Background

In repeat-dose toxicity studies, ALG-020572 was well tolerated. ALG-020579, a GalNAc-conjugated antisense oligonucleotide (ASO) that was being developed for the treatment of CHB by targeting the HBsAg coding region of the Hepatitis B Virus (HBV) genome. Once ALG-020572 enters hepatocytes via uptake through asialoglycoprotein receptors (ASGPRs), the GalNAc moiety is rapidly cleaved to release the active ASO moiety, ALG-020579.

Methods

- ALG-020572 was formulated in water for injection.
- CD-1 mice and cynomolgus monkeys were dosed subcutaneously (SC), twice weekly (BW) for two weeks and then weekly (QW) thereafter in 2-week (1 dose) and 4-week (7 doses) studies. Followed by chronic studies up to 20 weeks in mice or 24 weeks in monkeys (doses of 0.5, 1.5, 5, 10 mg/kg/dose). The toxicokinetic and toxicology assessments included clinical observations, clinical chemistry, histopathology, coagulation, cytokines and complement (monkey only) and anatomic pathology.

- A following a favorable toxicology and toxicokinetic profile, a two-part, double-blind, randomized, placebo-controlled Phase 1 study (NCT05010022) was initiated for ALG-020572 to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics.

- In Part 1, 32 healthy volunteers (96 active and 2 control cohorts) received single ascending subcutaneous (SC) doses of 50, 150, 300 and 480 mg ALG-020572, which were found to be well tolerated.

- Part 2 was designed to evaluate multiple ascending SC doses of ALG-020572 in virally suppressed HBsAg negative CHB subjects (ALG-020572 on placebo days 1, 4, 8, 11, 13, 22, and 29). A single cohort received 210 mg of ALG-020572 or placebo, SC, before the study was terminated.

- Assessments included treatment emergent adverse events (TEAEs), vital signs, physical examination, hematology, coagulation, cytokines, clinical chemistry, serum chemistry, clinical laboratory tests (ALT, AST, bilirubin, alkaline phosphatase, gamma-glutamyl transferase, electrolytes, glucose, uric acid, creatinine, BUN), and clinical diagnostic tests (urinalysis, urine pregnancy test, EKG).

ALG-020572 demonstrated a favorable nonclinical safety profile

- ALG-020572 and ALG-020579 were neither mutagenic in the in vitro Ames assay nor clastogenic in the in vitro or in vivo MNT assays.

- There were no cardiovascular, respiratory, or CNS findings in safety pharmacology or repeat-dose toxicity studies up to the highest doses tested of 50 mg/kg/dose.

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- In -week, 5-dose, range-finding studies in mice and monkeys, ALG-020572 was well tolerated with NOAELs at the highest dose tested of 50 mg/kg/dose BW/BiW.

- In -month, 7-dose, GLP studies in mice and monkeys, ALG-020572 was well tolerated with the NOAELs at the highest dose administered of 50 mg/kg/dose BW/BiW.

- In a pattern typical of rodent specific oligo-related inflammatory response, repeat-dose studies in mice demonstrated ALG-020572 attributed sporadic minimal to mild ALT/AST elevations with minimal non-adverse single cell necrosis noted and no exacerbation at 1-month compared to 2-week study.

- Minimal to moderate histopathological changes were noted at the injection site, lymph nodes, liver and kidney were consistent with oligo-related uptake in these tissues (monoclonal cell infiltration, basophilic granules within macrophages) with partial to complete recovery.

- There were no adverse changes in hematology, serum chemistry or coagulation parameters, hematology, cytokines, or complement activation (monkey only) in either species up to 50 mg/kg/dose.

- Chronic toxicity studies were discontinued at 20 weeks (22 doses) in mouse and 24 weeks (26 doses) in monkey due to clinical safety findings and termination of the program.

- No adverse toxicology findings were noted in either species.

- No significant worsening of ALT noted in the mouse chronic study (Day 93); No ALT changes were noted in monkeys.

Mice: Sporadic ALT elevations with minimal liver histopathology

Mice: Dosing of ALG-020572 resulted in sporadic ALT elevation and minimal single cell necrosis (circled red) in individual mice that was not dose responsive and did not correspond to liver concentrations of ALG-020579. Longer term dosing resulted in dose responsive ALT elevations but no single cell necrosis.

Monkeys: No changes in liver enzymes or adverse liver histopathology observed

- Rodents are generally more sensitive to pro-inflammatory and single-cell hepatocellular effects of oligonucleotides and effects in the liver of rodents generally have not translated to safety risks in humans, the relationship of ALG-020572-mediated effects observed in mice and the ALT flares seen in the MAD portion of the Phase 1 study is uncertain.

Conclusions

- The clinical outcome of multiple doses ALG-020572 at 210 mg in HBsAg negative CHB subjects was not predicted in nonclinical or SAD in healthy volunteer studies.

- Liver concentration of ALG-020579 at time of biopsy were high (2-8-fold above projected liver EC50) but remained 1.7-4.1-fold below the no observed adverse effect (NOAEL) liver concentrations observed in toxicology studies in monkeys. Given the time of biopsy was ~1 liver t1/2, the concentrations at the time of adverse effect were estimated to be similar to the monkey NOAEL liver concentrations.

- ALG-020572 was not detected in liver, demonstrating effective cleavage to the active parent ASO.

- No other concerning safety findings (TEAEs, laboratories, VS, EKG, physical examination) were observed.

References