ALPHA-ORBIT - A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Navenibart in Adolescent and Adult Participants with Type 1 and Type 2 Hereditary Angioedema (HAE)

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OBJECTIVE

Describe the design of ALPHA-ORBIT, a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of 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.

SUMMARY

1 **Navenibart is an investigational humanized IgG1 kappa light chain 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-C1INH Type 1 or Type 2 demonstrated potent pharmacodynamic activity and a pharmacokinetic profile that supports Q3M and Q6M administration.**

2 **In ongoing trials in participants with HAE-C1INH 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 along with a favorable safety and tolerability profile.**

3 **ALPHA-ORBIT 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-C1INH Type 1 or Type 2.**

ACKNOWLEDGMENTS: Authors acknowledge Larisa Miller, PharmD, CMPP for medical writing and data visualization

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Presented at American Academy of Allergy, Asthma and Immunology • February 28-March 3, 2025 • San Diego, CA

INTRODUCTION

- 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 humanized IgG1 kappa light chain 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 enhance pH-dependent neonatal Fc receptor binding and 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-C1INH, with administration every 3 or 6 months.

METHODS

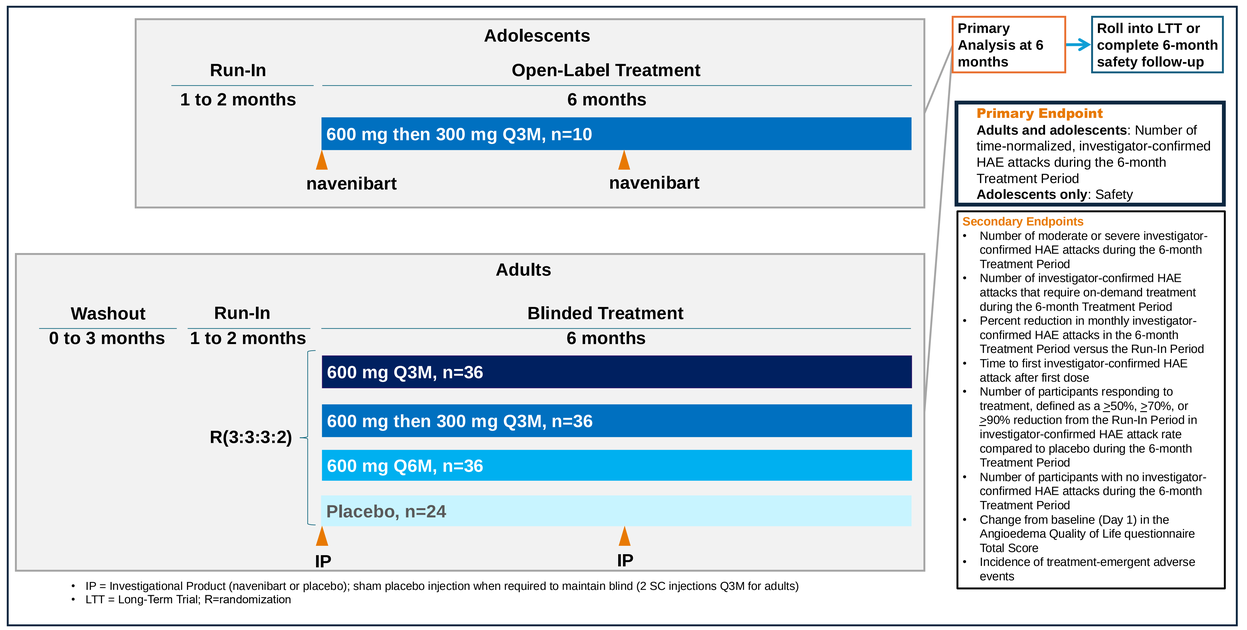
Table 1. ALPHA-ORBIT, a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Methodology

Trial population	Adults (≥ 18 years old); Adolescents (≥12 to <18 years old) with HAE Type 1 or 2
Location(s)	Global
Randomization	Adults (n=132) – 3:3:3:2 Adolescents (n=10) – all assigned to navenibart
Dosing	Adults: Two subcutaneous (SC) doses of Investigational Product (IP) at Day 1 and Day 91 Adolescents: Two SC doses of navenibart at Day 1 and 91
Assessment Frequency	Monthly, through 3 months after the last dose of IP
Assessments	HAE attack information (efficacy); Adverse Events, physical examinations, electrocardiograms, laboratory evaluations, pharmacokinetics, pharmacodynamics, immunogenicity, biomarkers, and quality-of-life evaluations

RESULTS

STUDY DESIGN

Figure 1. ALPHA-ORBIT - 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

Key Inclusion Criteria

- Documented diagnosis of HAE-C1INH Type 1 or Type 2, including:
  - documented clinical history consistent with HAE-C1INH
  - age at reported onset of first angioedema symptoms ≤ 30 years of age, or a family history consistent with HAE-C1INH Type 1 or 2
  - lab findings consistent with HAE-C1INH 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 for LTP 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