CANADIAN ALLERGY & IMMUNOLOGY TODAY

SPECIAL SUPPLEMENT

REVIEWING THE SCIENCE AND TREATMENT OPTIONS FOR HEREDITARY ANGIOEDEMA WITH A FOCUS ON BEROTRALSTAT FOR LONG-TERM PROPHYLAXIS

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The treatment of hereditary angioedema (HAE) has progressed significantly over the last decade. HAE is an autosomal dominant condition that is bradykinin mediated and affects approximately 1 in 50,000 people.[1] This condition continues to challenge allergists/immunologists (A/I) in promptly managing the disease to reduce attacks of potentially life-threatening angioedema, while improving quality of life in a population in which disease activity tends to increase with age.[2] Notably, delays in diagnosis may reach up to 8 years from initial presentation.[2] The impact of HAE extends beyond the patient, and can affect their caregivers, owing to the fear of acute attacks, which can lead to absenteeism both at school and in the workplace and ultimately negatively impact quality of life and career productivity.[3]

Astute A/I should rely on family history, clinical presentation, and early laboratory data to help increase their index of suspicion of bradykinin induced HAE, followed by definitive immunologic and genetic testing for the diagnosis of HAE type 1 or type 2. A family history of this autosomal dominant condition will suggest type 1 HAE. Clinically, bradykinin mediated HAE presents with non-pitting, non-pruritic subcutaneous tissue swelling of the face, extremities, and genitalia. Submucosal involvement of the gastrointestinal or respiratory tract may be extreme, and result in bowel obstruction and or laryngeal asphyxiation.[4,5]

Diagnosis of HAE remains dependent on immunologic evaluation of C1 Esterase Inhibitor (C1EI) levels and function (C1EI-F) in addition to measurement of C4 levels. During acute attacks of HAE, early laboratory evaluation may reveal elevated D-dimer levels and a shortened activated partial thromboplastin time (aPTT).[6,7] Although non-specific, these early markers may guide the consulting A/I or emergency medicine physician to pursue a diagnosis of bradykinin induced HAE instead of histamine induced HAE, which can facilitate administration of appropriate rescue therapy and follow up consultation by centres skilled in the management of HAE.

Understanding the pathways of HAE will allow the A/I to better investigate and treat HAE. Bradykinin

