

Vir bids to enter the hepatitis B race



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The first data with the RNAi project VIR-2218 mark Vir's attempt to join a race that Arbutus appeared to crash out of last month.

With Vir Biotechnology [setting itself up as the go-to Covid-19 player](#), its work in hepatitis B might not be getting much attention. But yesterday the company launched a bid to join Arrowhead and Dicerna in the race to develop a functional cure for this viral disease.

As would be expected, given Vir's coronavirus work, yesterday's announcement of the first results of a trial of VIR-2218 elicited no market reaction. But they will be of interest to Arrowhead, as well as to followers of another RNAi player in hepatitis B, Arbutus, which last month crashed on data that were read as disappointing.

The absolute results aside, of significant importance is what the market is pricing in. Arbutus is today capitalised at only \$80m, whereas Vir's valuation stands at over \$3bn, and that is just six months after the group completed its Nasdaq IPO.

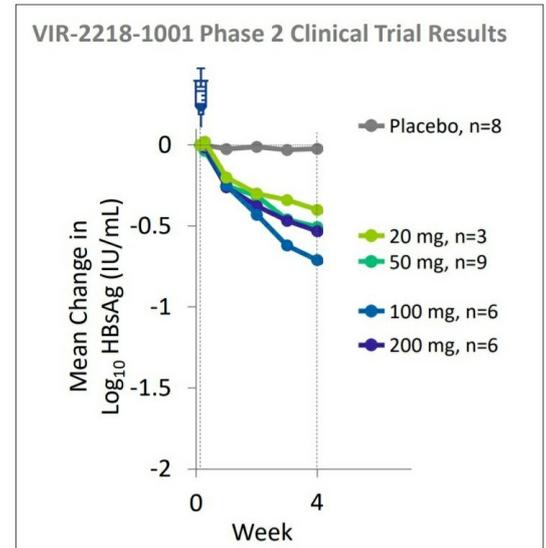
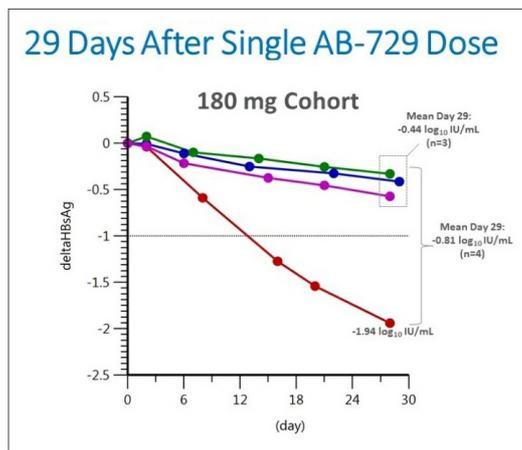
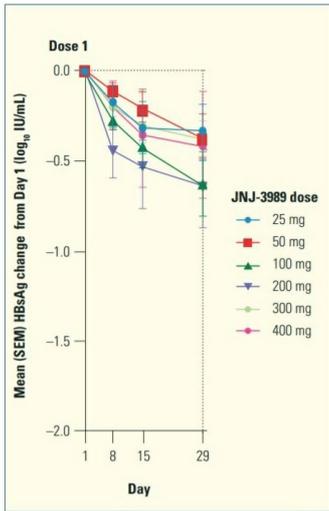
Vir is developing two approaches against hep B, but its antibody, VIR-3434, has yet to enter the clinic. Yesterday's data related to VIR-2218, an siRNA partnered with Alnylam that targets a conserved region in the HBV X gene; VIR-2218 is similar to ALN-HBV, a now-discontinued project, but contains an added Galnac moiety.

Surface antigen

Like Arbutus's disappointing trial of AB-729, a rival Galnac-delivered RNAi, the Vir study's key efficacy measurement related to reduction in levels of HBsAg, the surface antigen that is one of four major hep B transcripts the virus is believed to use to replicate and rebound.

Double VIR-2218 doses of 20-200mg were given, and after 16 weeks mean HBsAg levels were dose-dependently reduced by 0.8-1.5 \log_{10} , versus broadly unchanged for the placebo cohort. A key metric for cross-trial comparison was the point four weeks after the first injection, where HBsAg levels fell by 0.4-0.7 \log_{10} .

This second metric is relevant when considering [Arbutus's data from March](#), where AB-729 was given as a single 60mg or 180mg injection. At a similar time point (29 days) mean HBsAg reductions were 0.2 and 0.9 \log_{10} respectively. As an aside, this looks broadly similar to 29-day data generated by Arrowhead/Johnson & Johnson's JNJ-3989.



Cross-trial comparison of 4-week HBsAg reductions for Arrowhead's JNJ-3989 (left), Arbutus's AB-729 (middle) and Vir's VIR-2218 (right), adapted from company presentations.

On the face of it Arbutus's result looks broadly similar to Vir's, so why did the former's share price lose 46%? Firstly, [analysts had hoped for at least a 0.5 \$\log_{10}\$ reduction](#), and the 180mg result was driven by one outlier; if this subject is excluded the mean reduction comes up short, at 0.4 \log_{10} .

Secondly, the AB-729 study raised some safety concerns, with all four 180mg dose subjects seeing liver enzyme increases, though two were only grade 1 and the rest were unrelated. However, if the outlier subject is considered a fluke, the worry is that AB-729 might have to be dosed higher – a non-starter if adverse events also go up.

In the case of VIR-2218, Vir said it saw “no clinically significant” liver enzyme elevations, and highlighted its technology's “decreased propensity” to cause such elevations.

The relevance of HBsAg as a biomarker must also be considered; hep B is a relatively intractable virus, and the thinking is that to achieve a functional cure viral DNA and HBsAg must both be suppressed to prevent rebound infections. The virus also persists in a reservoir of cccDNA, but this alone is not thought capable of reviving infection.

Still, such minutiae are unlikely to be troubling Vir investors, given that after last week's \$250m endorsement from Glaxosmithkline the group is chiefly a Covid-19 player, and it is this that is sustaining its multi-billion dollar valuation.

Meanwhile, Arbutus has already failed with two previous hepatitis B projects; this might not yet be strike three, but the company has no coronavirus plan B.