

REVIEW

Breakthroughs in hereditary angioedema management: a systematic review of approved drugs and those under research

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Abstract

Hereditary angioedema (HAE) is a rare genetic disorder, characterized by recurrent and unexpected potentially life-threatening mucosal swelling. The impairment underlying HAE could be a defect in C1-inhibitor activity, or in its serum concentration. Patients affected by HAE should be treated with on-demand or prophylactic drugs. Lifelong C1-inhibitor supplementation is sometimes required. In this review, we review the currently approved drugs for HAE due to C1-inhibitor defect and to describe those under research. In particular, we focused on the mechanisms of action, routes of administration, and efficacy of these therapies. A systematic review of the literature was performed using the PubMed database for original articles and clinical trials of HAE treatments from 2005 to 2019. The approved HAE

treatments can minimize the risk of death, but they are not effective in complete healing from the disease. The new gene therapies seem to provide promising opportunities for the treatment of hereditary angioedema. However, there are still many unmet needs, including efficacy, route, and timing of administration.

Keywords: C1-INH, C1-inhibitor, gene therapy, HAE, hereditary angioedema, lanadelumab, serine protease, SERPING1.

Citation

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Introduction

Hereditary angioedema (HAE), in its two main forms (types I and II), is due to the lack or dysfunction in the C1-inhibitor (C1-INH). However, in other phenotypes of HAE, C1-INH levels are normal, and the disease is called 'hereditary angioedema with normal C1-INH.' This effect is associated with specific genetic mutations: HAE caused by FXII gene mutations (HAE-FXII),¹ hereditary angioedema due to mutations in the plasminogen gene (HAE-PLG),² and HAE associated with angiotensin-converting enzyme 1 gene mutations (HAE-ANGPT1).³

The clinical features of HAE are recurrent and unpredictable spontaneous edema attacks. Traumas, infections, stress, or medical procedures are potential triggers for HAE attacks, although they are not always so clearly detectable. Occasionally, angioedema could be associated with prodromal signs, including erythema marginatum.⁴⁻⁶

Most mild angioedema attacks involve lips, eyelids, or peripheral limbs, and these attacks are self-limiting and rarely

harmful. In this case, swelling arises slowly, lasting 2–5 days, and then progressively disappearing, even without therapy.

However, in cases of larynx, tongue, or abdomen involvement, HAE attacks could potentially be life-threatening. The most serious and feared complication of a larynx HAE attack is choking due to the swelling and thickness of vocal cords. In addition, bowel angioedema attacks may occur as nausea, vomiting, or abdominal pain due to intestinal wall edema. These could mimic other diseases, such as acute appendicitis or a surgical abdomen, thus increasing the likelihood of misdiagnosis and unnecessary surgery.⁷

The dysregulation of bradykinin pathways is responsible for angioedema attack onset. Bradykinin is, in fact, generated by the kallikrein-kinin system, and it usually binds to the bradykinin B2 receptors on endothelial cells. The C1-INH is a serine protease, the primary role of which is protease inhibition, including kallikrein.⁸ In the case of C1-INH dysfunction or deficiency, bradykinin production is not inhibited, with consequent vascular permeability increase and angioedema

swelling.⁹ The C1-INH protein is encoded by the serpin peptidase inhibitor clade G member 1 (SERPING1) gene on chromosome 11q12-q13.1.¹⁰

Due to the rarity of the disease and frequent misdiagnosis (i.e., histamine-mediated angioedema, angiotensin-converting enzyme inhibitor angioedema, etc.),¹¹ the delay in HAE diagnosis could be up to 20 years.¹² This delay causes a significant economic and psychological burden for both healthcare associations and affected patients.¹³

The proper and quick identification of the disease is increasingly important, as the treatment of the attacks and their prevention is possible due to the currently available drugs. These drugs can, in fact, improve the patient quality of life by reducing the number and severity of HAE attacks.

Many different approaches for HAE treatment are now available, and many are in the pipeline. This review aims to provide an overview of the newly approved drugs for HAE treatment in Europe, focusing on new approaches, including biologics and gene therapies.

