

Arbutus slides on poor results in hep B



[Elizabeth Cairns](#)

Early data from the phase IIa trial of Arbutus's hepatitis B RNA interference therapy ARB-1467 are in and are disappointing. The results concern the first two of three cohorts in the study, and show what some analysts refer to as "mediocre" activity against the virus.

Adding to the disappointment was the lack of a dose-response, with the lower of the two doses tested causing a greater decrease in a serum biomarker of hep B than the higher dose. Arbutus's stock is down 8% in early trading today.

The multi-dose study is enrolling 24 chronic hep B patients, split evenly between the three cohorts. In each cohort six patients receive three monthly doses of ARB-1467, and two placebo. The first two cohorts enrolled hepatitis B e-antigen (HBeAg)-negative patients, and the third group is currently recruiting HBeAg-positive patients.

Lacklustre

The Canadian group reported levels of HBsAg, a viral protein, in the patients' serum following single doses for both cohort 1 (0.2 mg/kg) and cohort 2 (0.4 mg/kg) and following multiple monthly doses for cohort 1.

The data showed modest reduction in HBsAg. After a single dose of 0.2mg/kg, patients had mean and mean maximum HBsAg reductions of 0.3 log and 0.4 log, respectively. After a single dose of 0.4mg/kg, patients had mean and mean maximum HBsAg reductions of 0.2 log and 0.3 log, respectively.

Analysts from Chardan wrote that the data demonstrate "at best mediocre efficacy" in HBeAg-negative hep B. They pointed out that a single dose of Arrowhead Pharmaceuticals' competing RNAi therapy ARC-520 generated an approximately 0.3 log suppression of HBsAg and this result was viewed as a clinical failure. It appears from the share price reaction that Arbutus's investors take a similar view.

HBsAg is believed to suppress the patient's immune response to the infection. Correlation between the extent of HBsAg reduction and clinical benefit is not well understood, but permanent HBsAg suppression is generally thought of as an important step to achieve a potential functional cure, Leerink analysts write.

Interim data from Arbutus's phase IIa trial of ARB-1467 (NCT02631096)

Cohort	Number of patients	ARB-1467 dose (mg/kg)	Single dose HBsAg reduction (log ₁₀ IU/mL)			Multiple dose HBsAg reduction (log ₁₀ IU/mL)		
			Mean*	Mean maximum**	Maximum†	Mean*	Mean maximum**	Maximum†
1	6	0.2	-0.3	-0.4	-1.0	-0.6	-0.7	-1.3
2	6	0.4	-0.2	-0.3	-0.8	NA	NA	NA
Placebo	4††		0	0	-0.1	0	0	-0.1

* Nadir value of the arithmetic mean of all values observed at each time point

** Mean of each patient's maximum reduction in serum HBsAg

† The best single reduction among all patients in a cohort

†† Based on two patients from each cohort. Multiple dose placebo results are based on the two placebo subjects in Cohort 1

As worryingly, there was little sign of a dose response when the single-dose data were compared. On a conference call, William Symonds, Arbutus's chief development officer, said that with such small cohorts it can be hard to see a dose-response, especially with a single dose, adding that the full three months' data would

allow a better determination of dose-response.

Safety

The trial's primary endpoint concerns the frequency and severity of treatment-emergent severe adverse events, but no data on this point, or any safety data, were released. Arbutus said that ARB-1467 was generally well tolerated, but also that detailed safety data will only emerge upon study completion.

More multi-dose data are due at the end of this year and final data from all three trial groups in early 2017. Arbutus is emphasising '1467's potential in combination with other therapies, but it could take years for combinations to make it through clinical trials.

Arbutus has a follow-on product, ARB-1740, which it says has been "significantly more potent" than ARB-1467 in animal models. But, again, ARB-1740 is not yet in clinical trials. The company has yet to determine exactly what the development strategy will be for these two drugs, Mark Murray, Arbutus's CEO, said on the call.

Full data for ARB-1467 may make that job a bit easier.

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