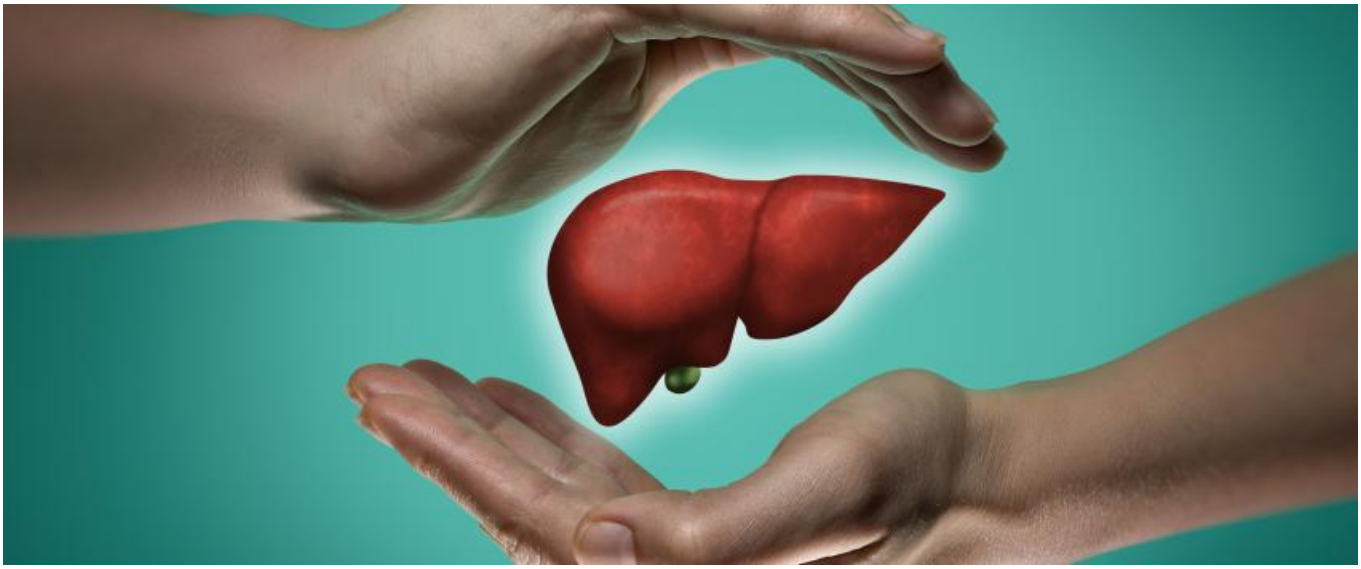
Evaluate Vantage

June 16, 2020

Inventiva gets a surprise hit in Nash

Madeleine Armstrong



Inventiva's mid-stage win has revived hopes for PPAR agonists in the liver disease, although safety questions remain.

Just last month it looked like Genfit had finally killed off hopes for PPAR agonists in Nash. But now Inventiva has breathed new life into the approach after scoring a result with lanifibranor in the phase II Native trial.

Tolerability has long been an issue with this drug class, and finding a therapeutic window for lanifibranor could yet prove difficult, with weight gain and peripheral oedema rearing their heads in Native. Differently acting projects are also making headway in Nash, notably Novo Nordisk's semaglutide, meaning lanifibranor could find it tricky to carve out a niche if it does make it to market.

Pan-PPAR positive

Inventiva's stock was up as much as 250% this morning, but from a low base. Lanifibranor's chances of success had looked slim after an earlier flop in the rare fibrotic disease systemic sclerosis, as well as the recent failures of other PPAR agonists including Genfit's elafibranor and Cymabay's seladelpar.

Lanifibranor is a pan-PPAR agonist, while elafibranor hits PPAR alpha and delta, and seladelpar targets the delta subtype. If this difference is the key to lanifibranor's efficacy it could provide a boost for Intercept, which licensed the pan-PPAR agonist bezafibrate from Aralez last year. The group might need a new project to pivot to should its twice-delayed Nash candidate obeticholic acid get knocked back by the FDA – a distinct possibility given mixed phase III data.

