(PS1778) CHARACTERIZATION OF ALN-CFB, AN INVESTIGATIONAL SIRNA TARGETING HEPATIC COMPLEMENT FACTOR B, IN NON-HUMAN PRIMATES AND CFB-HUMANIZED MICE

Topic: 11. Bone marrow failure syndromes incl. PNH - Biology & translational research

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Background

The alternative pathway (AP) of the complement system is a key component of innate immunity; its dysregulation contributes to paroxysmal nocturnal hemoglobinuria (PNH), rare kidney diseases, and dry age-related macular degeneration. Approved AP-directed therapies can be limited by suboptimal blockade or frequent dosing. ALN-CFB is an investigational RNA interference therapeutic; this GalNAc-conjugated siRNA reduces complement factor B (CFB) messenger RNA (mRNA), inhibiting production of CFB protein, an indispensable AP serine protease. The ALN-CFB target sequence is conserved between humans and monkeys.

Aims

To evaluate ALN-CFB in preclinical studies in monkeys and CFB-humanized mice.

Methods

A pharmacokinetic (PK) study was conducted in female cynomolgus monkeys receiving a single subcutaneous (SC) dose of 0.6, 2, or 6 mg/kg (n=5/group) on Day 1, followed to Day 116. Pharmacodynamic studies were conducted in monkeys (SC 2 or 6 mg/kg; n=3/group; to Day 113) and in CFB-humanized mice ($CFB^{Hu/Hu}$; SC 0.3, 1, or 10 mg/kg; n=5/group; to Day 70). Concentrations of ALN-CFB and its active metabolites were measured in monkey plasma and liver using a qualified high-performance liquid chromatography (LC) coupled with high-resolution mass spectrometry (MS) method. Serum CFB protein was quantified by LC/MS. AP activity was assessed using both the traditional AP hemolysis (AH) assay and the Wieslab complement AP (CAP) assay. Circulating Ba and Bb, CFB activation split products, were measured with a Quidel multiplex enzyme-linked immunosorbent assay. Hepatic *CFB* mRNA was evaluated by reverse-transcription quantitative real-time polymerase chain reaction.

Results

After SC administration in monkeys, ALN-CFB was rapidly absorbed and cleared from plasma, with predominantly hepatic distribution. Plasma PK was linear over 1 day, and hepatic PK was generally linear throughout the study across all doses, with minimal renal excretion. Drug and active metabolite levels persisted longer in the liver than in plasma, with a hepatic ALN-CFB half-life ranging between 18–22 days. ALN-CFB led to a potent, dose-dependent reduction of CFB protein in monkeys; at 6 mg/kg, suppression exceeded 95% by Day 15, was sustained through Day 64, and remained generally linear throughout the study across all doses. AP activity was inhibited in a dose-dependent manner, with the 6 mg/kg dose reducing CAP activity by ≥99% from Day 15 through Day 92 and AH activity by >95% from Day 15 through Day 64. CFB protein reduction strongly correlated with AP inhibition. At Days 22 and 43, ALN-CFB achieved >90% knockdown of hepatic *CFB* mRNA and reductions in circulating Bb, and >80% reductions in circulating Ba. These pharmacologic effects were reversible, with partial recovery by the end of the study.

Aligning with monkey studies, ALN-CFB yielded >95% reductions in circulating CFB from Day 7, sustained to Day 42 in $CFB^{Hu/Hu}$ mice.

Summary/Conclusion

Single SC doses of ALN-CFB produced robust, durable CFB protein reduction and near-complete AP inhibition in non-human primates, with marked suppression of hepatic *CFB* mRNA and prolonged hepatic drug/metabolite presence. Effects were consistent in $CFB^{Hu/Hu}$ mice. If translated to humans, these data suggest the potential for robust AP inhibition with convenient, infrequent SC dosing. ALN-CFB is under investigation in a phase 1/2 study for safety and efficacy in participants with PNH and persistent anemia on a C5 inhibitor (NCT07187401).