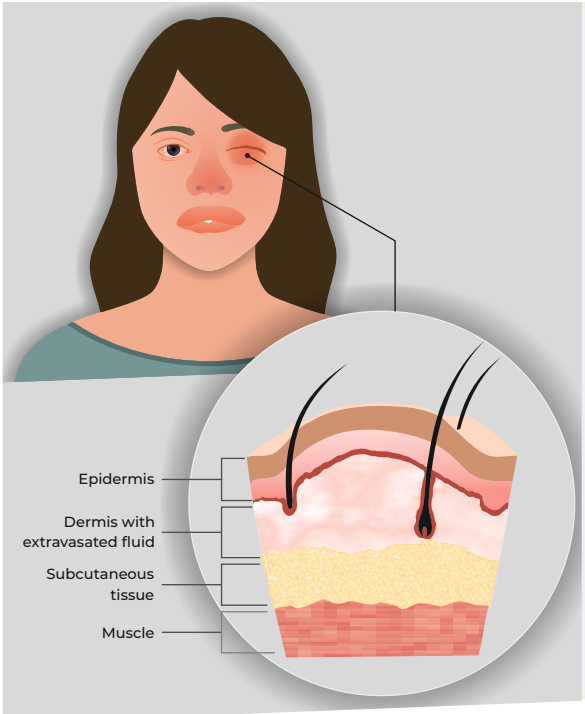
PlasmaMatters
IMMUNOLOGY EDITION
CSL Behring Asia South

CSL BEHRING ASIA SOUTH NEWSLETTER | JULY 2023

On-demand treatment of Hereditary Angioedema (HAE) - An Update



SCIENTIFIC EVENT HIGHLIGHT

It is postulated that there are close to 30,000 patients suffering from hereditary angioedema (HAE) in India. However, HAE is a highly underdiagnosed condition due to lack of awareness and diagnostic facilities in India.[1]

To bridge this gap, CSL Behring and Plasmagen Biosciences hosted an educational session by renowned international speaker, Prof Henriette Farkas from Hungary in a 2-day conference of 3rd National Conference of HAE Society of India on the 28th of May 2023. The session yielded meaningful discussions and valuable clinical insights. Through this newsletter, it's our endeavor to widely disseminate those insights and to spread awareness about the timely diagnosis and management of HAE in Indian patients.

KEY TAKEAWAYS

- Hereditary angioedema (HAE) caused by C1-esterase inhibitor deficiency is an autosomal-dominant disease resulting from a mutation in the C1-inhibitor gene
- Plasma-derived C1 inhibitor (C1-INH) concentrate is a standard-of-care for managing acute HAE attacks
- Berinert is a safe and effective C1-INH concentrate, delivering fast and sustained relief from acute HAE attacks in adult and pediatric patients
- In >90% of HAE attacks, patients demonstrate symptom relief within 1 hour after receiving Berinert
- Berinert has a proven safety profile in adult and pediatric patients with no proven viral transmission
- The availability of C1-INH concentrate, Berinert in India can meet a need-gap and potentially improve quality of life and health outcomes for patients with HAE

SPEAKER'S PROFILE

Professor Henriette Farkas MD, PhD, Dsc

Department of Internal Medicine and Hematology
Hungarian Angioedema Center of Reference and Excellence
Semmelweis University, Budapest, Hungary

I. What should be the treatment strategy for HAE?

Hereditary angioedema (HAE) caused by C1-esterase inhibitor deficiency is an autosomal-dominant disease resulting from a mutation in the C1-inhibitor gene. It is a rare condition that can cause attacks of swelling, and often pain, in specific parts of the body, including the abdomen, face, and throat. HAE is managed using a 3-pronged treatment strategy:

1. Management of acute attack
2. Short-term prophylaxis
3. Long-term prophylaxis

During the acute attack, the treatment strategy is to relieve the HAE attack rapidly, effectively and safely, regardless of the location and the severity of the swelling

II. Which treatment options can be used to manage an HAE attack?

The WAO/EAACI guidelines[2] recommend that HAE attacks are treated with either intravenous C1 inhibitor, ecallantide, or icatibant. On-demand therapy is essential to minimize the impact of HAE attacks. Because attacks are unpredictable and potentially life-threatening, readily available, effective, on-demand therapy is essential for all patients.