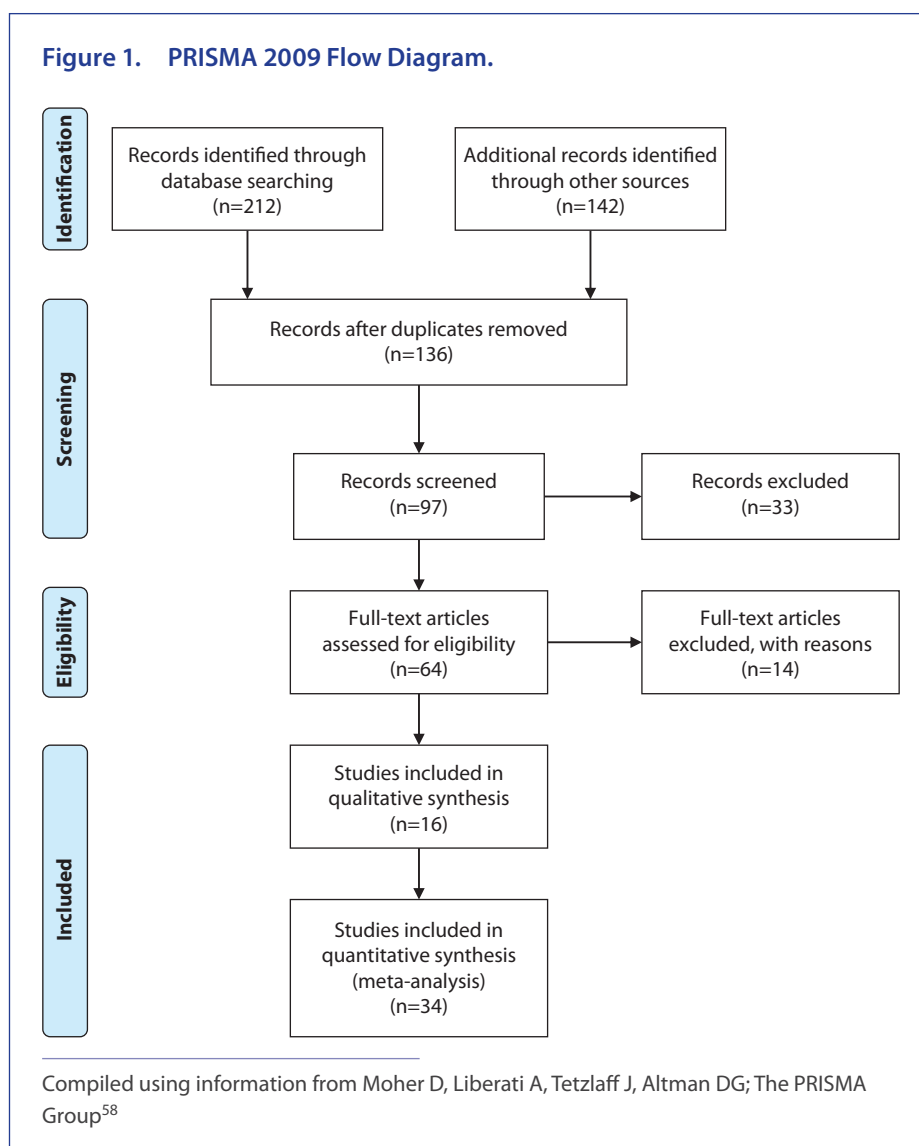
Materials and methods

Database and key words (MeSH)

A systematic review of the literature was performed, according to the PRISMA statement, by using the PubMed database for original articles and clinical trials of HAE treatments from January 2005 to August 2019 (Figure 1).

The following keywords alone and/or in combination were used: 'Hereditary angioedema treatment,' 'HAE and C1-INH management,' 'HAE and FXII management,' 'HAE and treatment,' 'HAE and biologics,' 'HAE and gene therapy,' 'HAE and molecular approach,' 'HAE and trials,' 'HAE and new therapies,' and 'HAE and management.'

In addition, reports coming from the website <https://clinicaltrials.gov> were evaluated, as well as notes released by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) concerning HAE treatment withdrawal or approval.



Selection criteria

We selected original articles and reviews assessing HAE-approved treatment and papers presenting preliminary data of phase 1, phase 2, or phase 3 clinical trials. In one case, we analyzed an *ex vivo* preliminary study on nonhuman primates.¹⁴

Data collection

Two researchers identified and selected the full-text papers. The selection was blind and completely independent of the two people. Discrepancies of the selected articles were resolved by consensus.

Therapeutic approved strategies for the management of HAE

Three different approaches are now available for HAE treatment, according to the frequency and severity of attacks.

Over the last few decades, FDA and EMA have approved new safe and effective drugs for hereditary angioedema treatment (Figure 2) (Table 1).