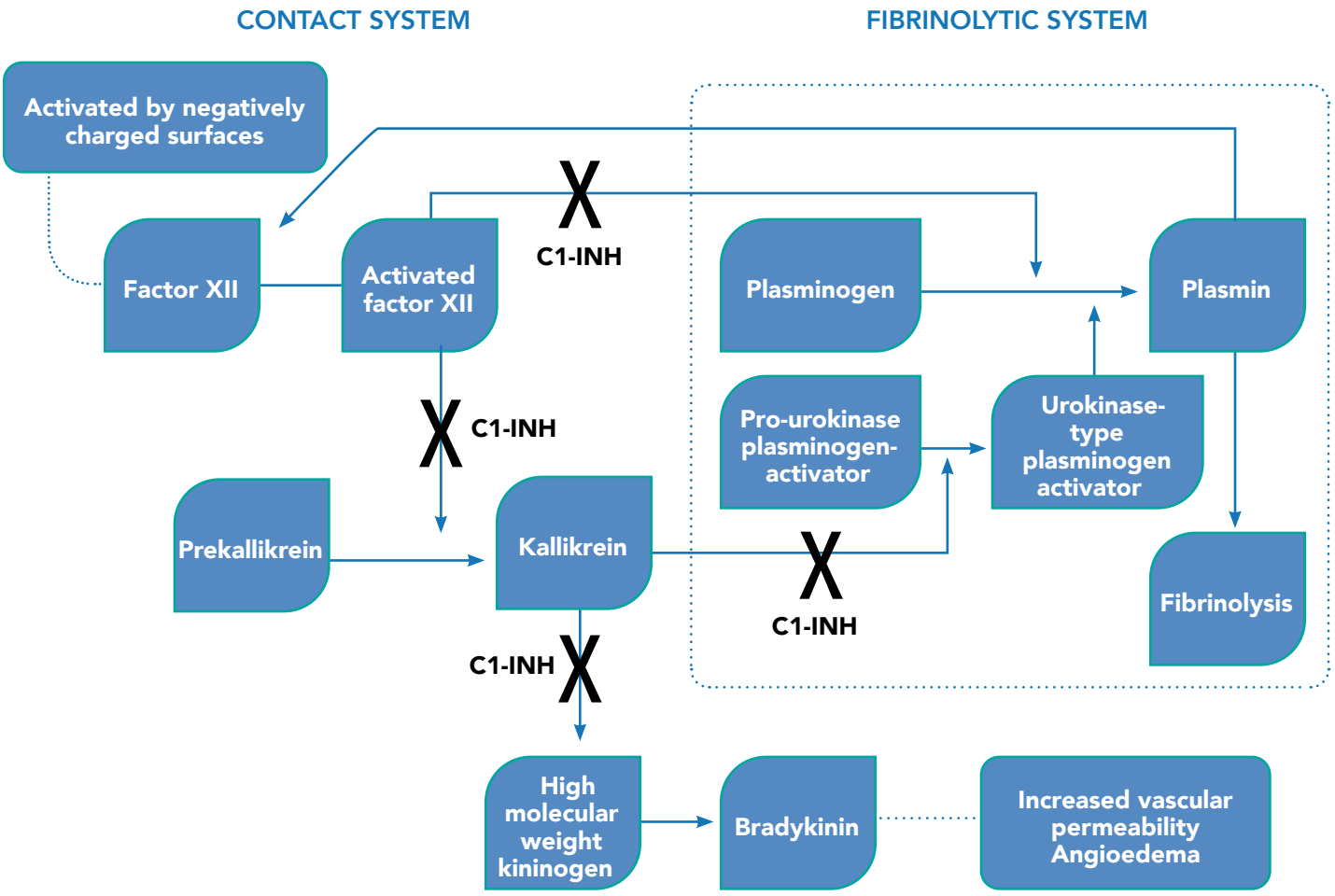


Figure 1. *Pathway of contact system activation and interaction with fibrinolytic system. Contact system activation starts with the activation of factor XII. Activated factor XII converts plasma prekallikrein into plasma kallikrein. Kallikrein cleaves high molecular weight kininogen to produce bradykinin.Bradykinin causes vasodilatation and increases vascular permeability, leading to angloedema. The fibrinolytic system can also lead to bradykinin formation and vascular leakage via factor XII activation by plasmin. Kallikrein regulates the fibrinolytic system by cleaving pro-urokinase plasminogen activator into uroklinase-type plasminogen activator, causing activation of plasminogen to plasmin. C1 Inhibitor (C1-INH) regulates these pathways via Inhibition (bold crosses); Adapted from Longhurst, HJ and Bork, K, 2019*

production is a direct outcome of the activation of the contact system. **Figure 1** provides an overview of the pathway of contact system activation. Activation of factor XII (aFXII) by negatively charged surfaces converts pre-kallikrein to kallikrein. Kallikrein production then mediates conversion of high molecular weight kininogen to bradykinin. Bradykinin subsequently leads to vascular permeability, which is the cornerstone of the upper airway, gastrointestinal tract, and subcutaneous edema. C1EI regulates the activity of aFXII and kallikrein. A deficiency in the plasma level and function of C1EI results in unopposed activation of aFXII and kallikrein and increased bradykinin production.[8] In 85% of cases of type 1 HAE, C1EI levels are deficient due to mutations in the *SERPING1* gene. In type 2 HAE, (representing 15% of cases) C1EI levels are normal, however its functional activity levels is reduced due to mutations in *SERPING1*.[8] The rarest type of HAE is linked to lymphoproliferative disorders that result in increased catabolism of C1EI, resulting in breakthrough angioedema in individuals lacking family history of HAE.[9]

The classification of bradykinin-induced Angioedema is thus based on the status of C1EI including both deficiency and/or defect of C1EI **(Table 1).** Genetic sources implicate both pathways; where available, genetic testing is extremely helpful in identifying the mutations implicated in HAE.