The figure 1 showcases multiple action points where the prodrome of HAE can be checked and one can appreciate the mechanism of action points of different treatment options. The drug class kallikrenin Inhibitor suppresses the kallikrenin to act on high molecular kininogen and prevents its conversion to Bradykinin. The BK2R antagonist prevents the action of bradykinin on the BK2R receptor. However, C1 inhibitor has more than 10 mechanism of action points on the pathomechanism of HAE, making it a versatile and highly effective treatment of HAE. Overall, in addition to the suppressive effect on the complement pathway, C1-INH also inhibits the kallikreinkinin system, bradykinin activation, lectin pathway, plasmin, and factors XIa and XIIa of the coagulation pathway.

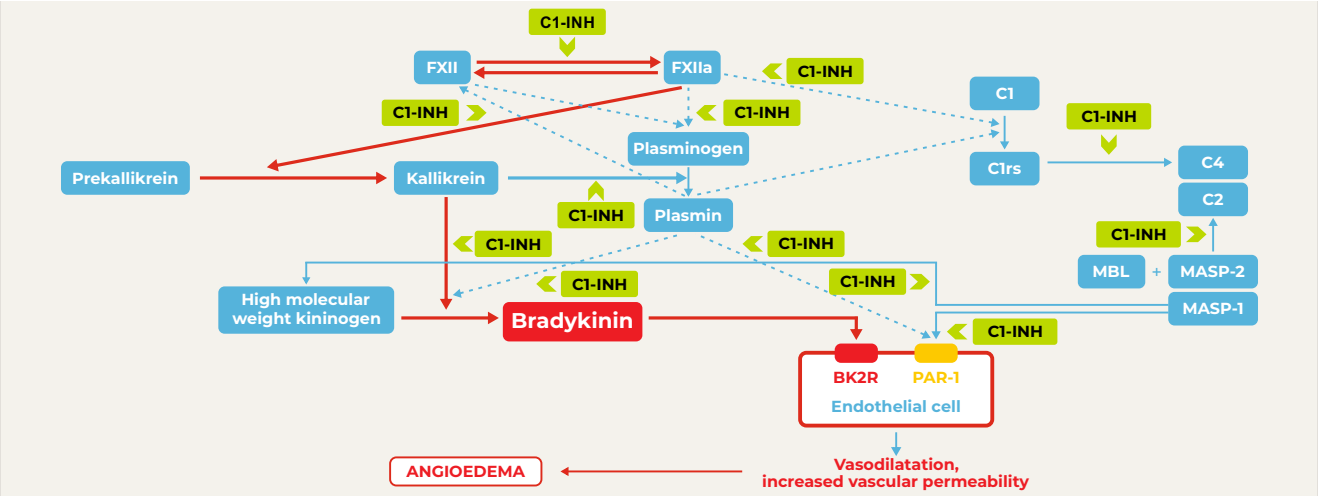


Figure 1. Multiple points of action of C1 INH in the patho-mechanism of HAE

III. What is Berinert and how can it be administered?

The plasma-derived C1-INH Berinert, manufactured by CSL Behring (Marburg, Germany), is a sterile, pyrogen-free, lyophilized white powder for intravenous (IV) administration after reconstitution with supplied diluents. It was first licensed in Germany in 1985. The figure 3 shows the timeline and evolution of C1 inhibitor therapy.

