A Phase 2, Open-label Study To Assess Safety, Tolerability, And Clinical Effect Of ANX005 In Patients With Warm Autoimmune Hemolytic Anemia And Evidence Of Complement Activation

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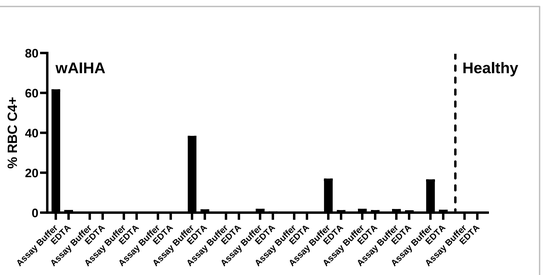
INTRODUCTION

- Autoimmune hemolytic anemia (AIHA) is caused by autoantibody destruction of red blood cells (RBCs) and may be classified as warm autoimmune hemolytic anemia (wAIHA) or cold agglutinin disease[1]
- In wAIHA, which accounts for 60-70% of AIHA cases, polyclonal immunoglobulin G (IgG) antibodies cause hemolysis of RBCs at core body temperatures[1]
- However, approximately 50% of patients with wAIHA exhibit direct antiglobulin tests reactive for complement as well as IgG, suggesting that these cases are not caused by pathogenic IgG alone[2]
- In a recent study of serum samples from 12 patients with wAIHA, four of 12 exhibited complement deposition activity, which is indicative of classical complement pathway involvement (**Figure 1**)[3]

Figure 1. Complement Deposition by a Subset of wAIHA Serum Samples In Vitro on Healthy Human RBCs



EDTA, ethylenediaminetetraacetic acid; RBC, red blood cell; wAIHA, warm autoimmune hemolytic anemia.

- The correlation between autoimmune hemolysis and presence of complement on RBCs in patients with wAIHA suggests a role for the complement system in the pathogenesis of wAIHA[1,2]
- Activation of the classical complement pathway and autoantibody activity against RBCs can be triggered by C1q binding to autoantibodies[4]
- ANX005 is a humanized IgG4 monoclonal antibody that selectively binds and inhibits C1q, blocking activation of the classical complement pathway; it has the potential to inhibit complement-mediated hemolysis in wAIHA
- The goal of this clinical study is to evaluate two once-weekly IV infusions of ANX005 in patients with wAIHA showing evidence of complement pathway activation in order to understand the effect of C1q inhibition on pathway markers and objective disease parameters

METHODS

- This is an open-label, repeat-dose, phase 2 study (NCT04691570) of ANX005 in patients with wAIHA and evidence of classical complement pathway activation
- Up to 12 eligible patients will be enrolled in this study (**Table 1**)

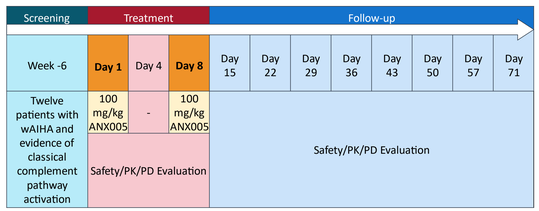
Table 1. Relevant Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Diagnosis of wAIHA at least 3 months prior to screening with: ○ DAT ≥1 positive for IgG ± C3 OR ○ Diagnosis of mixed AIHA that is DAT positive for IgG and C3, with the presence of a cold antibody with thermal amplitude of ≥30°C • HgB ≤10.0 g/dL (pre-transfusion) • Evidence of classical complement pathway activation within 6 months prior to dosing • If on corticosteroids, patients must be receiving a stable dose of ≤1 mg/kg prednisone or equivalent	• History of isolated CAD • Known genetic deficiencies of the complement cascade system • History of IVIg treatment within 90 days prior to dosing • History of plasmapheresis or immunoadsorption treatment within 60 days prior to dosing • Received any complement inhibitor (eculizumab, C1 esterase inhibitor) within 90 days or 5 half-lives prior to dosing

CAD, cold agglutinin disease; DAT, direct antiglobulin test; HgB, hemoglobin; IgG, immunoglobulin G; IgM, immunoglobulin M; IVIg, intravenous immunoglobin; LLN, lower limit of normal; wAIHA, warm autoimmune hemolytic anemia.