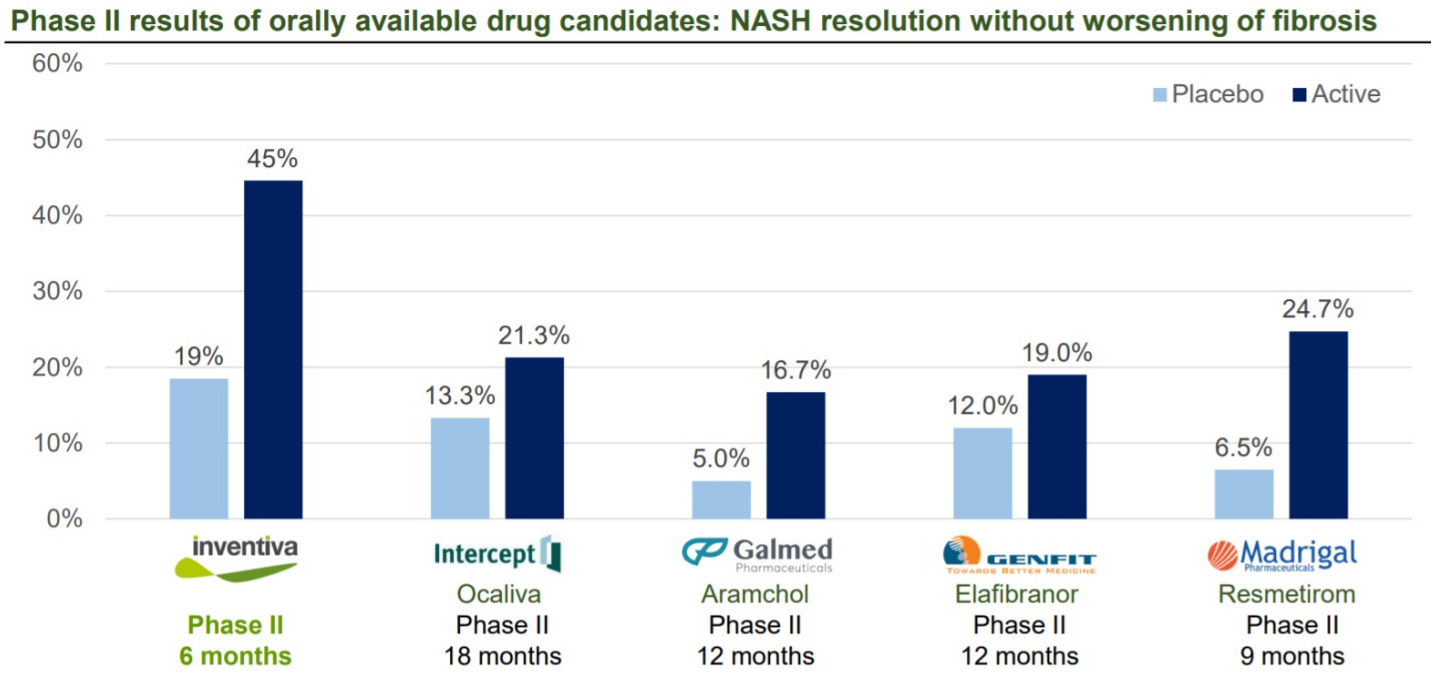
Still, bezafibrate is not in clinical trials for Nash and Inventiva says that lanifibranor is the only pan-PPAR agonist in development for the liver disorder, though some selective projects are still in play (*Upcoming events – Fibroid data for Obseva, as Inventiva turns to Nash, March 6, 2020*).

This might explain why Inventiva appears to be taking its time before pushing into phase III. Its chief executive, Frédéric Cren, refused to give any details on the pivotal trial design, despite being pressed repeatedly during a conference call today, saying that this would require a lot of thought and a deep dive into the Native dataset.

Go Native

Taking the higher 1,200mg dose of lanifibranor forward seems like a no-brainer. This was the only one to hit statistical significance on the primary endpoint of Native – a decrease of two points or more on the steatosis activity fibrosis (SAF) score with no worsening of fibrosis after six months of therapy. 49% of patients receiving 1,200mg of lanifibranor achieved this versus 27% in the placebo group.

The 800mg lanifibranor dose only just missed statistical significance, and Inventiva execs said on the call that it was possible this dose could show an effect with longer-term use.