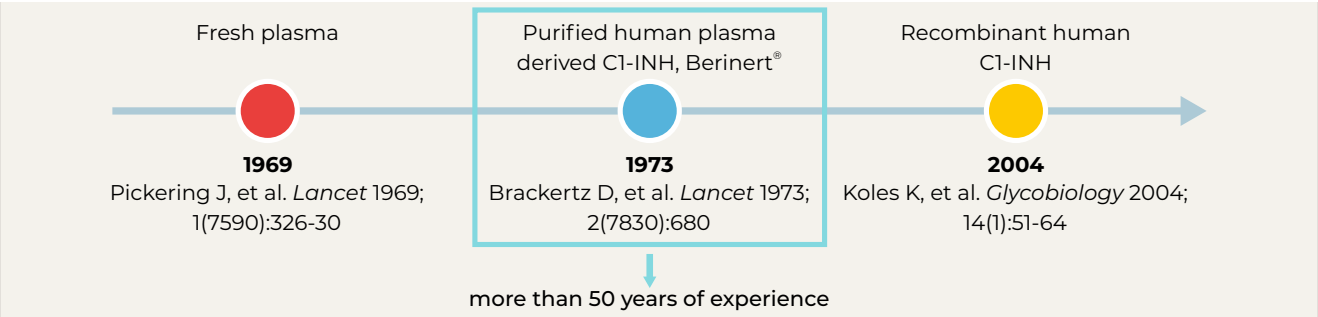


Figure 2. Purified human plasma derived C1-INH or Berinert has more than 50 years of experience

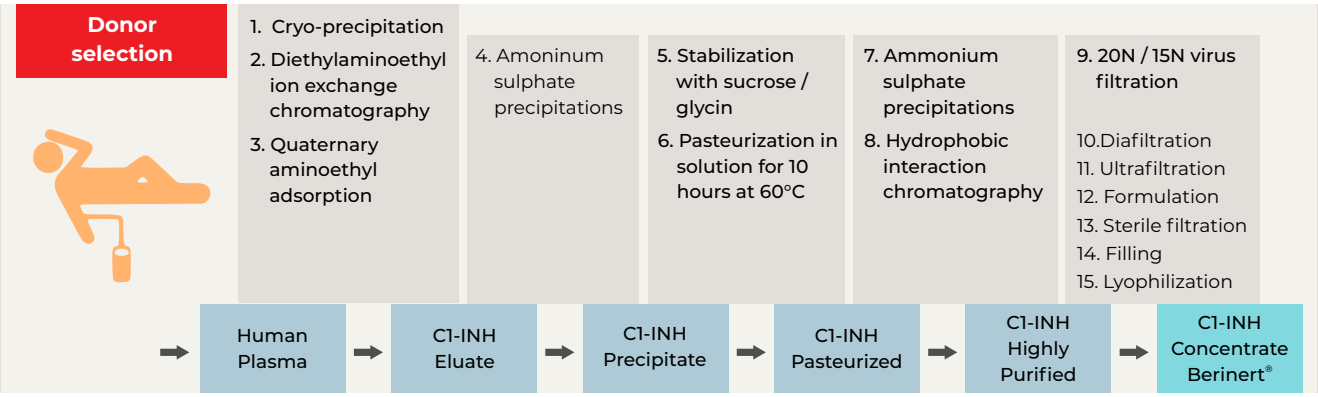


Figure 3. Manufacturing process of Berinert. Figure adapted from Gröner A, et al.[3]

IV. What are the key clinical trials of C1 inhibitor in HAE?

a. **I.M.P.A.C.T.** or International Multicenter Prospective Angioedema C1-INH Trials 1 and 2 are the pivotal trials of Berinert in HAE. The IMPACT 1 focussed on dose-finding and safety, whereas the IMPACT 2 study focused on open label extension of IMPACT 1 to evaluate the efficacy and safety of long term treatment with 20 IU/kg of C1 inhibitor for HAE attacks at any of the body locations.

