BSH19-OR-024
Inhibition of C3 with APL-2 Controls Haemolysis and Increases Haemoglobin Levels in Subjects with Autoimmune Haemolytic Anaemia (AIHA)

M. Gertz[1], E. Roman[2], B. Fattizzo[3,*], M. Shum[4], W. Hanna[5], G. Ortega[6], D. Liles[7], F. Senecal[8], S. Lentz[9], M. Hamdani[10], F. Stout[10], A. Shen[10], P. Deschatelets[10], C. Francois[10], F. Grossi[10]

[1]Mayo Clinic, Rochester, [2]Lakes Research, Miami, United States, [3]University of Milan, Milan, Italy, [4]The Oncology Institute of Hope and Innovation, Whittier, [5]University of TN Medical Center Cancer Institute, Knoxville, [6]Mid Florida Hematology Oncology, Orange City, [7]Eastern Carolina University, Greenville, [8]Northwest Medical Specialist, Tacoma, [9]University of Iowa Hospitals, Iowa City, [10]Apellis, Waltham, United States

Purpose: Autoimmune haemolytic anaemia (AIHA) is a group of rare autoimmune diseases characterized by haemolysis mediated by autoantibodies directed against red blood cells (RBCs). The two most common subclasses, warm antibody (wAIHA; 60-70%) and cold agglutinin disease (CAD; 20-25%), are defined by the immunoglobulin (Ig) isotype involved and its thermal optimum for binding RBCs. wAIHA is mediated predominantly by IgG while 90% of CAD is mediated by IgM isotypes. AIHA is associated with life-threatening outcomes such as thrombosis and pulmonary embolism, and no therapies have been approved for either CAD or wAIHA.

The complement system plays a central role in AIHA, mainly in CAD, where pentameric IgM directly fixes complement, but also in wAIHA where immune complexes formed by IgG and RBC antigens activate the classical pathway. C3b deposition on RBCs favors their phagocytosis in the liver and/or spleen (i.e. extravascular haemolysis), with C5b-9-mediated intravascular haemolysis also contributing to haemolysis.

By blocking the formation of C3b, APL-2, a cyclic peptide, has the potential to be a novel therapeutic for AIHA.

Design: Phase 2, open-label study conducted in the US and Brazil to assess the safety, tolerability, efficacy, and PK of daily subcutaneous (SC) doses of APL-2 administered to subjects with wAIHA or CAD.

Methods: Patients with primary AIHA are eligible. Patients are required to have haemoglobin (Hb) levels < 11 g/L, signs of haemolysis, and a positive direct agglutinin test (DAT) for IgG and/or complement C3. The study is recruiting up to 24 subjects (12 wAIHA and 12 CAD). APL-2 270 mg/d or 360 mg/d is administered for 48 weeks. Efficacy is assessed by change from baseline in Hb, transfusion requirements, absolute reticulocyte counts (ARC), lactate dehydrogenase (LDH), haptoglobin, bilirubin, and FACIT fatigue score.

Results: Efficacy and safety data from an interim analysis are available. Twelve CAD and 7 wAIHA C3 + subjects were enrolled as of November 2018. Data below reflect the results of subjects that reached Day 56 (5 CAD subjects, 5 wAIHA subjects). Mean Hb (SD) increased from 8.7 (1.2) to 12.1 (0.9) g/dL in CAD, and from 9.3 (0.9) to 11.3 (1.1) g/dL in wAIHA C3 +. Mean LDH, ARC, and indirect bilirubin returned within the normal range for both CAD and wAIHA C3 + subjects.

Nine of 12 CAD (75%) and 8 of 9 wAIHA subjects (89%) experienced at least one AE, mainly grade 1-2. Most AEs were considered unrelated to APL-2. Six subjects reported 10 SAEs; all were considered unlikely to be related to APL-2. Four subjects experienced 5 grade 3 AEs (oral squamous cell carcinoma, haemolytic flare, pneumonia, purpura, acute kidney injury); 2 subjects reported 5 grade 4 AEs (high calcium, high creatinine, hypoxia, haemolytic flare), and will withdraw from the study. No grade 3 or 4 AEs were considered related to treatment.

Summary/Conclusions: APL-2 increases Hb values both in CAD and in wAIHA (C3 +) within the first weeks of treatment. APL-2 reduces both intra- and extravascular hemolysis, as shown by reductions in LDH, bilirubin and reticulocytes. APL-2 appears to be safe and well tolerated in patients with AIHA.

Disclosure of Interest: None Declared

Keywords: AIHA, Autoimmune Haemolytic Anaemia, CAD, cold agglutinin disease, Haemoglobin, Haemolysis, IgG, IgM, wAIHA