Oral plasma kallikrein inhibitor BCX7353 for treatment of hereditary angioedema

Jacqueline R Hwang¹, Gloria Hwang², Ansh Johri² & Timothy Craig^{*,3}

¹University of Maryland School of Medicine, Baltimore, MD 21201, USA

²Pennsylvania State University College of Medicine, Hershey, PA 17033, USA

³Department of Medicine & Pediatrics, College of Medicine, Allergy, Asthma & Immunology, Pennsylvania State University, Hershey, PA 17033, USA

*Author for correspondence: Tel.: +1 717 531 6525; tcraig@pennstatehealth.psu.edu

Hereditary angioedema (HAE) is rare disorder caused by a *SERPING1* gene mutation that triggers severe swelling of the skin and upper airway. Treatment options for HAE with deficient and dysfunctional C1-inhibitor are expanding to include small-molecule drugs that inhibit protein interactions in the kallikrein-kinin system. Discovered by BioCryst Pharmaceuticals, BCX7353 is a synthetic, once-daily, small molecule drug that can be taken as an oral capsule to treat HAE attacks and for prophylaxis. This article will summarize recent and current BCX7353 clinical trials. Overall, results indicate BCX7353 is a promising form of therapy with a rapid 1 h onset of action, long duration of action, and acceptable tolerance.

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Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder caused by mutations in the *SERPING1* gene that trigger severe swelling of the skin, gastrointestinal tract, upper airway and extremities. Symptoms include pain, nausea, diarrhea, vomiting and difficulty breathing due to airway swelling, which can be fatal if left untreated. The onset of HAE most commonly occurs during childhood or adolescence and continues throughout life with attacks as often as every 1–2 weeks lasting 2–4 days [1]. Such recurrent and debilitating attacks warrant investigation of drugs that can be used to prevent and manage HAE.

The *SERPING1* gene is responsible for making C1 inhibitor protein, a serine protease inhibitor that inhibits the kallikrein–kinin pathway, which controls production of bradykinin and the resultant vascular permeability and swelling [2]. With dysregulation of the kallikrein–kinin system, there is over production of bradykinin. There are three types of HAE. Type I HAE (C1 inhibitor deficiency) and type II HAE (C1 inhibitor dysfunction) are characterized by abnormal C1 inhibitor levels or function and account for 85 and 15% of cases, respectively [1]. Previously called type III HAE, now referred to as HAE with normal C1-inhibitor, is characterized by normal C1 inhibitor levels and accounts for <1% of cases and has not been included in the BCX7353 studies [3]. BCX7353 has not yet been tested in patients with type III HAE.

There are two main approaches to manage HAE: treatment of sudden acute attacks and prevention of future attacks [4]. Attacks can be treated using C1 inhibitor protein (human derived or recombinant), kallikrein inhibitors (ecallantide) and bradykinin B2 receptor antagonists (icatibant) [5]. However, these treatment options must be administered via injection or infusion, placing a therapeutic burden on a patient's quality of life [9]. Human derived and recombinant C1-inhibitors require intravenous injections, while ecallantide and icatibant are delivered subcutaneously [10]. Adverse side effects include hypersensitivity reactions and anaphylaxis for ecallantide and a painful burning sensation at the injection site for icatibant [6]. Currently, recombinant C1 inhibitor concentrate is only approved for treatment of attacks, but has been used off label for prophylaxis [6].

Oral prophylaxis medications include long-term androgen therapy (danazol) or antifibrinolytics (ε-aminocaproic acid and tranexamic acid) [7]. Although androgen therapy effectively decreases the number of HAE attacks in both males and females, it cannot be used to treat children and pregnant women due to risks of hypogonadism and abnormal sexual development [8]. Other harmful side effects include hypertension, hepatotoxicity, hyperlipidemia

and increased risk of hepatocellular adenoma or carcinoma; these adverse effects have caused 25% of patients in prior studies to discontinue treatment [9]. Antifibrinolytics are not recommended for use due to poor efficacy and potential thrombotic and neurotoxic effects.

The two most recently approved medications, subcutaneous C1-inhibitor (Haegarda®) and lanadelumab (Takhzyro®) are administered via subcutaneous injection. Both medications are highly efficacious, with an 85% reduction in the number of reported HAE attacks [11]. Lanadelumab is injected once every 2–4 weeks, while subcutaneous C1-inhibitor is injected once every 3–4 days. Subcutaneous C1-inhibitor is advantageous in that it has a 40-year history of safety, while lanadelumab's advantage is that the drug burden is much less [12].