IMPACT 1		IMPACT 2	
A randomized, double-blind, placebo-controlled study in 125 patients with C1-INH-HAE		An open-label extension study of I.M.P.A.C.T. 1 to evaluate the safety and efficacy of long-term treatment with 20 U/kg C1-INH for successive HAE attacks at any body location	
Primary endpoint	Time between start of Berinert® administration and onset of relief of symptoms as determined by patient's assessment	**Primary endpoint**	To investigate the efficacy and safety of multiple treatments with Berinert®
Secondary endpoint	Time between start of study treatment and complete resolution of all symptoms, as determined by patient assessment	**Secondary endpoint**	To investigate the safety of Berinert®: adverse events, vital signs, viral safety and anti-C1-INH antibody

V. What are the recommendations in the WAO/EAACI guidelines and the key clinical evidence substantiating it?

a. *EFFICACY*

1. Recommendation: Attacks should be treated as early as possible

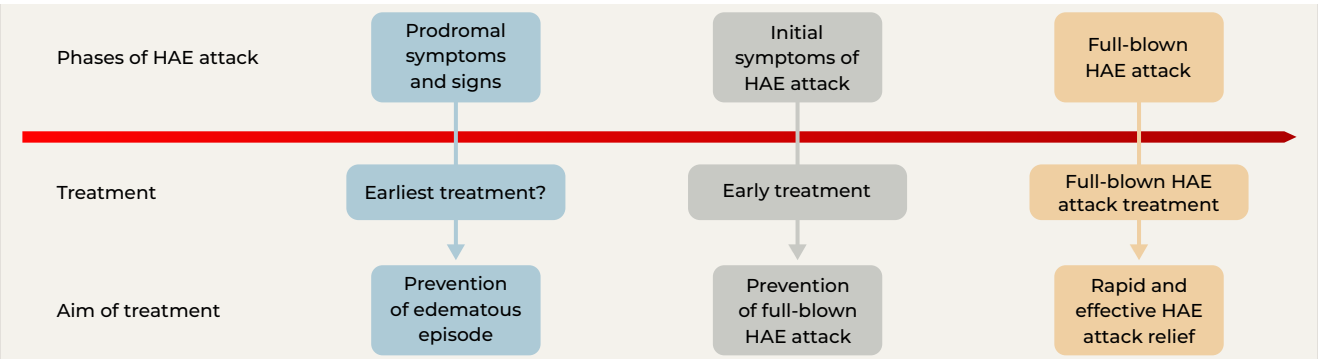


Figure 4. The phases of HAE attack and the aims of treatment

In IMPACT 1, treatment with C1-INH within less than 6 hours after start of an attack resulted in considerably shorter times to onset of symptom relief (HR 3.36) and complete resolution (HR 4.30) vs placebo. The benefit of C1-INH compared with placebo was reduced when administered after 6 or more hours (HR, 1.18 for times to onset of symptom relief and 1.61 for complete resolution). Analysis of IMPACT 2 data indicated slower complete resolution of symptoms with later start of treatment. Thus early treatment with 20 IU/kg pdC1-INH results in rapid improvement of symptoms and results in shorter duration of HAE attack.

2. Recommendation: All attacks should be considered for on-demand treatment

20 IU/kg of C1-INH concentrate provides reliable efficacy in the long-term treatment of successive HAE attacks at any of the body locations.

