2019
Seladelpar	Cymabay	PPAR delta agonist	Primary biliary cholangitis	Phase II Nash data due mid-2019
Phase II				
Lanifibranor	Inventiva	Pan-PPAR agonist	Diffuse cutaneous systemic sclerosis, Nash, Nafld	Failed in dcSSc, Nash data due 2020
Bezafibrate	Aralez/Intercept	Pan-PPAR agonist	Primary biliary cholangitis	Approved OUS for hyperlipidaemia; Intercept plans phII trial plus Ocaliva in PBC
Source: EvaluatePharma.				

The Fasst trial of lanifibranor in diffuse cutaneous systemic sclerosis failed to meet its primary or any secondary endpoints, prompting Inventiva to abandon work in the disease, a multi-organ fibrotic disorder.

Lanifibranor, dosed at either 800mg or 1,200mg a day, plus immunosuppressive therapy was compared versus immunosuppressive therapy plus placebo.

Not so Fasst

Inventiva had hoped that lanifibranor would spur a significant improvement in the modified Rodnan skin score, which assesses skin thickness across 17 defined points on the body. This is a measure of skin fibrosis, which according to the company is correlated with internal organ fibrosis.

Inventiva is clinging to the fact that there were no safety issues as a good sign for the ongoing Native trial in Nash. Older PPARs have been linked with cardiac side effects and rhabdomyolysis, muscle breakdown that can lead to kidney failure.

Of course, lanifibranor’s lack of adverse events might merely reflect the difficulty in finding a therapeutic window for this class of drugs.

The primary endpoint of the Native trial in Nash is a composite of fibrosis, steatosis and Nash activity, so the latest fibrosis flop in systemic sclerosis does not bode well for the upcoming readout. It might also be bad news for Inventiva's PPAR peers.