HAE associated with normal levels of C1EI is the most challenging to diagnose. This condition results in increased bradykinin production owing to several multiple genetic sources leading to increased bradykinin production, including mutations of FXII, plasminogen, and angiopoetin-1 genes. These forms of HAE are separate from isolated HAE, which is typically caused

Classification of angioedema

Bradykinin-induced AE				Mast cell mediator-induced AE		Unknown mediator
C1-INH deficiency/ defect		C1-INH normal		IgE-mediated	non-IgE-mediated	Idiopathic AE
Inherited Acquired	Acquired	Inherited	Acquired			
HAE-1 HAE-2	AAE-C1-INH	HAE-n-INH (HAE-FXII, HAE-PLG, HAE-KNG1, HAE-HS3ST6, HAE-ANGPTI+, HAE-MYOF+, HAF-UNK)	ACIE-AE other drug-induced AE*	Angioedema with anaphylaxis Angioedema with or without wheals (Urticaria)	Unknown mediator Idiopathic AE Angioedema with or without wheals (Urticaria)	

Table 1. *Note: HAE-1: hereditary angioedema due to C1-inhibitor deficiency; HAE-2: hereditary angioedems due to C1-inhibitor dysfunction: AAE-C1-INH: acquired angioedema due to C1-inhibitor deficiency: HAF-C1-INH: hereditary angioedema with normal C1-Inhibitor levels, either due to a mutation in FXII(Factor 121, ANGPT1 (angiopoietin-1), PLG (plasminogen), KNG1 Ikininagen), MYOF (myoferlin) and HS3ST6 (heparan sulfate-glucosamine 3-0-sulfotransferase 6) or unknown (UNK) HAE-ANGPT1 and HAE-MYOF are due to mutations involving the vascular endothelium and the role of bradykinin as mediator of angioedema symptoms seems to be an indirect or conditional one. ACEI-AE angiotensin-converting enzyme inhibito-induced angioedema, *other drugs like angiotensin receptor blockers, gliptins, neprilysin inhibitors or tissue plasminogen activators are thought to potentially induce bradykinin-mediated AE; Adapted from Maurer, M et al, 2022*

by a deficiency or dysfunction in C1-INH. Genetic testing is essential to evaluate HAE with normal levels of C1EI. Historically, exogenous hormonal therapy (oral contraceptives and hormonal therapy during pregnancy) appeared to be associated with this condition. This is a unique gender specific issue for females with HAE. Men with HAE disproportionately present with acquired HAE due to exogenous angiotensin converting enzyme inhibitor induced HAE compared with women.[10]

HAE treatment has revolved around three scenarios in bradykinin control : (1) PRN or "on demand" therapy (2) short-term prophylaxis in situations that may increase the risk of an HAE flare, and (3) long-term prophylaxis (LTP).The decision for treatment is individualized and based on the severity and frequency of disease. For many years, treatment was limited to fresh frozen plasma (FFP) replacing C1EI levels via infusions.Other options included oral hormonal or anti-clotting therapy. The therapeutic options have changed significantly, to include replacement C1EI enzyme therapy, and targeted therapy to block bradykinin receptors.

The World Allergy Organization (WAO) guidelines[11] on evidence-based treatment for, "on-demand" acute therapy, requires treatment with any of the following (a) exogenous intravenous plasma derived (pd) C1-INH (Berinert or Cinryze) or recombinant human (rh) C1-INH (Ruconest) to replace absolute C1-INH levels or to augment their function, (b) bradykinin B2 receptor inhibitor (icatibant) or (c) either solvent-detergent treated plasma or FFP. Regarding C1-INH replacement, 1 unit of replacement corresponds to 1 mL of FFP. Each of the above on-demand therapies should be accessible for two units of treatment[11] to account for the possibility of life-threatening needs. Medications that block histamine release, including antihistamines and epinephrine, along with tranexamic acid and androgens[12] should be avoided.