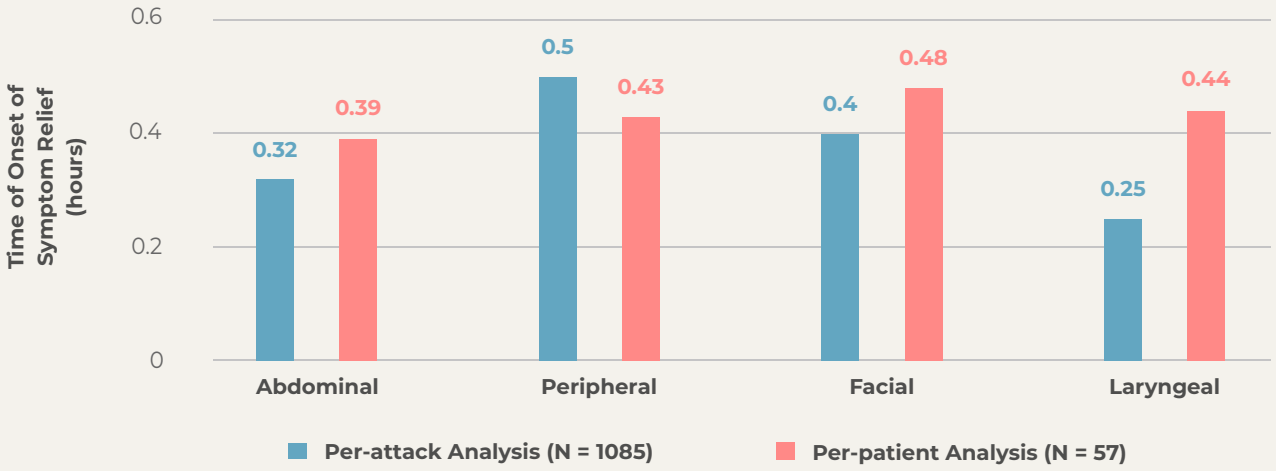


Figure 5: The time to onset of symptom relief

3. Recommendation: Any attack affecting or potentially affecting the upper airway must be treated.

Bork K et al.[4] showed that Berinert had a shorter time to onset of symptom-relief as compared with Cinryze. Time to onset of symptom relief was shorter with body weight-adjusted doses. Similarly, Craig et al. had shown that one hour after treatment, more than 75% of patients treated with C1-INH 20 IU/kg had reported onset of symptom relief, compared with approximately 40% of patients. Significant reduction in median time to onset of symptom relief (0.5 hours) with 20 IU/kg compared with placebo (1.5 hours). The median time to complete resolution of HAE symptoms was significantly lower with C1-INH 20 IU/kg (4.9 hours) than with placebo (7.8 hours).

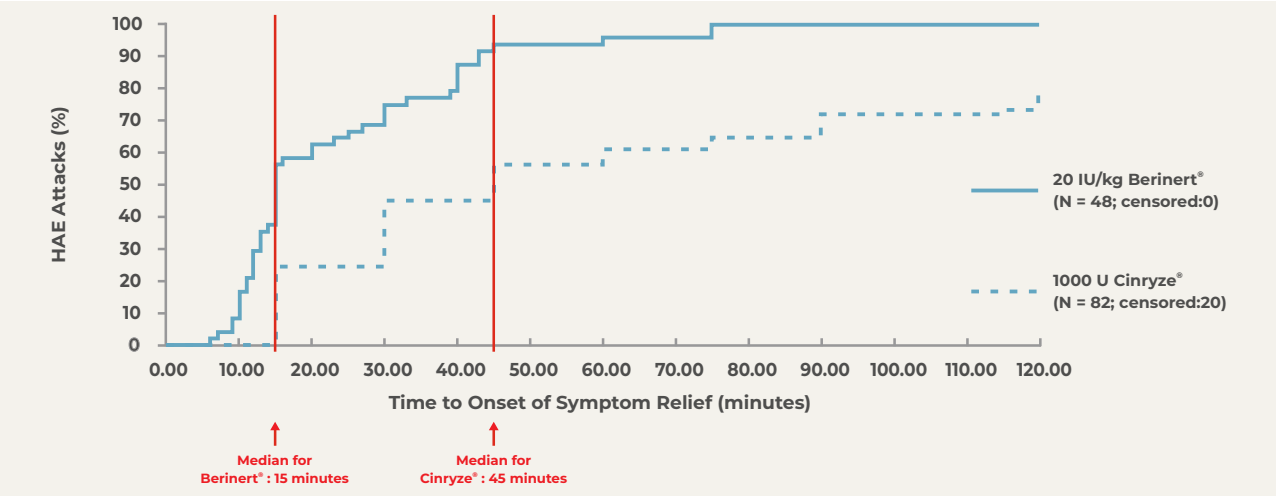


Figure 6. Time to onset of symptom relief for Berinert compared with Cinryze

Inference: Early treatment with 20 IU/kg of Berinert® results in rapid improvement of symptoms and shorter duration of attacks irrespective of location of attack on body.

