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Interview – Galmed's early move to open up liver market

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After the noise made by Intercept Pharmaceuticals few can be in any doubt about the purported promise – however unrealistic – of non-alcoholic steatohepatitis (NASH) as a multi-billion dollar indication.

A largely overlooked Israeli company, Galmed Pharmaceuticals, thinks that there is a large swathe of the market that Intercept and others are missing: early-stage NASH. However, the key to capturing these asymptomatic patients is a simple diagnostic test – an area where Galmed has made decent progress, the group's chief executive, Allen Baharaff, tells *EP Vantage.*

There is no doubt in Mr Baharaff's mind: "A diagnostic is the rate-limiting factor for the development of any NASH drug," he states, since the disease is currently diagnosed by liver biopsy – a risky and costly procedure.

The group's lead project, Aramchol, is a conjugate of cholic acid and arachidic acid that has completed a phase IIa NASH study, and will begin phase IIb later this year. Aramchol's key is that it is being aimed at early-stage patients (some 80% of the market), who are beyond non-alcoholic fatty liver disease – "not a disease", says Mr Baharaff – but have yet to develop liver fibrosis.

This contrasts sharply with the leaders in this space, Gilead Sciences and Intercept, which with simtuzumab and obeticholic acid (OCA) respectively are going after fibrotic NASH.

The pricing equation is important; super-bullish sellside forecasts for Intercept have been sustained by orphan pricing of some $65,000 per patient per year for the primary biliary cirrhosis indication. "We're going to price Aramchol at $7,000-10,000 a year – higher would never fly with the number of patients we're targeting," says Mr Baharaff.

Safety signal

The early stopping of OCA's Flint study for efficacy in January caused Intercept's stock to rocket, but recent disclosure has revealed that there was also a safety signal – elevations in LDL cholesterol.

Mr Baharaff says this had already been seen in earlier trials, and believes it had forced Intercept to go after late-stage NASH, which "suited their pricing strategy and the safety issues". He is quick to point out that Aramchol has been shown to be "very, very safe; we've not seen an effect on LDL".

The point is illustrated by the phase IIb plan involving 400mg and 600mg Aramchol doses, versus the 100mg and 300mg tested in phase IIa. This also makes sense on efficacy grounds, since phase IIa had shown statistically significant liver fat content reduction favouring 300mg Aramchol ($p=0.0097$), but the effect with 100mg was less pronounced.

It is interesting that Aramchol's cholic acid component shares similarities with Intercept's OCA, and to an extent with ursodeoxycholic acid, an approved drug for primary biliary cirrhosis. But Mr Baharaff insists that the pharmacological mechanisms are quite distinct.

While OCA is a ligand for the farnesoid X receptor, involved in bile acid synthesis, Aramchol inhibits the liver enzyme SCD1, increasing cholesterol elimination from cells via HDL through upregulation of a cholesterol transporter. Galmed's secret is that Aramchol is only 60-70% effective, enabling it to circumvent the toxicities of agents that block the entire SCD1 pathway.

Curiously, SCD1 inhibition is not really seen with cholic acid or even a combination of the standalone Aramchol components, says Mr Baharaff. OCA also upregulates a cholesterol transporter, but – crucially – using LDL to transport the cholesterol rather than HDL.

Diagnosis

Meanwhile, targeting early disease makes sense from a treatment angle, since NASH "symptoms and progression don't always develop side by side", says Mr Baharaff. "Early, asymptomatic patients are the ones

physicians want.”

Thus cheap and safe NASH diagnosis is vital, and Galmed is working with three companies here: with Zora Biosciences on lipidomic profiling, which will comprise an exploratory phase IIb endpoint; with Owl, a Spanish firm, looking at metabolomic analyses; and with Enterome on a stool-based NASH test.

In addition to Gilead and Intercept Mr Baharaff sees Galectin Therapeutics as another competitor that is looking at late-stage disease. The best comparator to Galmed is Genfit, which has a phase II oral agent, GFT505.

However, GFT505 is a glitazone – a safety issue-scarred drug class. Though toxicity with GFT505 has so far been ruled out, “I’ve spoken to many hepatologists who won’t treat their patients with glitazones”, says Mr Baharaff.

Still, one of the chief exec’s biggest problems is Galmed’s share price – off 50% since the group’s $40m float on Nasdaq in March. He admits that Aramchol has a relatively short patent life, and would likely come to market relying only on five years’ data exclusivity – an issue for jittery investors.

To mitigate this Galmed is developing Aramchol salts, a separate, patented chemical entity; it might actually be the salts, not the acid conjugate, that enters phase III, he says. Partnering is a separate matter, and given Galmed’s cash runway until the end of 2017 the company thinks it can wait until after the end of phase IIb to strike a global deal.

A final twist is that the company actually never intended to float on a wave of NASH exuberance. Mr Baharaff says he had filed confidential IPO documents last December, and by mere chance booked to visit the US for one day’s meetings on January 9 to test the water with prospective investors.

On that same day the Flint study was halted early. “We ended up staying for three weeks.”

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