Most recent drugs (Tables 2 and 3) can improve therapeutic efficacy, presenting fewer adverse events than the oldest drugs. The high frequency of virilization and liver impairment caused by androgens and the infectious risk related to frozen plasma administration are widely known.¹⁵

Patients can now be treated either with an on-demand therapy, which is administered immediately after the onset of

swelling, or they might receive a short-term prophylaxis, used to prevent HAE attacks related to high-risk procedures (e.g., surgical or dental practices). A third option could be long-term prophylaxis, indicated in patients who cannot achieve disease control from on-demand treatment alone. The primary purpose of long-term prophylaxis is to decrease the overall number and severity of HAE attacks.^{16,17}

On-demand therapy

Traditional approved drugs

Beriner[®]

In 2009, the FDA approved Beriner[®] (CSL Behring), a pasteurized plasma-derived C1-INH concentrate, available for intravenous (IV) administration in patients needing on-demand therapy. This drug was not approved for short-term prophylaxis but is used off-label for this purpose. A randomized, double-blind, placebo-controlled (DBPC) study in 125 patients affected by type I or type II HAE, Beriner[®], at a dose of 20 U/kg, showed a significant reduction in the time to the relief of HAE symptom onset (30 *versus* 90 minutes; $p=0.003$) and a shortening in time to complete symptom resolution (294 *versus* 468 minutes; $p=0.02$) compared with the placebo.¹⁸ The proper dose of Beriner[®] for an HAE attack is 20 U/kg IV given at 4 mL/min. In terms of safety, no seroconversions were observed for HIV, hepatitis virus, or human B19 virus during the approval studies or in real-life experiences.¹⁹

Cinryze[®]

A second intravenously administered plasma-derived C1-INH concentrate, with the marketing name Cinryze[®] (Shire), has

Figure 2. Site of action of current and under research therapies for HAE treatment.

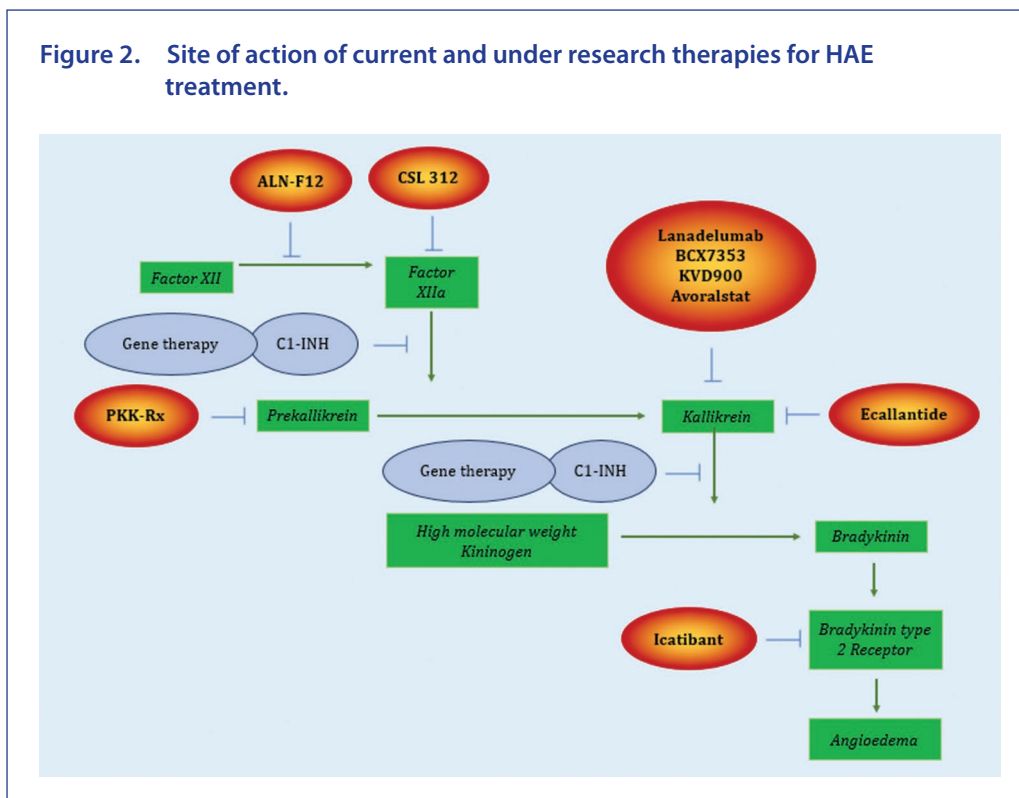


Table 1. Approved treatment options for C1-INH HAE.

