ALPHA-ORBIT - A Phase 3 clinical trial to evaluate the efficacy and safety of navenibart in participants with hereditary angioedema (HAE)

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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 DEMONSTRATES POTENT PHARMACODYNAMIC ACTIVITY AND A PHARMACOKINETIC PROFILE THAT SUPPORTS Q3M AND Q6M ADMINISTRATION.

2 IN PHASE 1B/2, THE ALPHA-STAR TRIAL IN PARTICIPANTS WITH HAE-C1INH, NAVENIBART TREATMENT DEMONSTRATES RAPID AND CLINICALLY-RELEVANT REDUCTIONS IN FREQUENCY OF HAE ATTACKS, REDUCTIONS IN THE NUMBER OF SEVERE ATTACKS, AND NUMBER OF HAE ATTACKS REQUIRING ON-DEMAND TREATMENT ALONG WITH A FAVORABLE SAFETY AND TOLERABILITY PROFILE.

3 ALPHA-ORBIT (NCT06842823) IS A PIVOTAL PHASE 3, MULTICENTER STUDY DESIGNED TO EVALUATE THE EFFICACY AND SAFETY OF NAVENIBART ADMINISTERED EVERY 3 OR 6 MONTHS FOR LONG-TERM PREVENTION OF HAE ATTACKS IN PARTICIPANTS WITH HAE-C1INH. THE STUDY INCLUDES A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED COHORT IN ADULTS AND AN OPEN-LABEL COHORT IN ADOLESCENTS.

OBJECTIVE

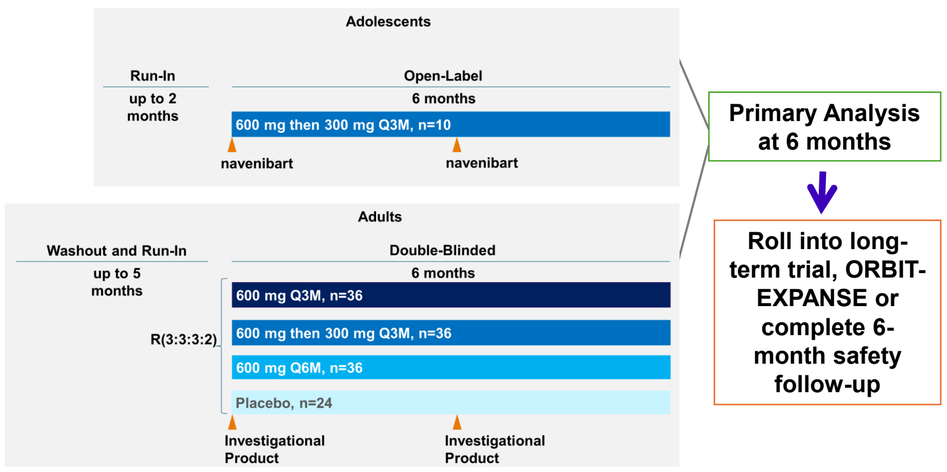
Describe the design of ALPHA-ORBIT (NCT06842823), a Phase 3, multicenter trial evaluating the efficacy and safety of an investigational therapeutic navenibart in preventing HAE attacks in participants with HAE-C1INH. The trial includes a randomized, double-blind, placebo-controlled portion in adults and an open-label portion in adolescents.

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-C1INH cases 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 demonstrate that navenibart is well-tolerated after 1 or 2 doses and reduced attack frequency, severity, and rescue medication use for at least 6 months.
- Navenibart has the potential to become an effective and safe long-term prophylaxis treatment for HAE-C1INH, 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)
- R=randomization

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

Trial population	Adults (≥ 18 years old); Adolescents (≥12 to <18 years old) with HAE-C1INH
Location(s)	Global, Multicenter
Randomization	Adults (n=135) – 3:3:3:2 Adolescents (n=10) – n/a - all assigned to navenibart
Dosing	Adults: Two subcutaneous (SC) doses of Investigational Product (navenibart or placebo) at Day 1 and Day 91 Adolescents: Two SC doses of navenibart at Day 1 and one dose on 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

RESULTS

Primary Endpoint

Adults and adolescents: Number of time-normalized, investigator-confirmed HAE attacks during the 6-month Treatment Period
Adolescents: Safety

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
- Incidence of treatment-emergent adverse events

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
  - lab findings consistent with HAE-C1INH
- 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 within 5 half-lives 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 C1INH for LTP within 14 days; androgens within 3 days; all other long-term prophylaxis require consultation with the medical monitor
- 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.

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