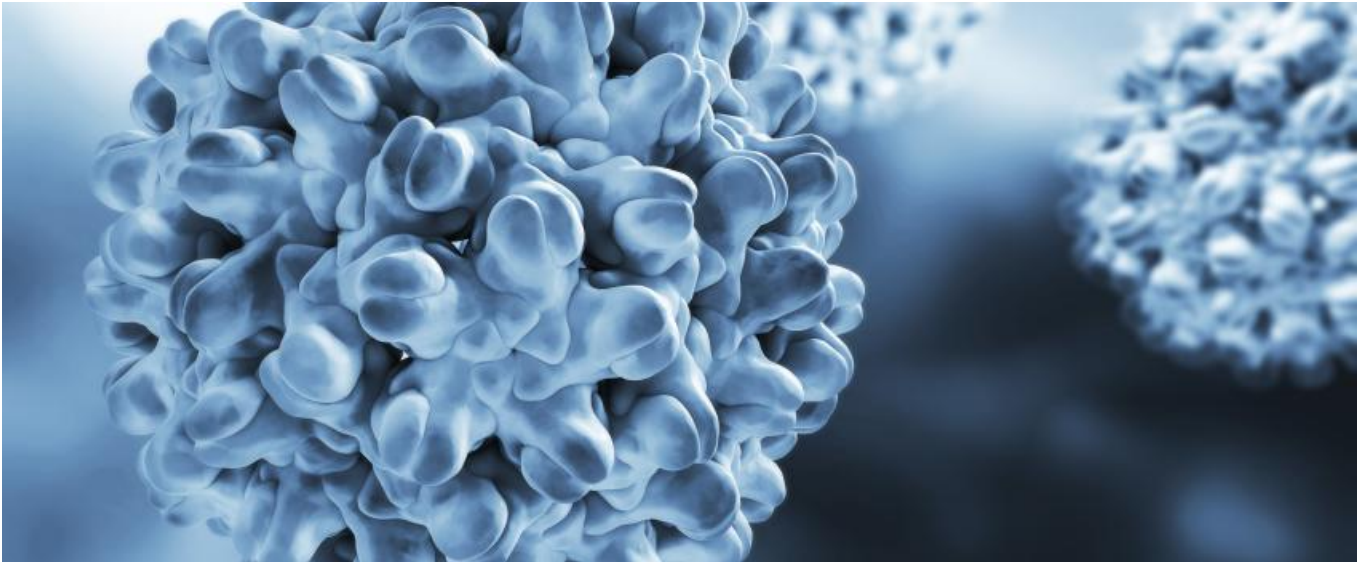


Looking for new mechanisms to cure hepatitis B



[Madeleine Armstrong](#)



A genome editing tie-up between Gilead and Precision Biosciences, and promising early data with Arrowhead's RNA interference project, are two novel approaches in hep B.

Yesterday's preclinical-stage deal between Gilead and Precision Biosciences shows the renewed interest in finding a functional cure for hepatitis B. But the project, which aims to eliminate hep B via Precision's Arcus genome-editing technology, is far from the closest to market.

Arrowhead's RNA interference candidate ARO-HBV, for which last week the company reported promising phase I/II data, is much closer to approval. But Arrowhead is not the only group with a mid-stage project, with big players including Glaxosmithkline and Johnson & Johnson, as well as Gilead, also in the race.

The current mainstay of hepatitis B treatment is antiviral therapy with pegylated interferons or oral nucleoside/nucleotide analogues, which are also used in HIV. These drugs can suppress viral replication but patients must be treated chronically, and adherence can be low - hence the need for a functional cure.

Selected mid-stage novel hep B projects

Project	Company	Mechanism of action	Ongoing trial(s)	Primary completion
ARO-HBV	Arrowhead Pharmaceuticals	Hep B polymerase RNAi therapeutic	NCT03365947	Reported
ARB-1467	Arbutus Biopharma	Hep B polymerase RNAi therapeutic	NCT02631096	Reported
Inarigivir	Spring Bank/ Gilead	RIG1 agonist	NCT03434353, Achieve (NCT02751996)	End 2018
REP 2139	Replicor	Hep B surface antigen inhibitor	NCT02565719	Sep 2018
REP 2165	Replicor	Hep B surface antigen inhibitor	NCT02565719	Sep 2018
IONIS-HBV-LRx	Ionis Pharmaceuticals/ Glaxosmithkline	HBV ligand conjugated antisense	NCT03020745	Nov 2018
IONIS-HBVRx	Ionis Pharmaceuticals/ Glaxosmithkline	HBV antisense	NCT03020745, NCT02981602	Nov 2018, Dec 2018
ABI-H0731	Assembly Biosciences	Capsid assembly modulator	NCT03576066, NCT03577171	Mar 2019, Apr 2019
GS-9688	Gilead Sciences	TLR 8 agonist	NCT03491553, NCT03615066	Apr 2019, Oct 2019
JNJ-6379	Johnson & Johnson	Capsid assembly modulator	NCT03361956	Oct 2019
Myrcludex B	Myr Pharma/ Hepatera	Viral entry inhibitor	NCT02888106	Dec 2019

Source: EvaluatePharma.