Drug name	Active substance	Type and action	Administration	Indication	T1/2
Kalbitor®, Dyax Corp	Ecallantide	Kallikrein inhibitor	SC	On-demand treatment	2 hours
Firazyr®, Shire	Icatibant	Bradykinin B2 receptor antagonist	SC	On-demand treatment	2–4 hours
Ruconest®, Pharming	Conestat alfa	Recombinant C1 inhibitor from milk of transgenic rabbits	IV	On-demand treatment	3 hours
Berinert®, CSL Behring	C1-INH	Plasma-derived C1-INH concentrate pasteurized	IV	On-demand treatment, Short-term prophylaxis	36–48 hours
Cinryze®, Shire	C1-INH	Plasma-derived C1-INH concentrate nanofiltered	IV	Long-term prophylaxis	36–48 hours
Haegarda®, CSL Behring	C1-INH	Human plasma-derived concentrate of C1 esterase inhibitor	SC, IV	Long-term prophylaxis	69 hours (SC), 56 hours (IV)
Takzhzyro®, Shire	Lanadelumab	Recombinant, fully human IgG1 monoclonal antibody inhibitor of kallikrein	SC	Long-term prophylaxis	14 days

C1-INH, C1-inhibitor; HAE, hereditary angioedema; IV, intravenous; SC, subcutaneous.

been approved by EMA for on-demand HAE attack treatment, short-term and long-term prophylaxis (see later).²⁰

Firazyr®

Icatibant (Firazyr®, Shire) is a bradykinin B2 receptor antagonist approved by EMA in 2008 as an on-demand treatment for HAE attacks in adult patients. In a randomized, double-blind, placebo-controlled study, icatibant significantly reduced the median time in symptom severity reduction (120 *versus* 1188 minutes; $p=0.001$) and the onset of symptom relief (90 *versus* 1110 minutes; $p=0.001$) compared with the placebo.²¹ Icatibant is given as a subcutaneous injection of 30 mg (in 3 mL), repeatable after 6 hours (at most three injections in 24 hours).²²

Kalbitor®

Ecallantide (Kalbitor®, Shire) is a potent kallikrein inhibitor approved by the FDA for the treatment of HAE attacks in patients aged ≥ 12 years, administered as a 30-mg subcutaneous dose. However, this drug was withdrawn in November 2011 because of the Committee for Medicinal Products for Human Use (CHMP) opinion, as the benefits of Kalbitor® did not outweigh its risks.²³

Biologic approved drugs

Ruconest®

To reduce the potential risk of blood-borne infections due to plasma-derived C1-INH, in 2010, the EMA approved a new

recombinant C1 inhibitor (Ruconest®, Pharming Healthcare) for on-demand treatment of HAE attacks in adolescents (≥ 12 years) and adults. The active ingredient in Ruconest® is conestat alfa, which is a glycoprotein similar to the human C1-INH produced by recombinant DNA technology in a transgenic species of rabbits called New Zealand White (NZW) and then purified from their milk. Its amino acid sequence is an analogue of endogenous human C1 inhibitor, having a shorter half-life due to a different glycosylation pattern.^{24,25} In a pooled analysis of two different studies comparing conestat alfa with placebo, Zuraw and his research group reported a significantly shorter time in the beginning of symptom relief in the conestat alfa group. The median time in minutes was 66 minutes (Ruconest® 100 U/kg), 122 minutes (Ruconest® 50 U/kg) and 495 minutes (saline), $p<0.001$ and $p=0.013$, respectively, referred to each dose compared with placebo (saline).²⁶ Because of the potential of rabbit protein in the preparation, Ruconest® is contraindicated in patients with a history or a suspicion of rabbit hypersensitivity.²⁴

Long-term prophylaxis

Long-term prophylaxis should be considered in symptomatic patients despite an optimized on-demand treatment of angioedema attacks. In addition, the frequency of attacks, disease activity level, and patient quality of life should be taken into consideration.¹⁶

Table 2. Ongoing trials for C1-INH HAE treatments (from the EU Clinical Trials Register website).

