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 (HAE)

D3.390

EMEL AYGÖREN PURSUN[1*], WILLIAM LUMRY[2], TIMOTHY CRAIG[3], ANDREA ZANICHELLI[4], MARKUS MAGERL[5], JOHN T. ANDERSON[6], STEPHEN D. BETSCHEL[7], RAFFI TACHDJIAN[8], ALEENA BANERJI[9], CLAIRE VANEENWYK[10], HAROLD WRIGHT[10], THEODORA COHEN[10], CHRISTOPHER MORABITO[10], MICHIHIRO HIDE[11], MARC RIEDL[12]

*Presenting Author

[1]GOETHE-UNIVERSITAT, FRANKFURT AM MAIN, GERMANY; [2]MEDICAL CITY CHILDREN'S HOSPITAL, DALLAS, TX, UNITED STATES; [3]PENN STATE HEALTH ALLERGY, ASTHMA AND IMMUNOLOGY, HERSHEY, PA; [4]DIPARTIMENTO DI SCIENZE BIOMEDICHE PER LA SALUTE, UNIVERSITÁ DEGLI STUDI DI MILANO, MILANO, ITALY & UNITÁ OPERATIVA DI MEDICINA, CENTRO ANGIOEDEMA, I.R.C.C.S. POLICLINICO SAN DONATO, SAN DONATO MILANESE, MILANO, ITALY; [5]UNIVERSITATSMEDIZIN, BERLIN, GERMANY; [6]ALLERVIE HEALTH, BIRMINGHAM, AL; [7]UNIVERSITY OF TORONTO, CANADA; [8]UNIVERSITY OF CALIFORNIA, LOS ANGELES, SANTA MONICA, CA; [9]MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA; [10]ASTRIA THERAPEUTICS, BOSTON, MA; [11]HIROSHIMA CITY, HIROSHIMA CITIZENS HOSPITAL; [12]UC SAN DIEGO, SAN DIEGO, CA

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 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 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 potent 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.**

ACKNOWLEDGMENTS: Authors acknowledge Jan Markind, PharmD, for medical writing and data visualization

Presented at European Academy of Allergy and Clinical Immunology June 13-June 16, 2025 • Glasgow, UK

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 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

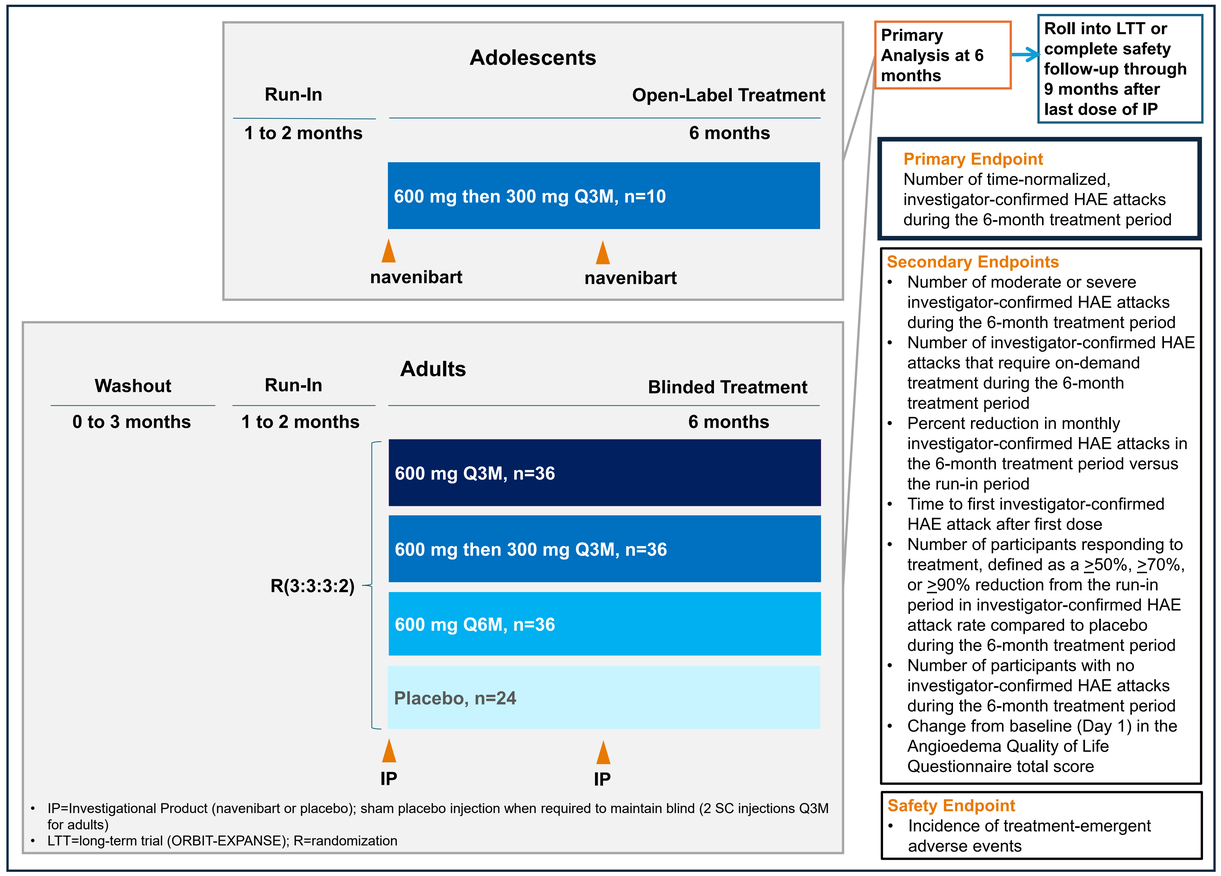
Table 1. ALPHA-ORBIT, a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Methodology

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) – 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



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