Evaluating the Efficacy and Safety of an Intravenous Human Plasma-Derived C1 Esterase Inhibitor (C1-INH) Concentrate in Participants with Congenital C1-Inhdeficiency for the Treatment and Pre-Procedure Prevention of Acute Hereditary Angioedema Attacks

Syed Rizvi, PharmD,[1] Annie Arrey-Mensah, MD,[2] Isaac Melamed, MD,[3] Syed Rehman, MD,[4] Maria Staevska, MD[5]

[1]Octapharma, Paramus, NJ; [2]Asthma Allergy & Immunology Institute, Southfield, MI; [3]IMMUNOe Research Center, Centennial, CO; [4]Asthma & Allergy Center, Toledo, OH; [5]University Hospital Alexandrovska, Sofia Medical University, Sofia, Bulgaria

BACKGROUND AND PURPOSE

- Hereditary angioedema (HAE) is an uncommon condition marked by attacks of edema that impact various parts of the body.[1]
- Three distinct types of HAE have been described, all presenting with similar symptoms.[2,3]
  - Type I HAE is the most prevalent and results from reduced production of complement 1 esterase inhibitor (C1-INH). In Type II HAE, C1-INH levels remain normal, but its functional activity is compromised. Type III HAE has an unclear pathophysiology, with both C1-INH levels and function remaining normal.[2,3]
- During an HAE attack, pharmacologic intervention may be required to lessen the severity and duration of symptoms.[3]
- Plasma-derived C1-INH products are currently available on the market. C1-INH replacement therapy with human plasma-derived C1-INH concentrate has proven to be an effective and well-tolerated option for managing acute HAE attacks.[4]
- At present, a limited number of plasma-derived and recombinant C1-INH products are commercially available.[3]
- Plasma-derived C1-INHs are commonly utilized in the treatment of HAE Types I and II, serving both on-demand and prophylactic purposes. Clinical trials involving intravenous (IV) administration of these products have demonstrated clear benefit over placebo.[5,6]
- This study will evaluate the safety and efficacy of an IV human plasma-derived C1-INH concentrate in participants with C1-INH deficiency for the treatment and pre-procedure prevention of acute HAE attacks.

METHODS

- This study is a prospective, multicenter, randomized, double-blind, parallel group, placebo-controlled, interventional efficacy and safety Phase 3 study in participants with congenital C1-INH deficiency and will be conducted in approximately 30 centers worldwide.
- The primary objective is to confirm the superiority of C1-INH (OCTA-C1-INH) in comparison to placebo administered in a double-blind manner by IV injection to relieve symptoms of an acute attack in adult and adolescent participants (≥12 to <18 years of age) (see **Table 1** for endpoints).
- Secondary objectives are to assess the safety of C1-INH (OCTA-C1-INH) in participants with an acute HAE attack and the quality of life (QoL) after treatment with C1-INH compared with baseline.
- Approximately 124 participants with Type I or Type II HAE are expected to be enrolled into the Waiting Period/Pharmacokinetic (PK) Evaluation, with approximately 112 participants ≥12 years of age needed (**Figure 1**).
  - Among the total participants enrolled, the following will be needed to participate in the PK study: at least 6 adolescents (12 and <18 years of age), 6 children aged 6 to <12 years of age, 6 children aged 2 to <6 years of age, and 30 adults (maximum of 10% of subjects receiving lanadelumab will be allowed).
- Participants who have a history of clinically relevant antibody development against C1-INH, medical history consistent with Type 3 HAE, or a history of allergic reaction to C1-INH or other blood/plasma products will be excluded from the study.
- The clinical study consists of two phases (**Figure 2**); while only adults may participate in the first study phase, the enrollment of participants is open for patients ≥2 years of age in the second study phase.
- In Phase 1, participants are expected to come to the study site within 5 hours of a qualifying attack (QAT) and will be randomly assigned 1:1 to double-blind C1-INH or placebo.
  - Participants will receive a second injection (double-blind switch from first investigational medicinal product [IMP] 4 hours after the first injection).
- In Phase 2, participants are also expected to come to the study site within 5 hours of the QAT and will be randomly assigned 1:1 to double-blind C1-INH or placebo (except for laryngeal attacks or for participants <12 years of age).
  - Participants will receive a second injection (double-blind switch from first IMP) 4 hours after the first.
  - Participants <12 years of age who experience a QAT and any participant who experiences a qualifying laryngeal attack will be treated with open-label C1-INH.
  - Any participant who receives open-label C1-INH will be followed for at least 15 days.

Figure 1: Study Screening/Enrollment

- Approximately 124 participants with Type I or Type II HAE are expected to be enrolled into the Waiting Period/Pharmacokinetic (PK) Evaluation, with approximately 112 participants ≥12 years of age needed.
- Among the total participants enrolled, the following will be needed to participate in the PK study: at least 6 adolescents (12 and <18 years of age), 6 children aged 6 to <12 years of age, 6 children aged 2 to <6 years of age, and 30 adults (maximum of 10% of subjects receiving lanadelumab will be allowed).