Drug name	Active substance	Type and action	Administration	Indication	T 1/2
BCX7353 [®] , BioCryst Pharmaceuticals ⁵³	R)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride	Second-generation oral kallikrein inhibitor	PO	Long-term prophylaxis	50–60 hours
Berinert [®] , CSL Behring ⁵⁴	C1-INH	Plasma-derived C1-INH concentrate pasteurized	SC	Long-term prophylaxis	120

C1-INH, C1-inhibitor; HAE, hereditary angioedema; PO, orally administered; SC, subcutaneous.

The available treatments can be divided into two main groups: traditional approved drugs and new biologics. The former includes C1-nanofiltered inhibitor, widely described later, and attenuated androgens or antifibrinolytics, which, although commonly used in clinical practice, are not the purpose of this review. Among the new emerging biologics, lanadelumab is the first and the only biologic that has been approved by the EMA.

Traditional approved drugs

Cinryze[®]

In 2011, the EMA approved a new plasma-derived C1 inhibitor concentrate nanofiltered (Cinryze[®], Shire) for HAE management in adults. In 2016, the drug was also approved for treatment and pre-procedure prevention of HAE attacks in children from 2 years and as a routine prevention of angioedema attacks from 6 years.²⁰ Cinryze[®] is indicated as on-demand therapy, with a starting dose of 1000 Units IV as HAE arises, repeatable after 1 hour. In addition, the drug could be administered for short-term prevention of angioedema attacks, by giving 1000 U IV within 24 hours before the procedure. A third approved option is, finally, to use it as long-term prophylaxis, at the dose of 1000 U IV of Cinryze[®] every 3 or 4 days.²⁰

A randomized double-blind, placebo-controlled 12-week trial showed a significant reduction in the frequency of HAE in patients treated with twice weekly injections of 1000 U of Cinryze[®] versus placebo (6.3 attacks in the Cinryze[®] group versus 12.7 attacks in the placebo group; $p < 0.001$).²⁷

After marketing, several thrombotic events, thought to be secondary to the use of indwelling catheters rather than the drug, were reported, leading to a recommendation to avoid indwelling catheters for IV C1-INH prophylaxis.²⁸

Haegarda[®]

Haegarda[®] (CSL Behring) was approved by the FDA in 2017 as the first subcutaneous C1 inhibitor concentrate, also indicated for self-administration, at the dose of 60 IU/kg twice weekly. Nevertheless, the European Medicines Agency did not formally approve the marketing of the drug.²⁹

Table 3. Treatments for C1-INH HAE under research.

Drug product	Type
Gene therapy to correct C1 inhibitor deficiency ⁵⁵	Delivering an extrachromosomal copy of <i>SERPING1</i> by using an adeno-associated virus vector.
ALN-F12 [®] , Alnylam ⁵⁶	Inhibiting factor XII by using RNA interference to reduce its expression.
CSL312 [®] , CSL Behring ⁴⁵	Phase I trial for a human monoclonal antibody against factor 12.
KVD900 [®] , KalVista pharmaceutical ⁵¹	Phase I trial for an on-demand orally administered plasma kallikrein inhibitor.
IONIS-PKK [®] , Ionis Pharmaceuticals ⁴⁷	Completed phase I trial for an antisense oligonucleotide to reduce the production of prekallikrein.
ATN-249 [®] , Attune Pharmaceuticals ⁵⁷	Preclinical studies on monkeys for a new oral kallikrein inhibitor.
Avoralstat [®] , BioCryst Pharmaceuticals ⁵⁰	Phase 3 trial for a long-term prophylaxis orally administered small kallikrein inhibitor.

Biologic approved drugs

Takhzyro[®]

Lanadelumab (SHP643; previously DX-2930) is a fully human IgG1 monoclonal antibody that selectively inhibits plasma kallikrein,¹⁸ marketed by Takeda with the name Takhzyro[®]. This agent was approved in October 2015 by the EMA³⁰ as an orphan drug for prophylaxis in HAE attack prevention, available

for adult patients and adolescents aged ≥ 12 years. The half-life of the drug is indeed ≥ 2 weeks.³¹ The recommended dose is 300 mg every 2 weeks, which may be extended to every 4 weeks in well-controlled patients who did not complain of any attacks in the last 6 months.^{31,32} The Hereditary Angioedema Long-term Prophylaxis (HELP) Study™ was a multicentric, randomized, double-blind, placebo-controlled parallel group trial in 125 patients who are 12 years of age or older with HAE, over 26 weeks, that evaluated the efficacy and safety of subcutaneously administered lanadelumab (at the dose of 150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg every 2 weeks) *versus* placebo.³³ The primary endpoint measured the HAE attack incidence over 6 months (26 weeks), whereas the secondary endpoints evaluated how many attacks required an acute treatment and the number of attacks with severity that was moderate or severe. The three aforementioned doses of lanadelumab showed a significant superiority compared with the placebo for all primary and secondary endpoints ($p < 0.001$ for all comparisons). No severe treatment-emergent adverse events or deaths were reported.³³