Short-term prophylaxis therapy in HAE, otherwise known as "situational prophylaxis," is indicated for prevention of HAE exacerbations due to medical or surgical procedures. The preferred treatment is plasma derived CI-INH with parenteral dosing of 1000 units or 20 units/kg for pd C1-INH or rh-C1-INH.[13] C1-INH is preferred over treatment with attenuated androgens and is recommended by the WAO 2021 guidelines.[11]

Over regarding scenario 3, over the last few years research has yielded increased options for outpatient management of HAE for LTP. The decision to initiate LTP treatment is based on an overall assessment of frequency of attacks, impact on quality of life, and the goal of normalization of life resulting in near and complete control of type 1 and type 2 HAE.[14] With the knowledge that HAE activity often increases with age, a discussion on ideal LTP management should occur on a yearly basis between the patient and physician. Options are now available for both subcutaneous and oral therapies covering different mechanisms involved in in the prevention of HAE attacks.[15-17]

C1-INH remains the therapeutic intervention with the longest history of use for LTP in HAE patients. Historically available only by the intravenous (IV) route, subcutaneous pdC1-INH (Haegarda®, CSL) is now available for twice weekly injection, and is preferred over IV dosing for more favourable steady state levels of C1-INH.[18] In the COMPACT trial, dosing at 60 units/kg resulted in a tenfold drop in HAE attacks with minimal adverse effects.[19] Subcutaneous injections of pdC1-INH (Haegarda®, CSL) provide superior convenience compared with the IV formulation and often provide quick relief from disease within 2 weeks.[19] Haegarda® may be stored at room temperature.

Lanadelumab (Takhzyro®) is a subcutaneous fully human plasma kallikrein inhibitor, now also indicated for LTP as first line use. It is administered through a subcutaneous injection of 300 mg every 2 weeks, or at a dose of 300 mg every 4 weeks if the patient is well controlled. It has received a strong recommendation with an evidence level of Grade A for use in LTP management in patients with HAE types 1 and 2.[11] Lanadelumab is best suited for LTP prophylaxis owing to its long time of 70 days to reach a steady state. It may be used in patients from ≥ 12 years of age.

A breakthrough in the LTP of HAE types 1and 2 was achieved with the formulation and clinical trials of an oral kallikrein inhibitor known as berotralstat. This inhibitor binds to kallikrein and inhibits its proteolytic activity, thereby reducing the production of bradykinin.[20] Berotralstat, was officially studied in the Angioedema Prophylaxis Trial 1 (APeX-1).[21] This phase 2 trial was a double blinded randomized placebo-controlled dose response trial that aimed to identify effective dosing ranges to reduce HAE attacks, while following pharmacokinetics, pharmacodynamics, and safety/adverse reactions. Inclusion criteria required patients having a minimum of 2 attacks per month, for 3 consecutive months over a 6-month period.