Small molecule drugs (<900 Daltons) play important roles in select physiologic pathways by inhibiting proteins or blocking protein–protein binding [13]. In the form of natural metabolites or synthetic compounds, these molecules can be administered orally and are absorbed effectively through the enteral pathway. BCX7353 is a new, synthetic small molecule developed to inhibit plasma kallikrein and thus, bradykinin to prevent HAE attacks. Importantly, it does not inhibit tissue kallikrein. The drug, discovered by BioCryst Pharmaceuticals (NC, USA), is administered orally as once-daily capsules with minimal side effects [14]. BioCryst Pharmaceuticals has also named other drugs that are being studied for different therapeutic functions. BCX9930 is an oral Factor D inhibitor being studied to treat complement diseases, BCX9250 is another oral drug that inhibits ALK-2 to treat fibrodysplasia ossificans progressiva, and BCX4430 (galidesivir) is an intravenous antiviral for hemorrhagic fevers.

Angioedema Prophylaxis (APeX) studies have evaluated the safety, efficacy, pharmacokinetics and pharmacodynamics of BCX7353 in patients with HAE. To date, there has been successful completion of two Phase II clinical trials, APeX-1 and ZENITH-1. Ongoing studies, like APeX-2, APeX-S and APeX-J, will further test the safety and efficacy of BCX7353 while evaluating the long-term effects of the drug. The aim of this manuscript is to summarize published data on BCX7353.

Methods

We searched PubMed for BCX7353. We included all manuscripts published in English. We focused on the mechanism, drug development and different phases of research.

Results

The Angioedema Prophylaxis 1 (APeX-1) trial was a three-part, Phase II, double-blind, randomized trial (NCT02870972) conducted from 2016–2017 [15]. The goal of this study was to identify a safe and efficacious dose of BCX7353. Eligible subjects were required to have a documented rate of at least two attacks per month for three consecutive months and not be on any other preventative HAE medication. Out of a total of 77 subjects enrolled with type I or type II HAE, 55 patients were given a daily dose of oral BCX7353 (7 at 62.5 mg, 14 at 125 mg, 15 at 250 mg and 18 at 350 mg) and 23 were given a placebo for 28 days. During the trial, patients were routinely monitored and mandated to report the frequency and severity of their HAE attacks in paper diaries that were evaluated by a third-party group. Quality of life was also measured before and after treatment using the Angioedema Quality of Life Questionnaire (AE-QoL) [15].

Of the four experimental doses, the 125-mg dose proved to be most effective, reducing the number of peripheral (hands, arms, legs, feet or genitalia) and abdominal HAE attacks by 73.8% compared with the placebo group ($p < 0.001$) and resulted in 43% of attack-free HAE patients compared with 9% in the control group ($p = 0.033$). There were no severe side effects reported at this dose, however, 29% of patients developed some mild gastrointestinal discomfort. Overall, patients reported a significant improvement in quality of life at the end of the treatment period, with AE-QoL scores averaging four-times higher than the minimum clinically important difference ($p < 0.001$) [15]. Within the 250- and 350-mg test groups, BCX7353 also decreased frequency of HAE attacks by 44.6 and 45.5%, respectively. However, gastrointestinal-related symptoms were more severe and common at 50 and 44%, respectively, and three patients who received the 350-mg dose discontinued the trial due to grade-3 gastrointestinal events [15].

Following the APeX-1 trial, BioCryst Pharmaceuticals organized another three-part, Phase II, double-blind, randomized clinical trial, referred to as ZENITH-1 (NCT03240133) [16]. The goals of this study were to determine if BCX7353 could effectively treat acute angioedema attacks and confirm a safe dose range to use in future Phase III trials. A total of 58 patients with type I or type II HAE were randomly divided into three BCX7353 dosing groups (11 were given 250 mg, 14 were given 500 mg and 33 were given 750 mg). The study was designed to allow patients to self-administer the drug in the convenience of their home within a 1 h onset of symptoms. Each patient was given blinded BCX7353 in a randomized sequence to treat three HAE attacks (two with the drug, one

with placebo). If needed, patients were still allowed to use their standard, pre-approved medication, but were asked to wait 4 h after the study dosing. Symptoms were quantified using Visual Analog Scale (VAS) scores and reported in patient diaries before dosing and at 1, 2, 3, 4, 8 and 24 h after drug administration [16].