Short-term prophylaxis

Short-term prophylaxis is administered with the aim of preventing HAE attacks in patients who need to undergo invasive procedures potentially acting as a trigger, such as dental care, surgery, endoscopic examinations, childbirth, and stressful situations.

Although the risk of potentially life-threatening invasive procedures is high, no controlled trials compared the efficacy of different approaches for short-term prophylaxis.

In 2017, the International World Allergy Organization, in cooperation with the European Academy of Allergy and Clinical Immunology (WAO/EAACI), released a new update of the HAE guidelines. In the revision, WAO/EAACI recommends a preprocedural C1-INH concentrate administration in all cases of medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract (Evidence grade: C; strength of recommendation: Strong).¹⁶

Nevertheless, HAE attacks can still occur despite proper preprocedural prophylaxis. For this reason, all patients should stay under medical supervision a few hours following the procedure. In addition, on-demand treatment (C1-INH or icatibant plasma concentration) should be available in cases of unpredictable acute attacks.¹⁶ The drugs of choice for this approach are C1 INH plasma concentrate.

Novel biologic drugs and gene therapies in the pipeline

The new era of gene therapy and monoclonal antibodies (mAbs) has led to the development of several new approaches for HAE management, which are now being investigated.

The most interesting treatments are gene therapy, which aims to restore the lack in C1-INH by administering a new extrachromosomal copy of SERPING1 into patient cells by using an adeno-associated virus vector, the use of an antisense oligonucleotide to reduce prekallikrein production (Ionis-PKK), the use of an RNA interference to reduce Factor XII expression (ALN-F12, ARC-F12), a human monoclonal antibody against Factor XII (CSL312), and a recent kallikrein inhibitor (ATN-249).

The main purpose of these novel approaches is to reduce the need for medications and to improve the quality of life of HAE patients by modifying the course of the disease.

AAVrh.10hC1EI

Qui and his research group are evaluating in a preclinical study the efficacy of gene therapy on C1-INH HAE. They hypothesized that C1-INH deficiency could be restored by administering an additional extrachromosomal copy of the SERPING1 gene into the cells of affected patients using an adeno-associated virus vector.³⁴ The authors created a C1-INH-deficient mouse model presenting the clinical and molecular phenotype of HAE due to a frameshift mutation, which leads to an early stop codon in exon 3, and they called it the 'S63 mouse model'.³⁴ These authors hypothesized that one injection of a serotype rh.10 adeno-associated virus (AAV) vector, which encodes the human C1 esterase inhibitor (C1EI) (AAVrh.10hC1EI), is sufficient for recovering from the disease. The expression of human C1EI would indeed be persistent, and no more HAE manifestations will appear. In this study, the authors analyzed the vascular permeability in both S63+/- and wild-type control mice with or without vector treatment. For the assessment, the authors used Evans blue dye and evaluated mouse outcomes after 2, 6, and 24 weeks from the AAVrh.10C1EI (1011 gc) administration.³⁴

The authors demonstrated that, in both *in vivo* and *in vitro* assessments and independent of mouse gender, a single administration of AAVrh.10hC1EI allowed enough systemic production of C1-INH to prevent the vascular permeability causing HAE manifestations.

One of the major limits of this study is that the evaluation was restricted to 24 weeks, although the authors revealed that they have demonstrated long-term expression measured over several years.³⁵⁻³⁷

This study establishes that a gene therapy expressing C1-INH helps in HAE healing in a mouse model. Nevertheless, it is mandatory that additional toxicology and safety studies assess the efficacy and feasibility of this approach in clinical practice, focusing on dosing regimens and drug safety.

