Antisense oligonucleotides (ASOs) have been shown to substantially reduce HBsAg levels in chronic hepatitis B (CHB). 1, 5  
Covariant conjugation with N-acetylgalactosamine (GalNAc) has been shown to enhance the delivery of ASOs to hepatocytes. 6, 11
Compared to unconjugated ASOs, GalNAc-conjugated ASOs have demonstrated better tolerability in terms of ALT elevations at the cost of reduced antiviral activity. This could be due to differences in dose and frequency of administration of GalNAc-conjugated ASOs and/or the result of additional immune activation caused by unconjugated ASOs. 2, 3
ALG-020572 is a GalNAc-conjugated 18-mer phosphorothioated ASO. Covalent conjugation with N-acetylgalactosamine (GalNAc) has been shown to reduce HBsAg levels in chronic hepatitis B (CHB). 9, 12, 13

**RESULTS**

- Plasma concentrations of ALG-020572 were quantified using a validated liquid chromatographic hybridization method. Liver concentrations of ALG-020572 (conjugated) and ALG-020579 (unconjugated) were determined by a qualified LC/MS/MS method.
- Reported here are data from the single cohort enrolled in Part 2.

**BASELINE CHARACTERISTICS**

Baseline characteristics were comparable between subjects receiving ALG-020572 and placebo.

**PHARMACOKINETICS**

- Plasma PK parameters at Day 1 in the 4 subjects with significant ALT flares (blue) appeared to be higher than those without these flares (black), but there was no significant overall difference in exposure to ALG-020572 among CHB subjects compared with healthy volunteers in Part 1.
- The concentration of ALG-020572 was associated with some degree of HBsAg reduction in liver biopsies, while subjects treated with placebo had no change in HBsAg levels.
- No correlation between ALT elevation and HBsAg reduction was observed.

**IMMUNE CYTOKINE ANALYSIS**

- Immune cytokines were analyzed at predose and 24 hours post dosing on Day 1 in serum and plasma.
- Cytokine upregulation or indications of a significant inflammatory response were not observed.
- Typical makers of an immune response, like INF-alpha and INF-gamma, were not detected.

**FAC'TORS INFLUENCING ALG-020572 CONCENTRATIONS**

- Administration of as few as two 210 mg doses of ALG-020572 was associated with some antiviral activity and significant ALT flares, likely due to DILI.
- DILI was unexpected given that observed human plasma and liver PK levels were up to 6.4-fold below the NOAEL and hepatotoxicity was not observed in toxicology studies in monkeys even in Part 1 of this study.
- No correlation was observed between intensity of ALT flares and unconjugated ASO ALG-020579 liver exposure in vivo and/or magnitude of HBsAg reduction.
- Development of ALG-020572 has been terminated.

**CONCLUSIONS**

- The authors wish to thank the subjects for participating in this clinical study. We are also grateful to the staff of the clinical sites and Novotech for assisting in the conduct of this study. We also express our appreciations to Aligos compound development team members who supported this study but are not listed in authors of this manuscript.
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