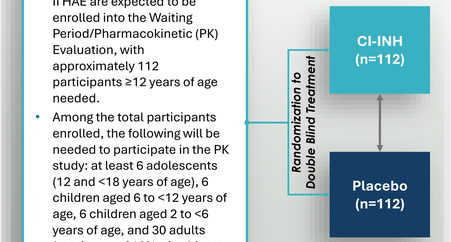


Table 1: Key Endpoints

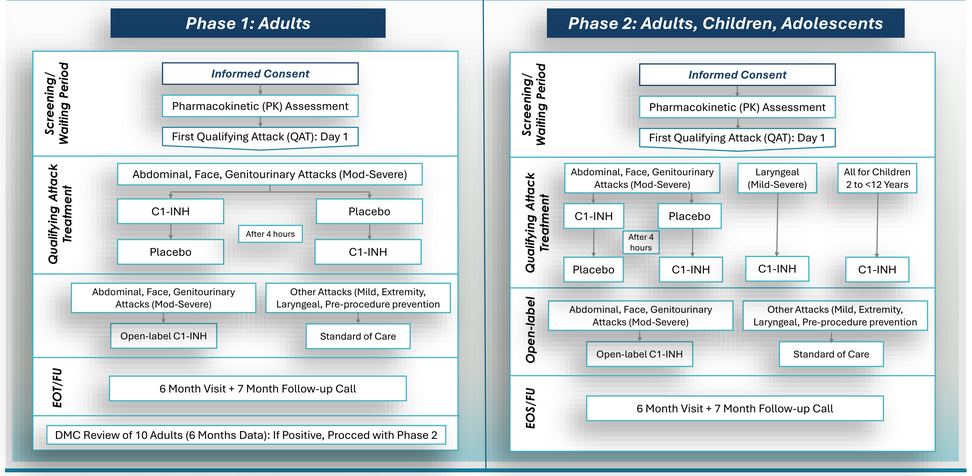
Primary Endpoint

- The primary efficacy endpoint will evaluate the time to the beginning of unequivocal symptom relief at the defining attack site (site of swelling or pain) in blinded participants.

Secondary Endpoints

- The percentage of participants responding to treatment.
- Time to the beginning of unequivocal symptom relief at all sites involved within 4 hours after injection.
- Changes in symptom severity at the defining site by visual analog scale rating from pre-injection over 4 hours after injection.
- Changes in quality of life (QoL) at the end of the study compared with baseline.
- The safety profile and PK will also be evaluated.

Figure 2: Study Design



C1-INH: complement 1 esterase inhibitor; DMC: Data Monitoring; EOT: end of treatment; FU: follow-up; Mod = moderate.

RESULTS

- This study is ongoing. The primary efficacy endpoint will evaluate the time to the beginning of unequivocal symptom relief at the defining attack site (site of swelling or pain) in blinded participants (**Table 1**).
- Participants will rate symptom relief for the defining site from the start of the IMP injection every 15 minutes over 4 hours.
- Unequivocal relief is defined as having 3 consecutive reports of "absent now but present before", "absent now and absent before", or "present, symptoms better" on the 5-grade symptom relief rating scale; assessments on this scale are made compared to the previous time point.
- Secondary endpoints include:
  - The percentage of participants responding to treatment.
  - Time to the beginning of unequivocal symptom relief at all sites involved within 4 hours after injection.
  - Changes in symptom severity at the defining site by visual analog scale rating from pre-injection over 4 hours after injection.
  - Changes in quality of life (QoL) at the end of the study compared with baseline.
  - The safety profile and PK will also be evaluated.

CONCLUSIONS

- Plasma-derived C1-INHs are commonly utilized in the treatment of HAE Types I and II, serving both on-demand and prophylactic purposes.
- Clinical studies conducted with IV administration of plasma-derived C1-INH products have shown clear benefit in comparison to placebo.
- Previously, a highly purified concentrate of C1-INH derived from human plasma has been studied in a Phase 2a, prospective, open-label, single-arm, multicenter, PK, and safety single-dose study in 20 participants with congenital C1-INH deficiency and HAE.
- The investigators of this study aim to comprehensively assess the safety, efficacy, and PK of C1-INH across a diverse patient population.
- Introducing a new C1-INH to the market will help meet the needs of HAE patients.

REFERENCES

1. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130(3):692–697.
2. Ghazi A, Grant JA. Hereditary angioedema: epidemiology, management, and role of icatibant. *Biologics Target Ther*. 2013;7:103–113.
3. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guidelines for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 2018;73:1575-1596.
4. Martinez-Saguer I, Cicardi M, Suffritti C, et al. Pharmacokinetics of plasma-derived C1-Esterase inhibitor after subcutaneous versus intravenous administration in subjects with mild or moderate hereditary angioedema: the PASSION study. Transfusion. et al. *Transfusion*. 2014;54(6):1552–1561.
5. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009;124(4):801–808.
6. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010;363(6):513–522.

ACKNOWLEDGMENTS

This study was sponsored by Octapharma. The authors would like to thank Shireen Dunwoody, Kandyss Najjar, and Chelanna O'Brien of Dunwoody Consulting for assistance with poster design and development.

Presented at the: Immunoglobulin National Society (IgNS) **2025 Annual Meeting – October 16-19 in Dallas, Texas**