(PB3151) FIRST-IN-HUMAN, FIRST-IN-PATIENT STUDY OF ALN-CFB, AN INVESTIGATIONAL SIRNA TARGETING HEPATIC COMPLEMENT FACTOR B: TREATMENT OF PERSISTENT ANEMIA IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening disease characterized by complement-mediated hemolysis. Despite treatment with C5 inhibitors, many people with PNH remain anemic due to extravascular hemolysis (EVH), caused by deposition of proximal alternative pathway components and phagocytic removal of red blood cells. Complement factor B (CFB) is a critical component of the alternative pathway. ALN-CFB is a novel GalNAc-conjugated small interfering RNA targeting hepatic production of CFB; by cleaving *CFB* messenger RNA, single subcutaneous (SC) doses of ALN-CFB may deeply and durably reduce circulating CFB protein, abrogate EVH, and possibly control hemolysis in PNH.

Aims

We describe the study design of a phase 1/2 trial that will evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of ALN-CFB in people with PNH and persistent anemia despite receiving a stable dose of an approved C5 inhibitor.

Methods

This is an ongoing, first-in-human (FIH), first-in-patient, 2-part, randomized, double-blind, placebo-controlled study (NCT07187401). In Part A, up to 24 participants will be randomized to single-ascending SC doses of ALN-CFB or placebo on a background of their approved C5-inhibitor therapy. Interim safety, PK, and PD data from Part A will then be used to identify the dose and dosing regimen for Part B, the multiple-dosing safety and efficacy expansion part of the study. Key inclusion and exclusion criteria for Part A are shown in the Table.
Part A consists of a ~28-day treatment period with a post-treatment follow-up period lasting up to Day 365. The overall study duration will be approximately 57 weeks, including the screening period. The primary endpoint will be the occurrence and severity of treatment-emergent adverse events (AEs) during treatment until the end of the study. Secondary endpoints will include absolute and percentage change from baseline in CFB concentration, and concentrations of combined ALN-CFB and major metabolites in plasma (throughout the study) and urine (24 hours following ALN-CFB administration). Throughout the study, safety assessments will include vital signs, body weight, physical examination, electrocardiograms, laboratory tests, and monitoring of anti-drug antibodies and AEs.

Results

Part A of the study is actively recruiting in the UK, Canada, and South Korea.

Summary/Conclusion

This FIH study will provide the first clinical evaluation of ALN-CFB in participants with PNH and persistent anemia on C5 inhibitors, generating safety, PK, PD and preliminary efficacy data and informing dose selection for future studies.

Key inclusion criteria	Key exclusion criteria
• Adults (aged ≥18 years) with PNH • Persistent anemia, defined as hemoglobin ≤10 g/dL (Canada) or ≤10.5 g/dL (UK and South Korea) • Reticulocyte count of ≥100 x 10^9/L at screening Visit 1 • ≥24 weeks on stable C5 inhibitor therapy (eg, eculizumab or approved biosimilar, ravulizumab or crovalimab) or on expanded access program	• Recipient of an organ/bone marrow transplant • History of meningococcal infection or similar recurrent infections by other encapsulated bacterial organisms • Any active, ongoing or recent infection requiring ongoing systemic treatment with antibiotics, antivirals or antifungals within 2 weeks of screening or during screening • Laboratory evidence of bone marrow failure