Results showed a clear dose response in rapidly alleviating HAE symptoms and reducing the use of standard medication. The largest number of HAE attacks were treated in the 750-mg cohort, with 64 attacks, while 21 and 25 attacks were treated in the 250- and 500-mg groups, respectively. This was in comparison with the 11, 11 and 31 attacks treated with placebo. For the 750-mg cohort, compared with placebo, symptoms and VAS scores improved as quickly as 1-h postdose and lasted 24 h. At the 4-h time point, 67.7% of BCX7353-treated attacks were deemed stable by VAS scores compared with 46.7% of placebo-treated attacks ($p = 0.0387$). Use of standard rescue medication was reduced to 29.7% when treated with BCX7353 compared with 61.3% when treated with the placebo ($p = 0.0029$). All dose levels were generally well-tolerated with no or mild symptoms reported in 64.1% of BCX7353-treated attacks compared with 32.3% of placebo-treated attacks ($p = 0.0038$). There were no severe adverse events reported. In a news report, chief medical officer of BioCryst Pharmaceuticals, Dr William Sheridan, commented on the results of ZENITH-1 highlighting the quick 1 h onset of action, the long 24-h duration after a single dose of BCX7353, as well as the range of efficacious dosages [17].

A Phase III, randomized, double-blind, APeX-2 trial (NCT03485911) was conducted to determine the optimal dosing of BCX7353 for HAE prophylaxis treatment [18]. This trial compares two doses of BCX7353 at 110 and 150 mg specifically used for prophylaxis. In order for patients to qualify for this study, a number of documented HAE attacks were required over a run-in period of 56 days. The average baseline attack rate was 3 per 28 days. Of the 121 patients enrolled, 41 were given 110 mg of BCX7353, 40 were given 150 mg of BCX7353 and 40 were given a placebo for 48 weeks. After the first 24 weeks, patients in the placebo group were re-randomized into the 110 or 150-mg group until completion of the 48-week study.

Results from the first 24 weeks of the study showed that patients receiving the 110-mg dose had 30% fewer HAE attacks compared with the placebo group ($p = 0.024$). Those receiving the 150-mg dose had 44% fewer attacks compared with the placebo group ($p < 0.001$). Overall, the 150-mg dose was more efficacious than the 110-mg dose. Compared with each patient's baseline attack rate, 50% of patients in the 150 mg group had a 70% or higher reduction in the number of attacks per month, versus 15% in the placebo group ($p = 0.002$). There were no reported serious adverse side effects and both doses were well-tolerated. Less than 10% of patients reported minor side effects of nausea, dyspepsia and diarrhea [17].

APeX-S (NCT03472040) is a long-term safety study of BCX7353 being conducted simultaneously with the APeX-2 study to evaluate the long-term effects of the 110- and 150-mg doses over a 48-week period [19]. The trial is an open label study with 160 type I and II HAE patients enrolled. Patients who have participated in previous clinical trials of BCX7353 were given priority for recruitment, followed by those who have never been administered the drug. Jon Stonehouse, chief executive officer, reported that the oral form of BCX7353 is 'eliminating (patients') current injection-based treatment programs'. Principal investigator of the APeX-S trial, Dr. Henriette Farkas, also emphasized the 'convenient, easy-to-administer, oral remedy, developed on purpose for the prophylaxis of angioedema attacks' [19].

In Japan, a Phase III, randomized, double-blind, APeX-J trial (NCT03873116) is being conducted in a similar manner to the APeX-2 study being done in the USA, Canada and Europe [20]. The trial is structured to test the 110- and 150-mg dose in 24 Japanese HAE patients over a 24-week duration with a 28-week safety extension. Patients' vital signs, liver enzyme levels and plasma levels of antidrug antibodies will be closely monitored along with the frequency of HAE attacks and changes in quality of life. This study expands HAE treatment through readily available, safe, convenient therapeutic trials for HAE patients across the globe. In 2015, BCX7353 was one of the first therapies given Sakigake designation by the Japanese Pharmaceuticals and Medical Devices Agency [21]. Along with an expedited review of the drug by the Japanese NDA and scientific support, the Sakigake designation recognizes BCX7353 as a promising, revolutionizing therapy for HAE.