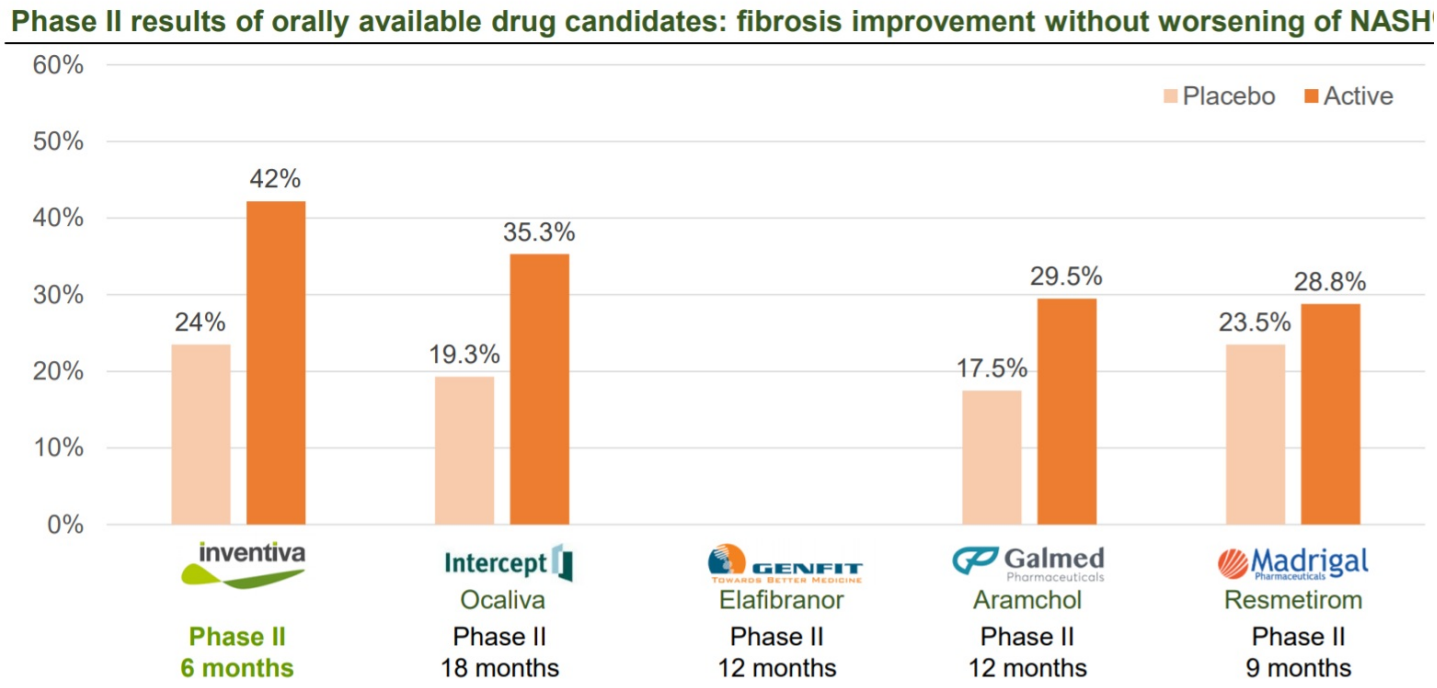


Source: Company presentation

The secondary endpoints of Native included resolution of Nash without worsening of fibrosis, where according to Inventiva both doses hit statistical significance; and improvement with fibrosis without worsening of Nash, where only the 1,200mg dose prevailed.

These secondary endpoints did not use SAF but rather the Nafld activity score, which has featured in other Nash trials and is accepted by regulators. Indeed, Inventiva was keen to point out how the 1,200mg dose of lanifibranor stacked up against its rivals on these measures.

Inventiva did not rule out using the SAF score in phase III, but said it would be guided by the regulators.



Source: Company presentation

Inventiva described lanifibranor's tolerability profile as favourable, but the signal on weight gain and oedema in Native might not reassure those who fear the side effects that have hit other insulin-sensitising agents like the diabetes drug Actos (pioglitazone).

Patients gained a mean of 2.4kg and 2.7kg in the 800mg and 1,200mg lanifibranor arms respectively, while 12 out of the 14 patients in the trial who reported peripheral oedema received lanifibranor. But Inventiva execs pointed out during the call that no patients dropped out of the study because of oedema.

They stressed that rates of oedema with lanifibranor were much lower than those historically seen with pioglitazone, and concluded that the former looked safer.

This will need to be borne out in phase III. But Inventiva, which had just €47m in the bank at the end of the first quarter, will need to find investors or a willing partner to fund this.