All eyes are now on Arrowhead after the company's presentation last week at the World Gastroenterologists Summit in Auckland, New Zealand. But it is worth noting that the results, which sent the group's stock up 38%, came in only eight patients treated with the first two doses of ARO-HBV: 100mg and 200mg.

The trial found a reduction in serum hepatitis B surface antigen (HBsAg) of 2.0 log in the 100mg cohort and 1.4 log in the 200mg cohort. HBsAg is a viral protein used to assess a patient's response to therapy, and its permanent suppression is regarded as an important step towards achieving a functional cure.

Arrowhead said activity was seen in all patients, including those who were negative for hepatitis B e-antigen (HBeAg) - notable because the company's older RNAi project, ARC-520, did not show an effect in this group.

The results look promising, but investors will be waiting to see if a dose response emerges with data from the higher-dose cohorts; there are a total of 10 cohorts in the trial. Arrowhead hopes to present more comprehensive results from the study at the AASLD Liver Meeting in San Francisco in November, and has also said that a combination approach would likely be needed to produce a functional cure for hep B.

The ARO-HBV data set up a battle with Arbutus Biopharma, Arrowhead's closest competitor in hep B RNAi.

Early data with Arbutus's ARB-1467, evaluating monthly dosing, were disappointing ([Arbutus slides on poor results in hep B, 30 September 2016](#)). But biweekly [dosing led to an average serum HBsAg reduction of 1.4 log](#), in line with the ARO-HBV results.

Arbutus is now carrying out a phase II trial of longer-term biweekly therapy with ARB-1467 plus Gilead's antiviral Viread and pegylated interferon, and interim data are expected in the fourth quarter.

Triple combos?

The most valuable novel hepatitis B project, with forecast 2024 sales of \$995m according to *EvaluatePharma* sellside consensus, is Spring Bank Pharmaceuticals' oral Rig-1 agonist inarigivir, which targets a modulator of antiviral immune defence. Gilead is involved in its development, and is testing the project in combination with its marketed antiviral Vemlidy.

Interestingly, Arrowhead highlighted inarigivir during its World Gastroenterologists Summit presentation last week, leading to speculation that ARO-HBV could be added to this combo. Indeed, Spring Bank has said that it expects inarigivir to be included in a triple combination with an RNA interference project "or a different mechanism", with clinical trials set to begin in the first half of 2019.

Last month, Spring Bank reported data [from the third dosing cohort](#) of the ongoing Achieve trial, which appeared to support a dose response with inarigivir monotherapy. Topline results from the final, highest-dose cohort are expected by the end of the year.

At the same time, the company announced that the Gilead-funded study of inarigivir plus Vemlidy would enrol two new higher-dose cohorts; this will allow Spring Bank to skip the planned phase IIb portion of the Achieve trial and go straight into phase IIb/III in early 2019.

Meanwhile, Gilead has its own project, the TLR 8 agonist GS-9688, in two phase II trials - one in treated and one in treatment-naive patients - that are due to complete next year.

TLR agonists are thought to activate patients' innate immune response against the hepatitis B virus. Roche has been investigating a similar mechanism with the TLR 7 agonist RO6864018, but its status is currently unclear after [a phase II trial](#) was completed last year.

And, in another sign that all might not be rosy with the TLR approach, Gilead appears to have shifted its attention to HIV with its TLR 7 agonist GS-9620, which was once in development for hepatitis B.

CAM on

Still, there are plenty more approaches being tested. At the World Gastroenterologists Summit, Arrowhead also made a nod to JNJ-6379, a capsid assembly modulator (CAM), triggering rumours that partnership with J&J could also be in the offing.

Data from the phase I [HPB1001 trial](#) of JNJ-6379 were presented at the same conference, showing a reduction in HBV DNA versus placebo - but no changes in HBsAg. A phase II study of JNJ-6379 is due to complete next year.

CAMs are designed to disrupt the "shell" around the virus, thereby blocking replication. Other groups looking at this mechanism include Assembly Biosciences, whose first-generation project, ABI-H0731, should yield phase II data next year.

Arbutus also has the next-gen capsid inhibitors AB-423 and AB-506 in phase I development, according to its website.

Meanwhile, other mechanisms being tested include an antisense approach, by Ionis and Glaxosmithkline, and targeting HBsAg, where Replacor is active.

Myr Pharma's Myrcludex B takes yet another approach, aiming to inhibit entry of the hepatitis B virus into a patient's cells, and the company claims that this is the only hepatitis B project in development to work in this way.

Gilead's latest deal might show a lack of confidence in its more advanced approaches - or perhaps the group is just hedging its bets. Then again, if Arrowhead is right and combos are the way forward, maybe Gilead wants all the components in house.

Curing hepatitis C might not have made good business sense, but Gilead seems determined to repeat the same trick in hep B.

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