Discussion

While there are effective and safe HAE medications available across Western Europe and North America, most of them are administered through injections (with the exception of androgens and antifibrinolytics). For a disease as chronic and unpredictable as HAE, oral medication may greatly improve the quality of life for patients by lowering the risk of drug burden, being more environmentally sustainable and decreasing stress in the 25% of Americans who are needle phobic [22]. In addition, a recent survey by Jose *et al.* concluded that HAE patients want an oral

Table 1. Comparison of the study designs of BCX7353 Phase II and III trials.

Study	APeX-1	ZENITH-1	APeX-2	APeX-S	APeX-J
Length of study	August 2016–August 2017	July 2017–December 2018	February 2018–October 2020	February 2018–February 2021	February 2019–May 2020
Patient count	77	58	121	160	24
Regions	Europe, Canada and Australia	Europe and Israel	USA, Canada and Europe	Europe, Australia, Hong Kong, Israel, Korea, New Zealand, Serbia and South Africa	Japan
HAE attacks	Prophylaxis	Treatment	Prophylaxis	Prophylaxis	Prophylaxis
Formulation of BCX7353	Oral	Liquid	Oral	Oral	Oral
Dosing	62.5 mg, 125 mg, 250 mg, 350 mg	250 mg, 500 mg, 750 mg	110 mg, 150 mg	110 mg, 150 mg	110 mg, 150 mg
Adverse effects	Little to none, mild GI discomfort, common cold, diarrhea, nausea and headache	No severe adverse events reported	Less than 10% of patients reported nausea, dyspepsia and diarrhea	Not released	Not released

APeX: Angioedema prophylaxis; HAE: Hereditary angioedema.

medication, proving that there is a demand [23]. The shift from injectable medicine to oral medicine has already revolutionized the way we treat diseases such as migraine headaches, arthritis and diabetes [23].

The cost to make simple drugs such as BCX7353 as compared with the more elaborate process to produce monoclonal, plasma and recombinant products is a definite advantage. Future studies are needed to compare and reveal the efficacy of BCX7353 and other medications that may appear to have greater efficacy considering the affordability of BCX7353. APeX-1 Phase II reported the oral, once-daily 125-mg dose of BCX7353 to present the highest efficacy [15]. The higher doses (250 and 350 mg) were associated with more gastrointestinal adverse effects, indicating increased toxicity at higher levels [24,25]. It is assumed that the intestinal adverse effects were interpreted by subjects as early symptoms of a HAE attack, which resulted in decrease efficacy of the higher doses compared with the 125-mg dose. The lowest dose (62.5 mg) was not as effective as the 125-mg dose and did not show significant differences in angioedema attack rates compared with placebo [26]. In APeX-2, there were no reported serious adverse side effects and both doses were well-tolerated. Less than 10% of patients reported minor side effects of nausea, dyspepsia and diarrhea (Table 1) [17,18].

The adverse effects of injectable and intravenous HAE medications may present difficulties for patients that can be avoided in those taking oral BCX7353 medication. A large proportion of patients in the lanadelumab, subcutaneous C1-inhibitor, icatibant and intravenous C1-inhibitor therapy trials experienced local adverse effects pertaining to the injection site. With intravenous drugs the scarring of veins, difficulty in injecting in obese patients and small risk of infection all add to the drug burden. In addition, intravenous and subcutaneous C1-inhibitor require administration every 3–4 days. With the once-daily oral form of BCX7353, injection site pain and other side effects may be successfully avoided. Administration of BCX7353 for a duration of 28 days was found to be safe and well tolerable in HAE patients. Common side effects included the common cold, diarrhea, nausea, headache and abdominal pain, which were minimally reported in the 125- and 62.5-mg dose groups. Furthermore, patient compliance throughout the 28-day duration with daily dosing was reported as greater or equal to 98% for all treatment groups. The AE-QoL component of the study revealed improved daily functions of life, mood, emotional health and food intake [24,25]. In addition, the long half-life of BCX353 when used for on-demand therapy, as compared with other rescue medications, such as icatibant, should decrease the rebound that often occurs with the use of short acting on-demand therapies.

