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)

2

TIMOTHY CRAIG[1*], WILLIAM LUMRY[2], EMEL AYGÖREN PURSUN[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]PENN STATE HEALTH ALLERGY, ASTHMA AND IMMUNOLOGY, HERSHEY, PA, UNITED STATES; [2]AARA RESEARCH CENTER, DALLAS, TX, UNITED STATES; [3]GOETHE-UNIVERSITAT, FRANKFURT AM MAIN, GERMANY; [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, UNITED STATES; [7]UNIVERSITY OF TORONTO, CANADA; [8]UNIVERSITY OF CALIFORNIA, LOS ANGELES, CA, UNITED STATES; [9]MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MA, UNITED STATES; [10]ASTRIA THERAPEUTICS, BOSTON, MA, UNITED STATES; [11]HIROSHIMA CITY, HIROSHIMA CITIZENS HOSPITAL, HIROSHIMA, JAPAN; [12]UC-SAN DIEGO, LA JOLLA, SAN DIEGO, CA, UNITED STATES

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.

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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

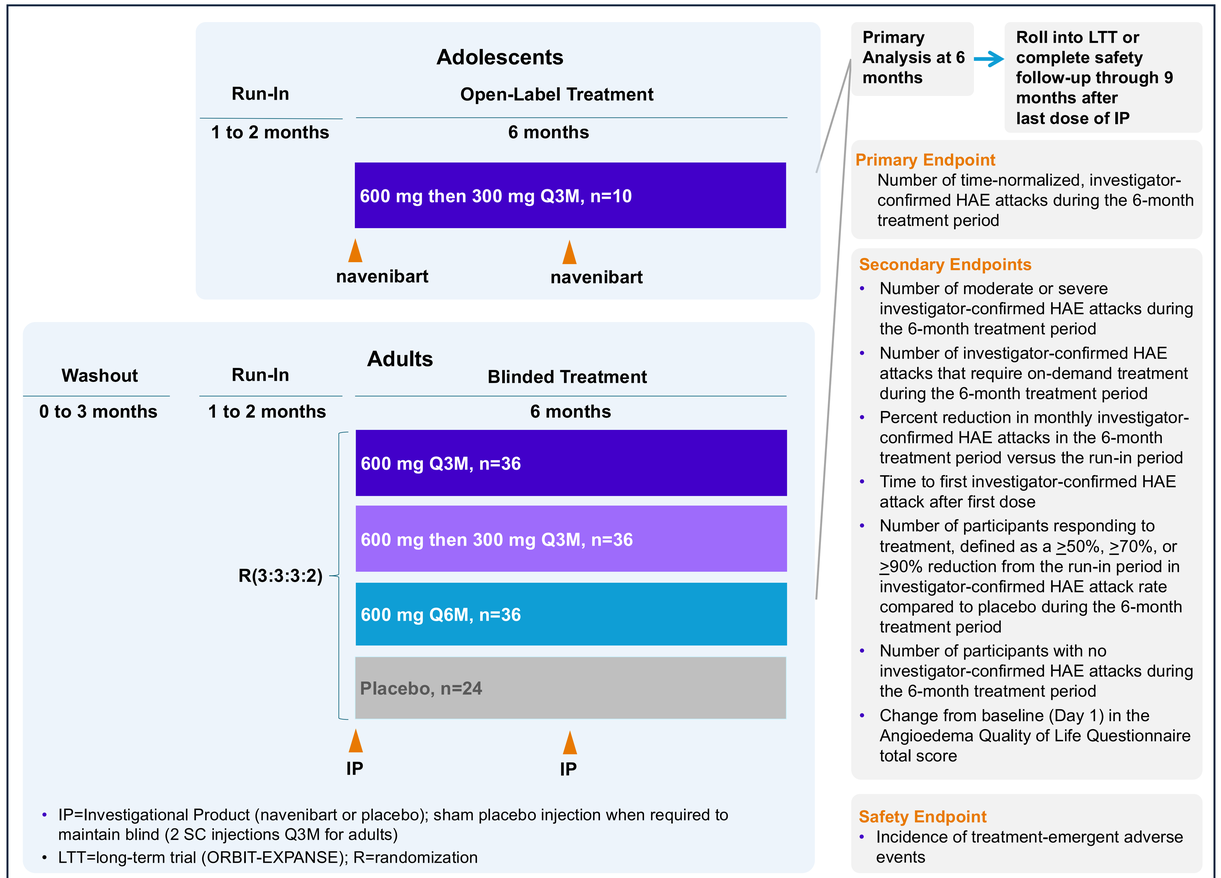
Table 1. ALPHA-ORBIT, a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Methodology

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