Warm Autoimmune Hemolytic Anemia (wAIHA) and Cold Agglutinin Disease (CAD)

- Age 18 or older
- With a primary diagnosis of wAIHA who had a recurrence, did not respond to, or did not tolerate at least one prior wAIHA treatment such as prednisone or rituximab, or with CAD in the presence of red blood cells (RBCs) being destroyed prematurely
- With a positive Coombs test, which measures presence of antibodies and/or complement proteins bound to the surface of RBCs
- With abnormal laboratory values of any markers that indicate RBC destruction
Autoimmune Hemolytic Anemia (AIHA)

A group of rare autoimmune disorders characterized by premature destruction (hemolysis) of red blood cells (RBCs) by autoantibodies at a rate faster than they can be replaced.

**Warm**

1. 70%-75% of adult AIHA
2. Optimally active at 37°C (98.6°F)
3. IgG-mediated disorder
4. Primary or idiopathic (35%-40%); secondary associated with malignancy or autoimmune disease (60%-65%)

**Cold**

1. 15%-20% of adult AIHA
2. Optimally active at 4°C (39.2°F)
3. IgM-mediated causing RBC clumping
4. Acute secondary to infections; chronic associated with lymphoproliferative and neoplastic disease

---

**Role of Complement in wAIHA and CAD**

- CAD is entirely complement-mediated, and complement plays a major role in wAIHA.
- Antibody recognizes self-proteins on the surface of RBCs, and that complex can activate the classical complement pathway.
- In a second hit, free heme from destroyed RBCs can lead to activation of the alternative pathway of complement activation.
- C3b coating of RBCs triggers extravascular hemolysis, when macrophages engulf RBCs in the liver. In severe cases of CAD, intravascular hemolysis may occur by forming membrane attack complexes in RBC membranes.
  - wAIHA: extravascular hemolysis has been reported as the unique route of hemolysis.
  - CAD: extravascular hemolysis is the predominant route of hemolysis, while intravascular hemolysis is mainly seen in severe cases.
This open-label study will assess the safety, tolerability, preliminary efficacy, pharmacokinetics, and pharmacodynamics of multiple doses of APL-2 in patients with autoimmune hemolytic anemia.1

There are 2 arms to this study1:
1. Subjects to enroll in the wAIHA clinical trial arm (N=6)
2. Subjects to enroll in the cold agglutinin disease clinical trial arm (N=6)

### Purpose of AIHA Clinical Trial

1. At least 18 years of age
2. Weight <125 kg
3. Primary diagnosis of wAIHA or CAD as defined by the presence of hemolytic anemia and positive direct antiglobulin test (DAT) for wAIHA (IgG) or CAD (C3)
   - wAIHA: Did not respond to, relapsed after, or did not tolerate, at least one prior wAIHA treatment regimen (eg, prednisone, rituximab)
4. Hemoglobin <11 g/dL
5. Clinical symptoms of hemolysis with abnormal values by any of the hemolytic markers:
   - Increased absolute reticulocyte count above upper limit of normal (ULN)
   - Reduced haptoglobin below lower limit of normal (LLN)
   - Increased lactase dehydrogenase (above ULN)
   - Increased indirect bilirubin (above ULN)

### Key Exclusion Criteria

1. Prior treatment with rituximab within 90 days
2. Deficiency of iron, folic acid and vitamin B₁₂ prior to treatment phase
3. Abnormal liver function as indicated by a direct bilirubin above normal level, and/or an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 2x ULN
4. Active aggressive lymphoma requiring therapy or an active non-lymphatic malignant disease other than basal cell carcinoma or carcinoma in situ of the cervix
5. Presence or suspicion of active bacterial or viral infection, at screening, or severe recurrent bacterial infections
Dosing of APL-2

Subjects from the wAIHA and the CAD cohorts will be randomly (1:1) assigned to receive either 270 mg/day or 360 mg/day of APL-2 treatment for up to 12 months to identify an optimal dose for the new disease indication. The dose will be delivered SC with a programmed pump designed for self-administration.

The first 3 daily SC doses of APL-2 (day 1 to 3) and doses on day 7 and 14 will be administered at the clinical site. From day 4 to day 336, daily doses of APL-2 will be administered off-site by a study nurse or self-administered by the subject and/or caregiver, except for those days where dosing is at the clinical site.

PLAUDIT Key Endpoints

Study endpoints will be assessed at months 2, 3, 6, and 12

Primary Safety Endpoints:
Incidence and severity of treatment-emergent adverse events (TEAEs) following administration of multiple doses of SC APL-2

Efficacy Endpoints:
• Change from baseline in hemoglobin (Hb)
• Number of red blood cell (RBC) transfusions during study
• Change from baseline in absolute reticulocyte count
• Change from baseline in LDH
• Change from baseline in haptoglobin
• Change from baseline in indirect bilirubin
• APL-2 serum concentrations and pharmacokinetic (PK) parameters as appropriate
• Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) scale and the Linear Analog Scale Assessment scale (LASA) including energy level, ability to perform daily activity, and overall quality of life (QoL)

Exploratory PD markers:
• Complement (eg, CH50, AP50, C3, and Bb) activity and levels
• C3 deposition on RBC cells
What Is APL-2?

APL-2 is a small (13-amino-acid) cyclic peptide coupled via a linker to each end of a linear 40-kDa polyethylene glycol (PEG) chain. APL-2 binds to complement C3 and exerts broad inhibition of the complement cascade, a biological process that is part of innate immunity and is involved in multiple inflammatory processes. PEGylation imparts longer residence time in the body after administration of the drug.

Why Evaluate APL-2 in AIHA?

• APL-2 has the potential to prevent C3-mediated extravascular and MAC-mediated intravascular hemolysis in AIHA patients.
• APL-2 blocks both the classical and the alternative pathways

By targeting C3 at the point of convergence of all complement activation pathways and upstream of C5, APL-2 may halt or diminish complement-mediated hemolysis of red blood cells in patients with AIHA and thus reduce the risk of anemia and the associated signs and symptoms of anemia.

In What Other Hematologic Conditions Is APL-2 Being Studied?

APL-2 is currently being developed for the management of paroxysmal nocturnal hemoglobinuria (PNH), another a rare, chronic, debilitating blood disorder that is caused by the presence, in the bone marrow, of mutant stem cells that lack important surface proteins that protect against activation of the complement system.1,2
Plaudit Study Locations

For qualified patients who do not live near the study locations, Apellis will reimburse for costs associated with travel to one of the study locations, if needed.

To Recommend a Patient for This Trial, Email
apellisclinicaltrials@cherryhcc.com
Or visit
https://aihaclinicaltrial.com

References