b. *SAFETY*

Berinert® is proven to be safe and well tolerated leading to less than 0.1% serious adverse events and treatment discontinuation. With respect to virus safety, no confirmed seroconversions during the studies.[5], [6]

Inference: Berinert® is safe and well tolerated

c. *REPEATED ADMINISTRATION*

The effectiveness of Berinert does not change after repeated administration. In a study done by Craig TJ et al. 18 patients were treated with Berinert® for ≥ 15 attacks. The 'time to onset of symptom relief' and the 'time to complete resolution' were both not affected by repeated treatment with C1-INH concentrate. The median time to onset of symptom relief (per-attack) was 22 minutes, and the median time to complete resolution of symptoms (per-attack) was 15 hours.

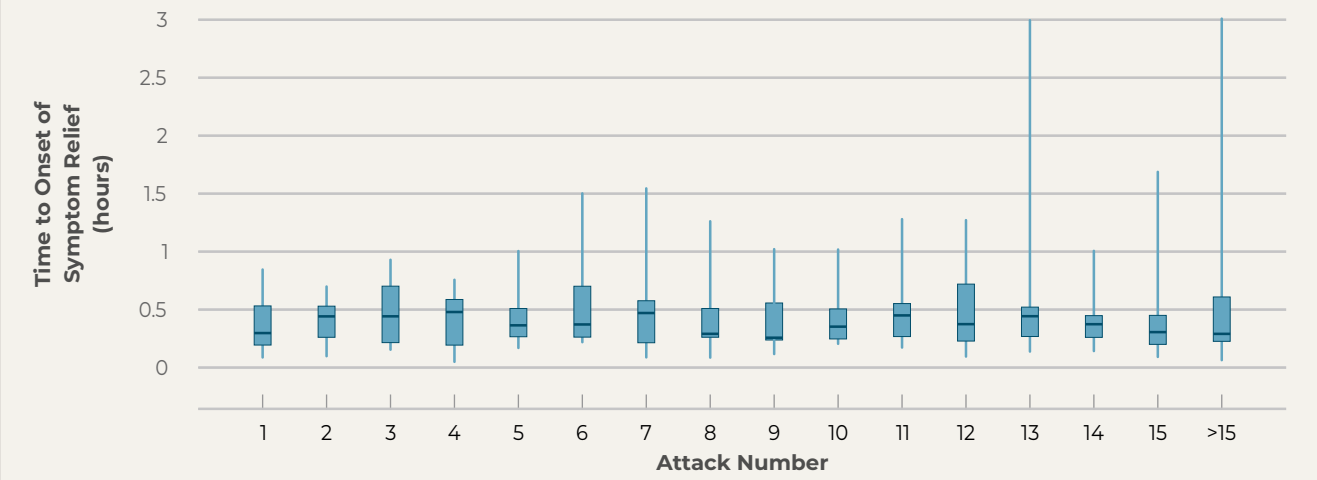


Figure 7. Median time to onset of symptom relief (per-attack)

Inference: Berinert can be administered repeatedly with no decline in efficacy

d. *HOME ADMINISTRATION*

Recommendation: All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer

The post hoc analysis of IMPACT1 and IMPACT2 studies shows that attack duration is shorter in the home group compared to the clinic group.

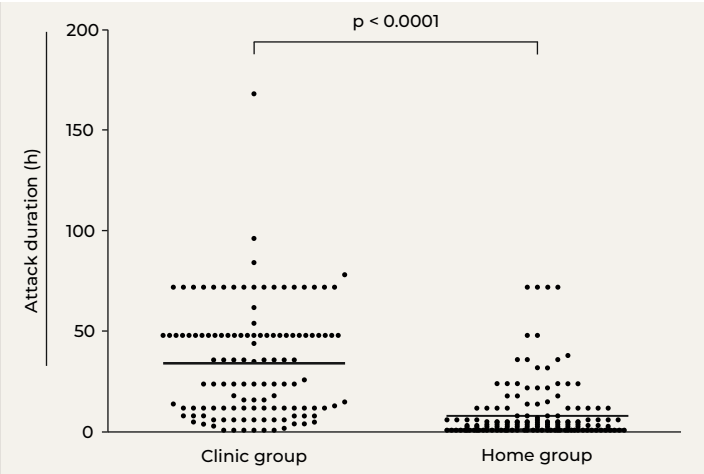


Figure 8. *Post hoc* analysis of IMPACT1 and IMPACT2

Inference: Educating the HAE patients on home treatment empowers them to reduce the attack duration.