At last, three other oral medications are in development suggesting that the future of HAE treatment will be in the form of a pill. It is premature to predict how many of these therapies will be approved, but if appears, BCX7353 may be the first oral therapy to prevent and treat attacks of HAE.

Summary

BCX7353 is a promising therapy for prophylaxis and treatment of HAE attacks. It appears the balance between side effects and efficacy favors the 150-mg dose for prophylaxis of HAE. BCX7353 has a rapid 1 h onset of

action, long duration of 24 h and few adverse events thus appropriate for prophylaxis. The use of BCX7353 as a rescue medication for treatment of HAE attacks is interesting and we are hoping for preliminary data soon. While BCX7353 appears safe and effective, further research is needed to determine the long-term safety and pharmacodynamics of the drug.

Executive summary

- Hereditary angioedema (HAE) with deficient and dysfunctional C1-inhibitor (type 1 and 2) is a rare genetic disorder caused by mutations in the *SERPING1* gene that leads to decreased functional levels of C1-inhibitor and over production of bradykinin that triggers severe swelling of the skin, gastrointestinal tract and upper airway [1].
- There are two main approaches to managing HAE: treatment of sudden attacks (on demand therapy) and prevention of future attacks (prophylaxis) [4].
- BCX7353 is a new, synthetic, small-molecule drug administered orally as once-daily capsules to inhibit plasma kallikrein activation and thus production of bradykinin to prevent HAE attacks [14].
- Multiple Angioedema Prophylaxis (APeX) studies have evaluated the safety, efficacy, pharmacokinetics and pharmacodynamics of BCX7353 in patients with HAE through successful completion of two Phase II clinical trials, APeX-1 and ZENITH-1.
- Ongoing studies, APeX-2, APeX-S and APeX-J, will further test the safety and efficacy of BCX7353 while evaluating the long-term effects of the drug.

Results

- The Angioedema Prophylaxis 1 (APeX-1) trial identified a safe and efficacious dose level of BCX7353 to be 125 mg, which effectively reduced the number of peripheral and abdominal HAE attacks by 73.8% compared with the placebo group ($p < 0.001$) and resulted in leaving 43% of HAE patients attack-free compared with 9% in the control group ($p = 0.033$) [15].
- The ZENITH-1 assessed BCX7353 effectiveness to treat acute attacks and showed the 750-mg cohort, when compared with placebo, reduced symptoms as quickly as 1 h (measured by a Visual Analog Scale) [16].
- In the Phase III APeX-2 Trial, the 150-mg dose was more efficacious than the 110-mg dose with 44 versus 30% fewer attacks compared with placebo in each of the respective doses with less than 10% of patients reporting minor side effects of nausea, dyspepsia and diarrhea [18].
- APeX-S is a long-term safety study of BCX7353 being conducted simultaneously with the APeX-2 study to evaluate the safety and long-term effects of the 110- and 150-mg doses over a 48-week period [19].
- In Japan, a Phase III, randomized, double-blind, APeX-J trial is being conducted similarly to the APeX-2 study being done in the USA, Canada and Europe and is structured to test the 110 and 150-mg dose in 24 Japanese HAE patients over a 24-week duration with a 28-week safety extension [20].

Discussion

- Oral medications greatly benefit quality of life for patients by lowering drug burden of injections, being more environmentally sustainable and benefitting the 25% of Americans who are needle phobic [22].
- Patient compliance throughout the 28 days administration of BCX7353 with daily dosing was reported as greater or equal to 98% for all treatment groups with AE-QoL revealing improved daily functions of life, mood, emotional health and food intake [24,25].
- APeX-1 Phase II reported the oral, once-daily 125-mg dose of BCX7353 to present the highest efficacy among the higher doses of 250 and 350 mg [15].
- Existing data on on-demand use of BCX7353 are limited making discussion for this purpose difficult.

Financial & competing interests disclosure

Conflict of interests: Only Timothy Craig has conflicts. He does research for CSL Behring, Takeda and BioCryst Pharmaceuticals. He speaks for CSL Behring, Takeda and Pharming. He consults with CSL Behring, Takeda, Pharming, Grifols and BioCryst Pharmaceuticals. No funding was required for the development of this manuscript and the manuscript was developed independently from the manufacturer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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