ALPHA-ORBIT - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Navenibart in Participants with Hereditary Angioedema

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SUMMARY

1 NAVENIBART IS AN INVESTIGATIONAL MONOCLONAL ANTIBODY DESIGNED TO BE A HIGHLY POTENT AND SPECIFIC PLASMA KALLIKREIN INHIBITOR. INITIAL RESULTS FROM CLINICAL TRIALS WITH HEALTHY PARTICIPANTS AND PARTICIPANTS WITH HAE TYPE 1 OR TYPE 2 DEMONSTRATED ROBUST PHARMACODYNAMIC ACTIVITY AND A PHARMACOKINETIC PROFILE THAT SUPPORTS Q3M AND Q6M ADMINISTRATION.

2 IN ONGOING TRIALS IN PARTICIPANTS WITH HAE TYPE 1 OR TYPE 2, NAVENIBART TREATMENT HAS DEMONSTRATED ROBUST AND CLINICALLY-RELEVANT REDUCTIONS IN FREQUENCY OF HAE ATTACKS, SEVERITY OF HAE ATTACKS, AND NUMBER OF HAE ATTACKS REQUIRING ON-DEMAND TREATMENT, IMPROVED QUALITY OF LIFE, ALONG WITH A FAVORABLE SAFETY AND TOLERABILITY PROFILE.

3 ALPHA-ORBIT (NCT06842823) IS A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF NAVENIBART IN PREVENTING HAE ATTACKS IN PARTICIPANTS WITH HAE TYPE 1 OR TYPE 2.

OBJECTIVE

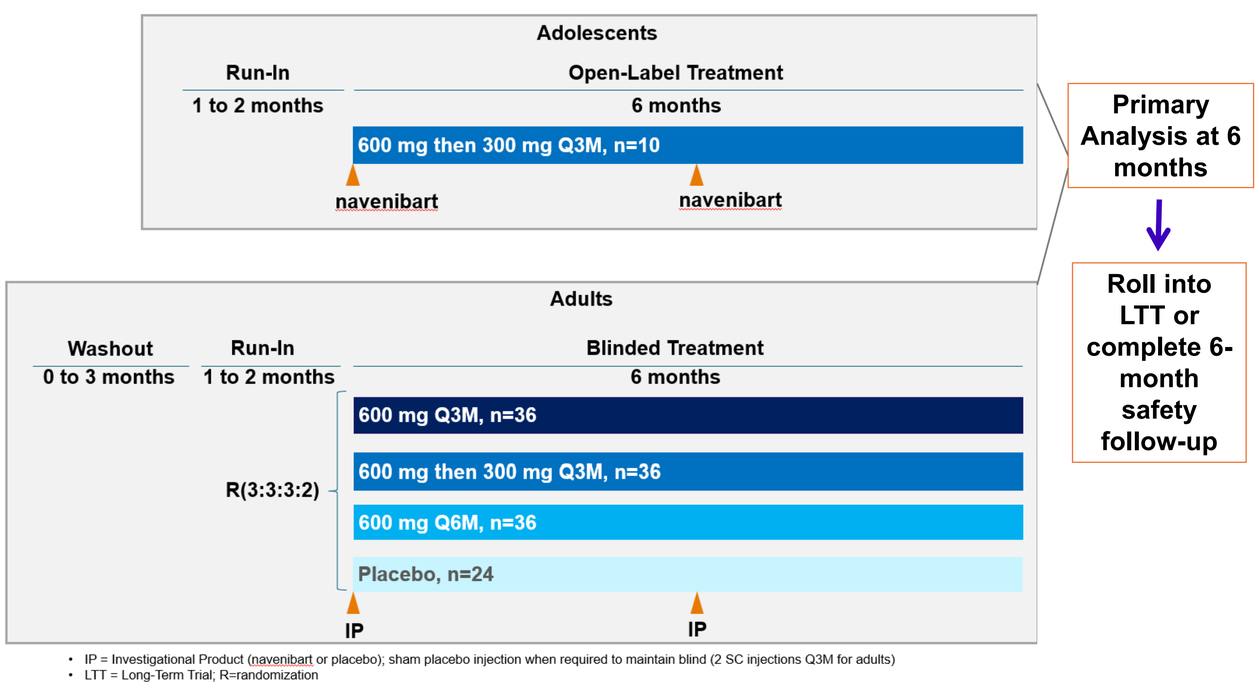
To describe the design of ALPHA-ORBIT (NCT06842823), a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the investigational therapeutic navenibart in preventing HAE attacks in participants with HAE-C1INH Type 1 or Type 2. The trial will be conducted in adolescents and adults.