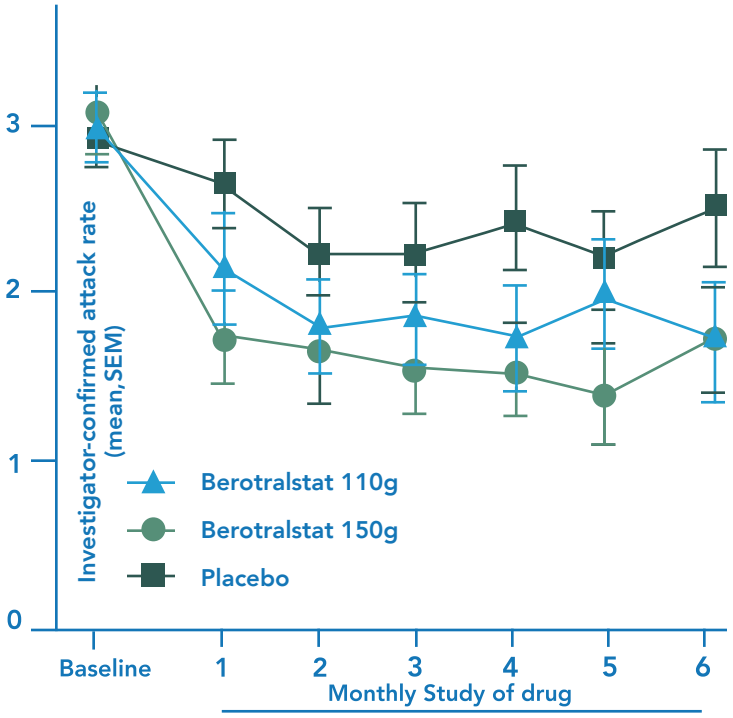
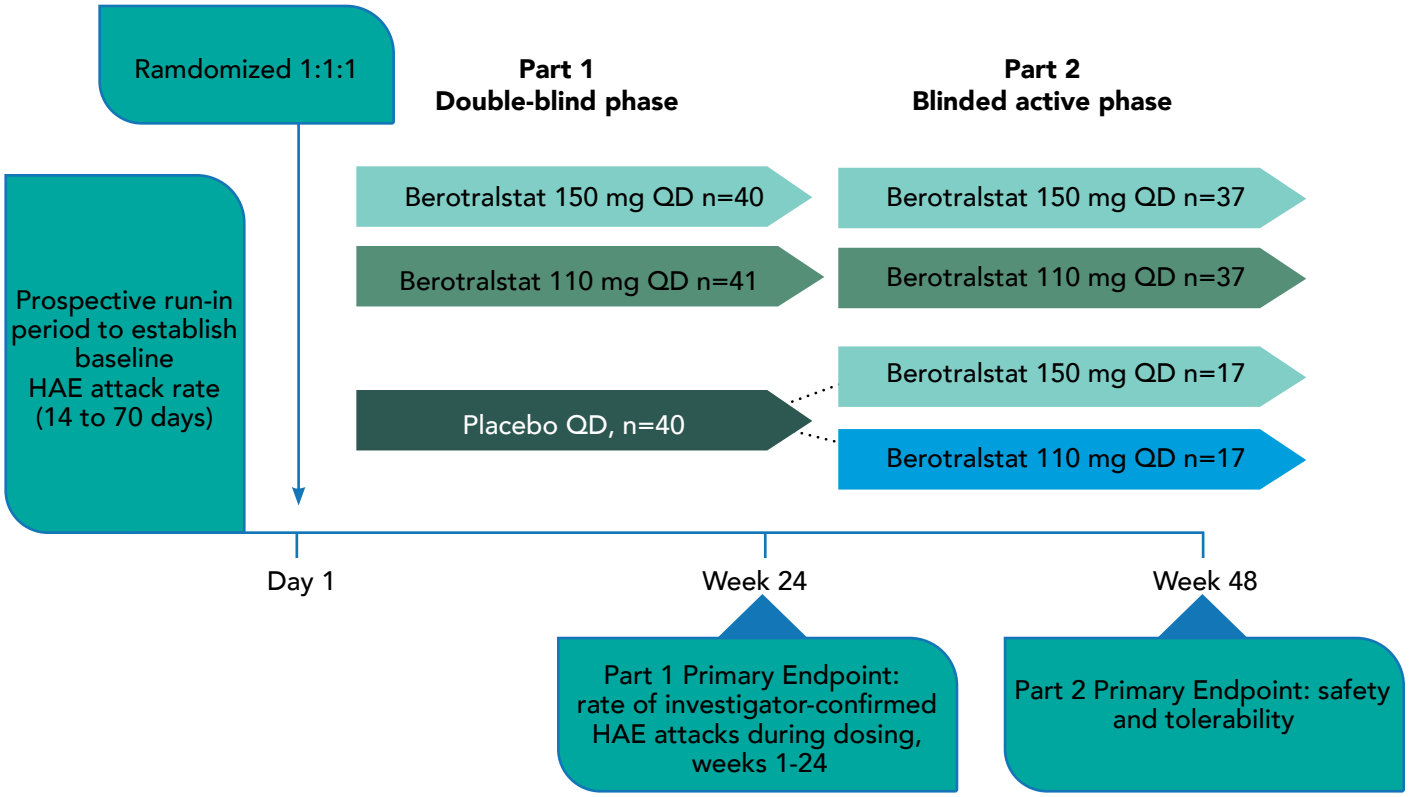


Figure 2. *Mean investigator-confirmed attack rate by month in the intent to treat population; Adapted from Wedner, H. James et al, 2021*

The primary endpoints was the number of HAE attacks in 1 month along with secondary endpoints related to anatomical location of attacks and quality of life scores (QOL). The study demonstrated that oral berotralstat at a dose of 125 mg once daily reduced attacks of HAE by 74% over 4 weeks.[20] Higher dosing resulted in a decreased efficacy in reducing HAE attacks. Peak drug levels were recorded 4 hours post ingestion. Grade 1 gastrointestinal adverse effects were identified in 75% of the patients, i.e., gastrointestinal pain and nausea. Overall, berotralstat was well tolerated with dose dependent gastrointestinal adverse events.