- Patients will receive two doses of ANX005 on Days 1 and 8 following a screening period of up to six weeks prior to Day 1 **(Figure 2)**

Figure 2. Study Design and Dosing Scheme



PD, pharmacodynamic; PK, pharmacokinetic; wAIHA, warm autoimmune hemolytic anemia.

METHODS

- Safety and pharmacokinetic (PK)/pharmacodynamic (PD) evaluations will be completed on Days 1, 4, 8, 15, 22, 29, 36, 43, 50, 57, and 71
- Individual study duration will be up to 16 weeks, and patients will complete study participation on Day 71
- Primary and secondary objectives and endpoints are reported on **Table 2**

Table 2. Primary and Secondary Objectives and Endpoints

Primary Objective	Endpoints
• To evaluate the safety and tolerability of two once-weekly IV infusions of 100 mg/kg ANX005 in patients with wAIHA	• Number and percentage of patients experiencing TEAEs
• To evaluate the clinical effect of two once-weekly IV infusions of 100 mg/kg ANX005 in patients with wAIHA	• Change from baseline in HgB over time up to Day 71 • Maximum absolute change in HgB from baseline • Change from baseline in biomarkers of hemolysis over time up to Day 71 ○ Reticulocyte count ○ Haptoglobin ○ LDH ○ Total and indirect bilirubin
Secondary Objectives	**Endpoints**
• To evaluate the PK profile of ANX005 in patients with wAIHA	• ANX005 plasma concentration profiles and PK parameters such as AUC, C_{max}, T_{max}, accumulation ratio, $t_{1/2}$, λ_z, CL, and Vss
• To evaluate the effect of ANX005 on classical complement pathway inhibition as measured by complement system-related biomarkers in patients with wAIHA	• Inhibition of classical complement activity from baseline over time up to Day 71 • Change and percent change from baseline in serum complement biomarkers over time up to Day 71
Exploratory Objectives	**Endpoints**
• To investigate the relationship of ANX005 PK parameters with PD responses in serum in patients with wAIHA	• Correlation between selected ANX005 PK parameters and changes from baseline in serum complement biomarkers
• To investigate the relationship of ANX005 PK parameters with disease activity markers in patients with wAIHA	• Correlation between selected ANX005 PK parameters and changes from baseline HgB levels, and changes from baseline in markers of hemolysis ○ Reticulocyte count ○ Haptoglobin ○ LDH ○ Total and indirect bilirubin

AUC, area under the curve; CL, clearance; C_{max}, maximum concentration; HgB, hemoglobin; LDH, low-density lipoprotein; PD, pharmacodynamic; PK, pharmacokinetic; TEAEs, treatment-emergent adverse events; T_{max}, time to maximum concentration; $t_{1/2}$, half-life; Vss, steady state volume of distribution; wAIHA, warm autoimmune hemolytic anemia; λ_z, terminal elimination rate constant.

CURRENT STATUS

- Results from the phase 2 trial (NCT04691570) are expected by the end of 2022

SUMMARY

- This is a phase 2 study of ANX005 in patients with wAIHA and evidence of classical complement pathway activation
- Patients will receive two IV doses of ANX005 one week apart with the goal of evaluating its safety, tolerability, PK/PD, and clinical effect
- This study will improve our understanding of the classical complement pathway in wAIHA as a target for effective therapy

References

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Disclosures

UJ: Annexon Biosciences: advisory board
CB: Alexion: other; Sanofi: research support, other; Annexon Biosciences: advisory board, research support; Incyte: research support, advisory board; Argenx: research support, advisory board
RG: None
AP: Incyte: honoraria; Novartis: honoraria; Sanofi: honoraria; Pfizer: honoraria
AR: Roche: research support, consultant, honoraria; Alexion: consultant, honoraria; Apellis: consultant, honoraria; BioCryst: consultant, honoraria; Bioverativ (a Sanofi company): consultant, honoraria; Grifols: consultant, honoraria; Kira: consultant, honoraria; Novartis: consultant, honoraria; Sanofi: consultant, honoraria
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