RATIONALE

- Hereditary Angioedema (HAE) is a rare, autosomal dominant genetic disease characterized by severe, recurrent, unpredictable, often painful, and sometimes life-threatening swelling in the face, limbs, abdomen, and airway.
- Most HAE cases (Type 1 and Type 2) are caused by mutations in the SERPING1 gene that reduce the level or function of C1-esterase inhibitor protein (C1-INH) encoded by this gene, resulting in unregulated plasma kallikrein activity.
- Navenibart is a monoclonal antibody designed to be a highly potent and specific inhibitor of plasma kallikrein, thereby inhibiting the production of bradykinin.
- The Fc domain of navenibart incorporates a 3-amino acid YTE modification designed to extend circulating half-life.
- Results of a Phase 1b/2 trial demonstrated that navenibart was well tolerated after both 1 dose and 2 doses and reduced attack frequency, severity, and utilization of on-demand treatment for at least 6 months.
- Navenibart has the potential to become an effective and safe preventative treatment for HAE, with administration every 3 or 6 months.

METHODS

Figure 1. ALPHA-ORBIT (NCT06842823) - Trial Schema



- IP = Investigational Product (navenibart or placebo); sham placebo injection when required to maintain blind (2 SC injections Q3M for adults)
- LTT = Long-Term Trial; R=randomization

Table 1. ALPHA-ORBIT, a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Methodology

Trial population	Adults (≥18 years old); Adolescents (≥12 to <18 years old) with HAE Type 1 or 2
Location(s)	Global, Multicenter
Randomization	Adults (n=135) – 3:3:3:2 Adolescents (n=10) – n/a – assigned to navenibart
Dosing	Adults: Two subcutaneous (SC) doses of Investigational Product (IP) at Day 1 and Day 91 Adolescents: Two subcutaneous doses of navenibart at Day 1 and one dose at Day 91
Assessment Frequency	Monthly, through 3 months after the last dose of IP
Assessments	HAE attack information (efficacy); safety, pharmacokinetics, pharmacodynamics, immunogenicity, biomarkers, and quality-of-life evaluations

STUDY ENDPOINTS

Primary Endpoint

Number of time-normalized, investigator-confirmed HAE attacks during the 6-month treatment period

Secondary Endpoints

- Number of moderate or severe investigator-confirmed HAE attacks during the 6-month treatment period
- Number of investigator-confirmed HAE attacks that require on-demand treatment during the 6-month treatment period
- Percent reduction in monthly investigator-confirmed HAE attacks in the 6-month treatment period versus the run-in period
- Time to first investigator-confirmed HAE attack after first dose
- Number of participants responding to treatment, defined as a ≥50%, ≥70%, or ≥90% reduction from the run-in period in investigator-confirmed HAE attack rate compared to placebo during the 6-month treatment period
- Number of participants with no investigator-confirmed HAE attacks during the 6-month treatment period
- Change from baseline (Day 1) in the Angioedema Quality of Life Questionnaire total score

Safety Endpoint

Incidence of treatment-emergent adverse events

Key Inclusion Criteria

Documented diagnosis of HAE (Type 1 or Type 2), including:

- Documented clinical history consistent with HAE
- Age at reported onset of first angioedema symptoms ≤30 years of age, or a family history consistent with HAE (Type 1 or 2)
- Lab findings consistent with HAE (Type 1 or 2)

Participants will be eligible to exit the run-in period and enter the treatment period if they meet both of the following criteria:

- Participated in the run-in period for ≥1 month
- Experienced a total of 2 or more investigator-confirmed HAE attacks during the run-in period

Key Exclusion Criteria

- Any exposure to an investigational drug or device within 90 days or 5 half-lives (if appropriate; whichever is longer) before informed consent
- Has ever received gene editing therapy
- Long-term prophylaxis must not have been used for the following durations before the first day of run-in: lanadelumab within 90 days; berotralstat within 21 days; plasma-derived C1-INH within 14 days; tranexamic acid, oral danazol, oral stanazolol, and oral oxandrolone within 3 days
- Diagnosis of another form of chronic angioedema, such as acquired C1-INH deficiency, HAE with normal C1-INH, idiopathic angioedema, or angioedema associated with urticaria

CONCLUSIONS

ALPHA-ORBIT will provide pivotal evidence on the efficacy, durability, and safety of navenibart in hereditary angioedema. Results are anticipated to inform a potential new standard of care.

Conflicts of Interest

Study is funded by Astria Therapeutics, Inc. AZ declares no conflicts of interest. WRL has a working relationship with several pharmaceutical companies as listed below but does not have a direct financial interest in any of the companies listed. Consultant Arrangements: Astria, BioCryst, BioMarin, CSL Behring, Express Scripts/CVS, Intellia, KalVista, Magellan, Optum, Pharming, Pharvaris, Shire/Takeda. Speakers' Bureau: BioCryst, CSL Behring, Kalvista, Pharming, Shire/Takeda, Grifols, Astra Zeneca, Sanofi/Regeneron, GSK. Current Grants/Research Support:Astra Zeneca, Astria, BioMarin, CSL Behring, Grifols, Intellia, Ionis, KalVista, Lilly, Novartis, Pharvaris, Shire/Takeda, Teva, Up Stream Bio. Board Membership: US Hereditary Angioedema Association Medical Advisory Board. DFW Metroplex Allergy Society. TJC reports research, speaking and consulting relationships with CSL Behring, Takeda, Kalvista, Astria and Ionis; research activities with BioMarin, Pharvaris and Intellia; consulting activities with BioCryst, HAE-A medical advisory board and ACARE Center Director; Dr, Craig has also served in an advisory role throughout all activities. MM has had Speaker and/or Advisor roles for CSL Behring, Takeda, Pharming, Novartis, BioCryst, KalVista and Adivo. EAP has received honoraria as a speaker/advisor for and/or grant/clinical trial investigator support from Astria Therapeutics, BioCryst, BioMarin, Centogene, CSL Behring, Intellia Therapeutics, KalVista, Pharming, Pharvaris and Takeda/Shire. JTA has received personal fees for steering committee, advisory board, speaker bureau, and/or clinical research activity from BioCryst, BioMarin, CSL Behring, Cycle Pharmaceuticals, KalVista, Pharming, Pharvaris, and Shire/Takeda. SDB has received speaker/advisor fees and/or research funding from Astria, Canadian Blood Services, CSL Behring, Grifols, Ionis Pharmaceuticals, KalVista, Novartis, Octapharma, Pharvaris, Sanofi, and Takeda. AB has been involved in research activities with Ionis, Astria, and Intellia and Advisory Board activities with CSL, Ionis, Pharvaris, Intellia, KalVista, Astria, Takeda, ADARx. RT, CvE, HW, CM are employees of Astria Therapeutics, Inc. MH has received speaker/ consultancy fees for CSL Behring, KalVista, Pharvaris, Takeda and Torii. MAR discloses research support from Astria, BioCryst, BioMarin, CSL Behring, Ionis, KalVista, Pharvaris, Takeda. Consulting with Astria, BioCryst, BioMarin, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, Takeda.

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