In the phase 3, APeX-2 trial, berotralstat was studied for 24 weeks in HAE 1 and 2. HAE patients ≥ 12 years of age. were randomized 1:1:1 to placebo, 110 mg and 150 mg oral once daily therapy.[22] A total of 40 patients were assigned to each group. Inclusion in APeX-2 required that patients had experienced at least 2 HAE episodes over a 2-month period. The primary outcome was investigator documented HAE episodes over a 24-week period. In this APeX-2 trial, the higher dose of berotralstat (150 mg, once daily) was found to be both superior and effective in reducing HAE attacks to 1.3 attacks per month ($p<0.001$) **(Figure 2)**. Side effects were similar to those reported in the APeX-1 trial and were mainly gastrointestinal in origin with no severe adverse effects noted.



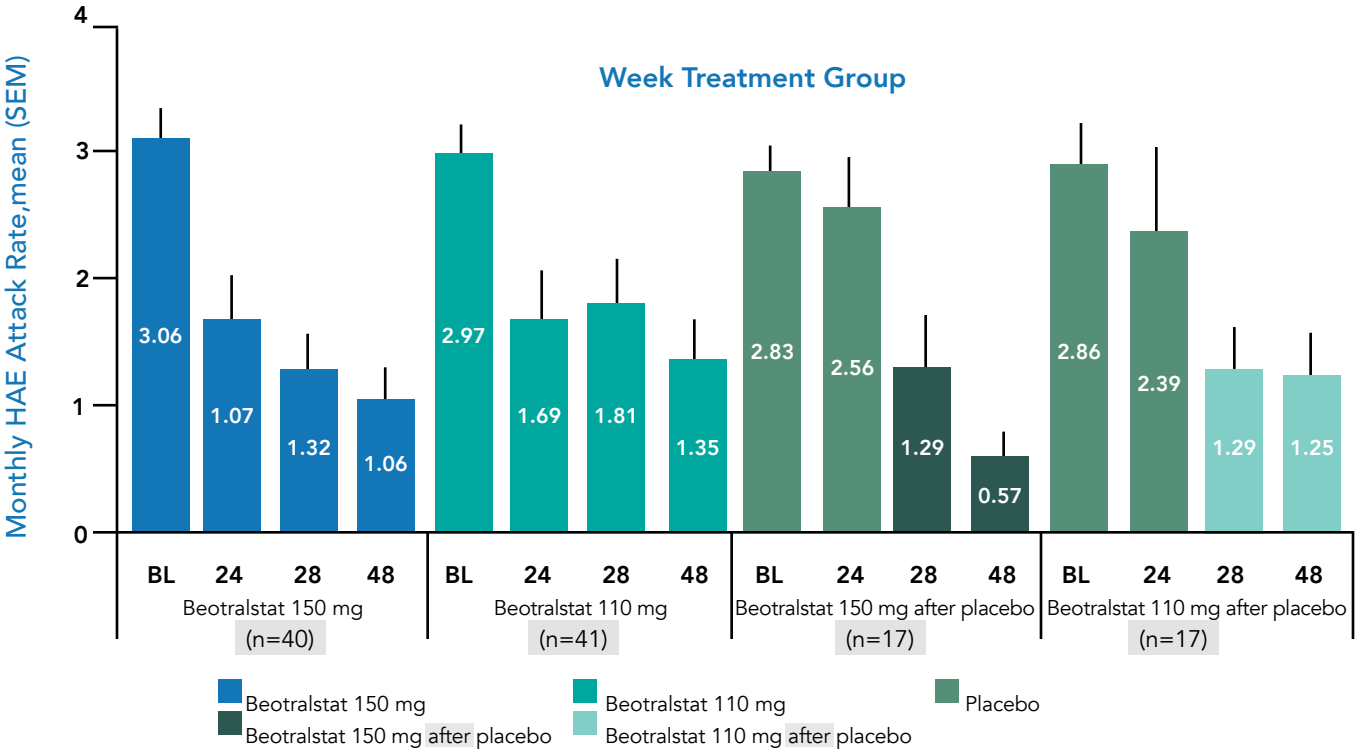
(Figure 3). APEX-2 study design. QD, Every day; *Adapted from Wedner, H. James et al, 2021*

Part 2 of the phase 3 APeX-2 trial was a longer (48 weeks) open label extension of once daily oral berotralstat therapy. In this trial, the HAE 1/2 patients who were randomized to receive placebo in Part 1 of APeX-2, were re-randomized to either receive berotralstat 110 mg or 150 mg once daily. The patients who received either 110 mg or 150 mg berotralstat in Part 1 of APeX-2 were monitored further for 24 weeks to evaluate both safety and tolerability.[22] **Figure 3** illustrates the study design of Parts 1 and 2 of the APeX-2 trial.