ARC-F12

ARC-F12™ is a new RNAi-based product developed by Arrowhead Pharmaceuticals. It is now under investigation for the treatment of diseases due to a dysfunctional Factor

XII. Some preclinical studies are ongoing, and ARC-F12™ will probably be proposed for future clinical trials.³⁸

ALN-F12

ALN-F12 is an FXII targeting small-interfering RNA (siRNA) conjugated with trivalent N-acetylgalactosamine (GalNAc) ligand, which was demonstrated to be able to compensate for the defect resulting from the loss of functional C1INH due to F12 mutations. Liu and coauthors evaluated the efficacy of ALN-F12 in mice, rats, and cynomolgus monkeys, as well as in an *ex vivo* assay assessing the relationship between the cleavage of high-molecular weight kininogen (HK) and plasma levels of human FXII. These authors demonstrated a significant dose-dependent decrease in plasma FXII levels in all rats, mice, and monkeys, after only one subcutaneous injection of ALN-F12. Moreover, an *ex vivo* human plasma HK cleavage assay indicated FXII-dependent bradykinin generation.¹⁴

Until recently, no studies for ALN-F12 *in vivo* human evaluation have been developed.

BCX7353

BCX7353, the active substance of which is (R)-1-(3-(aminomethyl)phenyl)-N-(5-((3-cyanophenyl)(cyclopropylmethylamino)methyl)-2-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide dihydrochloride, is a potent, synthetic small molecule demonstrated to be able to inhibit plasma kallikrein. The drug was developed for both long-term prophylaxis and on-demand treatment.^{39,40}

In 2016, the first-in-human phase 1 trial evaluated single or multiple once-daily oral administration of BCX7353 or placebo in healthy volunteers. The half-life of BCX7353 was shown to be 50–60 hours, and the target therapeutic plasma concentrations were reached in 7 days, without any AEs reported.⁴¹

According to these results, the phase 2 Angioedema Prophylaxis 1 (APeX-1) trial³⁹ evaluated BCX7353 in its four dose regimens (62.5, 125, 250, and 350 mg, administered once daily) for long-term prophylaxis in angioedema attacks over a 4-week period and compared them with the placebo.

The primary efficacy end point was the number of angioedema attacks, which was demonstrated to be reduced up to 73.8%. Key secondary end points included angioedema attacks according to anatomical location and the change from baseline in AE-QoL scores. Secondary endpoints also supported the efficacy of BCX7353 at doses of 125 mg or more. Three patients who received BCX7353 at a dose of 350 mg discontinued the trial regimen owing to adverse events, whereas the incidence in the 62.5-mg dose group was similar to that in the placebo group (18%).

A second phase 2, double-blind, placebo-controlled, randomized, crossover, dose-ranging trial, ZENITH-1, evaluated the efficacy of the 750 mg dose of BCX7353 in the treatment of

three HAE attacks: two treated with active drug and one with placebo, in a randomized sequence.

The results showed that at 4 hours post-dose, 67.7% of HAE attacks treated with BCX7353 and 46.7% of those treated with placebo were stable or improved (OR=2.771, $p=0.0387$). The evaluation was made by composite VAS, and the results were maintained at 24 hours.⁴⁰

Based on the results of ZENITH-1, the company plans to start a phase 3 trial with the 750 mg dose of oral BCX7353 in the summer of 2019.⁴²

CSL312

The fully human recombinant antibody 3F7 is a potent and highly specific inhibitor of the proteolytic activity of FXIIa that specifically binds to the catalytic domain of FXIIa with high affinity and completely inhibits its protease activity.⁴³ 3F7 was initially developed to provide thromboprotection as efficiently as heparin without increasing the bleeding risk,⁴⁴ but it was found to be effective also in the reduction of angioedema attacks in HAE III mouse models and in bradykinin-mediated angioedema induced by captopril in C1-INH-deficient mice,⁴⁵ laying the foundations for further studies.

In addition, a variant of 3F7 with improved affinity and potency developed by CSL Behring®, called CSL312, has been shown to effectively inhibit dextran sulfate-triggered FXII contact activation and bradykinin formation in the plasma of healthy donors and HAE murine models.⁴⁵

In October 2018, a multicenter, randomized, placebo-controlled, parallel-arm, phase 2 study was started to investigate the clinical efficacy, pharmacokinetics, and safety of CSL312 as prophylaxis to prevent attacks in subjects with HAE.⁴⁶

IONIS-PKCRX

The targeted inhibition of prekallikrein (PKK) expression using antisense oligonucleotide (ASO) technology is a novel emerging therapeutic approach for hereditary angioedema due to genetic deficiencies of PKK or FXII.