e. *SPECIAL POPULATION*

4. Recommendation: C1 inhibitor or icatibant can be used for the treatment of HAE attacks in children under the age of 12.

Roughly 1 to 107 vials per patients (50 IU/vial) were used in a cohort of pediatric HAE patients[7], and it was observed that the use of Berinert was safe and effective in pediatric population. No local or systemic adverse effects, or allergic reactions related to treatment. Treatment was not associated with any increase in the titers of anti-C1-INH antibodies. There was no evidence of any infectious complications.

Inference: There are no signs for pediatric-specific safety concerns with Berinert, and it can be safely used in paediatric patient population.

5. Recommendation: Plasma-derived C1 inhibitor is the preferred therapy during pregnancy and lactation.

The accumulated clinical evidence of use of C1-INH in 619 pregnancies in 280 female patients suffering from HAE shows that its safe and effective in pregnancy with no risk of teratogenic effects to the offspring. Another retrospective analysis[8] of clinical data in 118 pregnancies (82 full-term and 36 abortions) in 41 female patients Berinert was a safe and effective relief for attacks occurring in pregnant women with HAE in all three trimesters, the postpartum period and during breastfeeding, regardless of the localization of edema. In addition, no congenital abnormalities were detected in the newborns

Inference: The safety and efficacy of Berinert during pregnancy and lactation is well established.

SUMMARY

1. HAE attacks should be treated as early as possible
2. HAE attacks should be treated with either intravenous C1 inhibitor, ecallantide, or icatibant
3. Clinical studies have demonstrated that Berinert® is an effective therapy in the management of HAE attacks at all body locations
4. Berinert® is relatively safe and well tolerated
5. The efficacy and safety of Berinert® is not affected by repeated administration

References: 1. *Jindal AK, et al. Indian Dermatol Online J. 2021 Nov 22;12(6):796-804.*. **2.** *Maurer, M, et al. Allergy. 2022; 77: 1961–1990.* **3.** *Gröner, A., et al. Transfusion, 52: 2104-2112.* **4.** *Bork K, et al. J Emerg Med. 2016 Apr;50(4):567-80.e1.* **5.** *Craig TJ, et al. J Allergy Clin Immunol. 2009 Oct;124(4):801-8.* **6.** *Craig TJ, et al. Allergy. 2011 Dec;66(12):1604-11.* **7.** *Farkas H, et al. J Allergy Clin Immunol Pract. 2020 Jul-Aug;8(7):2379-2383.*. **8.** *Ibolya Czaller, et al. European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 152, Issue 1, 2010, Pages 44-49*

Plasmagen BIOSCIENCES

IND-BRN-0010-SEP2023

CSL Behring
Biotherapies for Life™

About CSL Behring

CSL Behring is a global biotherapeutics leader driven by its promise to save lives. Focused on serving patients' needs by using the latest technologies, the company develops and delivers innovative therapies that are used to treat coagulation disorders, primary immune deficiencies, hereditary angioedema, respiratory disease, and neurological disorders. The company's products are also used in cardiac surgery, burn treatment and to prevent hemolytic disease of the newborn.

CSL Behring operates one of the world's largest plasma collection networks, CSL Plasma. The parent company, CSL Limited (ASX:CSL;USOTC:CSLLY), headquartered in Melbourne, Australia, employs more than 27,000 people worldwide, and delivers its life-saving therapies to people in more than 100 countries. For inspiring stories about the promise of biotechnology, visit Vita at CSLBehring.com/vita and follow us on Twitter.com/CSLBehring.