For HAE patients who transitioned from placebo to active drug, safety data for nearly 1 year identified a similar rate of mild adverse gastrointestinal side effects and no increase of concern for safety or tolerability in the groups receiving 48 weeks of either 110 or 150 mg once daily berotralstat. The majority of adverse drug reactions were either Grade 1 or 2, and consisted of gastrointestinal symptoms including nausea, abdominal pain, and altered stool patterns, along with reports of upper respiratory infections. The 150 mg berotralstat group had the fewest recorded severe adverse effects (3), with reports of anal incontinence, chest, and back pain. Rates of HAE attacks declined further among patients in the 110 mg and 150 mg berotralstat groups from Part 1 to Part 2 of the APeX-2 trial, with the greatest reduction of HAE attacks in the 150 mg berotralstat group **(Figure 4)**. The data supports the durability of response to berotralstat therapy with a parallel improvement in the patients' quality of life scores.

It is important to note that until this APeX-2 extension study, prophylactic treatments for patients with HAE were all parenteral and required management of parenteral therapy, i.e., administration, access, and disposal of needle-based devices. The transition to oral therapy with berotralstat is an effective long term prophylactic therapy that has single handedly changed patient attitudes because of its simplicity of administration, yielding less trauma for HAE patients.[23]

Safety and tolerability of berotralstat (Orladeyo®) was further investigated with the open label extension study APeX-S, with interim analysis collected through August 2019.[24] Both berotralstat 150 mg and 110 mg once daily dosing cohorts were followed over 48 weeks. Treatment related adverse effects occurred in 91% of patients, mainly low grade events, consisting of upper respiratory infections or gastrointestinal related symptoms. It was noted in the APeX-S trial that patients' early discontinuation of berotralstat due to GI side effects occurred within the first month of treatment, helping identify these patients early. HAE attack rates in both berotralstat 150 mg and 110 mg groups had significantly reduced to 0.8 attacks/month, suggesting



(Figure 4). *Mean (standard error of the mean [SEM]) investigator-confirmed HAE monthly attack rates at baseline (BL), 24 weeks, 28 weeks, and 48 weeks by treatment arm. Intention to treat (ITT) population. Error bars represent the SEM. Attack rates are for the 4 weeks preceding each visit; Adapted from Wedner, H. James et al, 202*

continued improvement. Despite berotralstat's efficacy and safety, a group of patients withdrew from the trial (12 % due to perceived lack of efficacy and 8% due to lab abnormalities). The clinician is urged to follow HAE patients on berotralstat to ensure that adverse effects are not encountered and that adherence is maintained. Perception of HAE control requires close monitoring in this population to ensure that attack rates are closest to 0 as possible. HAE patient subgroups, depending on genetic abnormalities and mechanistic resistance to the effect of kallikrein inhibition, may respond differently.

For the clinician involved in the management of HAE, there have been significant advances in the last decade in treatment strategies beyond replacement C1-INH therapy. The discoveries in kallikrein inhibition and blockade of bradykinin have offered new options in the management of genetic defects underlying both types 1 and 2 HAE. The discovery of a novel oral kallikrein inhibitor, berotralstat offers options for HAE patients seeking alternatives to parenteral therapy. The APeX trials have demonstrated the efficacy and safety of single dose once daily oral berotralstat for LTP to help our patients gain control of HAE attacks and improve their overall quality of life.

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SPECIAL SUPPLEMENT

BEROTRALSTAT: A DATA REVIEW OF A NOVEL ORAL MEDICATION FOR THE TREATMENT OF HEREDITARY ANGIOEDEMA

Jason Ohayon, MD