IONIS-PKCRx, designed by Ionis Pharmaceutical™, is a second-generation 2'-O-(2-methoxyethyl)-modified antisense oligonucleotide of murine derivation that aims to reduce hepatic PKK mRNA by binding prekallikrein. IONIS-PKCRx was shown to be dose-dependent effective in reducing human prekallikrein mRNA in the liver and PKK protein in the plasma of mice expressing the human PKK transgene (hPKK-Tg) and dose- and time-dependent reductions of plasma PKK in Cynomolgus monkeys, showing a tissue half-life of 20.5–27.7 days.⁴⁷

Preliminary trials in healthy human volunteers demonstrated that IONIS-PKCRx was able to dose-dependently reduce plasma levels of PKK and bradykinin production, with a good tolerability and safety profile.

IONIS-PKCRx was evaluated in a Canadian phase 1 randomized DBPC study in healthy volunteers (BioPharma Services, Inc., Toronto, Canada) between May 2014 and January 2015. The subjects were randomly assigned 3:1 to receive a single subcutaneous IONIS-PKCRx injection (50, 100, 200, or 400 mg) or placebo.⁴⁷ The pharmacodynamic effects in healthy human volunteers were consistent with the preclinical results.⁴⁷

In the 300 and 400 mg cohorts, IONISPKCRx was effective in dose-dependent reduction of plasma PKK protein levels and bradykinin production after 29 days from injection, sustained up to day 113.

In addition, the finding of a conversion from FXII to the active form (FXIIa) is thought to be consistent with the role of PKK/kallikrein in activation of FXII.⁴⁷

ATN-249

ATN-249 is a novel, potent, selective, and oral-administered plasma kallikrein inhibitor for the treatment of HAE. Preclinical studies seemed to support ATN-249 as a highly selective and effective kallikrein plasma inhibitor. Upon the conclusion of the phase I study in healthy volunteers, a phase 2 trial is expected to commence. The aim of this phase 2 study, over a 4-week period, would be the assessment of dose ranging, as well as the tolerability, safety, pharmacodynamics, pharmacokinetics, and efficacy of ATN-249 as a prophylactic treatment in HAE patients.⁴⁸

Avoralstat

Avoralstat (BioCryst Pharmaceuticals, Durham, North Carolina), which was previously named BCX4161, is a potent, small molecule inhibitor of kallikrein.⁴⁹

The clinical trial named OPuS-2 (NCT02303626, EudraCT 2014-002655-26) is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study aimed to test the efficacy of avoralstat in long-term prophylaxis.⁵⁰

Patients were randomized in a 1:1:1 ratio to receive avoralstat 500 mg, 300 mg, or placebo, administered orally, three times per day for 12 weeks. The primary endpoint was the weekly confirmed number of angioedema attacks. Secondary efficacy

endpoints included the number of attack-free days, the weekly subject-reported attack rate, the average attack severity score, and the AE-QoL score.⁵⁰

The primary endpoint was not achieved, with confirmed attacks of 0.59, 0.68, and 0.59 for subjects in the three treatment arms ($p \geq 0.5$). In addition, except for quality of life, no other secondary endpoint was achieved.⁵⁰

KVD900

KVD900 is a potent and selective small molecule plasma kallikrein inhibitor developed for the on-demand treatment of HAE attacks. A phase 1 single ascending dose study evaluated the pharmacodynamics of the drug by testing 8 ascending doses from 5 to 600 mg in healthy men. The 600-mg single dose provided >90% inhibition of plasma kallikrein catalytic activity between 30 minutes and 6 hours post-dose and >50% inhibition for 10 hours. The authors suggested that the drug could be used as a rapidly acting oral treatment for HAE attacks.⁵¹

Conclusion

The severity and timing of HAE attacks are unpredictable, mainly due to the lack of a complete understanding of the mechanisms underlying the disease onset. In addition, swelling without urticaria is the feature of most HAE attacks, regardless of the molecular basis.

The approved treatments can actually avoid or minimize the risk of death, but they are not effective in complete healing from the disease. Moreover, a personalized approach becomes increasingly important to obtain adequate disease control. In the recent years, the development of many subcutaneous and oral drugs has allowed people to take these medications at home, reducing missed work days and healthcare-associated costs.⁵²

More recently, gene therapy approaches seem to provide promising opportunities for the treatment of hereditary angioedema.

However, there are still many unmet needs concerning new therapies, including efficacy, costs, route, and timing of administration.

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