Summary

Hereditary angioedema (HAE) is a genetic disease caused by a deficiency (type I), or dysfunction (type II), of C1-esterase inhibitor (C1-INH). It is characterised by unpredictable, recurring attacks of oedema at various sites of the body, including the hands, feet, face and abdomen; if oedema affects the upper airway it can be life-threatening. The frequency of attacks varies, but many of those affected will experience at least one attack a month. Each attack typically lasts two to five days before spontaneously subsiding. Attacks are also associated with raised levels of bradykinin, which is thought to mediate the formation of oedema by increasing vascular permeability. Episodes can be unpredictable, or triggered by factors such as trauma, drugs or dental treatment.

This review describes the available evidence for various drug treatment options for the management of HAE. A separate document summarises the primary outcomes of phase III studies together with the licensing status and availability of these drugs.
Hereditary angioedema (HAE) is a genetic disease caused by a deficiency (type I), or dysfunction (type II), of C1-esterase inhibitor (C1-INH). It is characterised by unpredictable, recurring attacks of oedema at various sites of the body, including the hands, feet, face and abdomen; if oedema affects the upper airway it can be life-threatening. The frequency of attacks varies, but many of those affected will experience at least one attack a month. Each attack typically lasts two to five days before spontaneously subsiding. Attacks are also associated with raised levels of bradykinin, which is thought to mediate the formation of oedema by increasing vascular permeability. Episodes can be unpredictable, or triggered by factors such as trauma, drugs or dental treatment.

HAE is caused by an autosomal dominant mutation of the gene for C1-INH (C1 esterase inhibitor). C1-INH controls the activation of plasma cascade systems such as the complement and contact pathways that, upon activation, generate inflammatory peptides. Acute angioedema attacks in HAE occur when these plasma cascades become activated due to dysregulation, via dysfunctional or deficient C1-INH, and release excessive amounts of vasoactive peptides, such as bradykinin and C2-kinin. These increase vascular permeability with resulting angioedema.

Attacks of HAE usually follow a predictable course. Many attacks are preceded by a prodrome (usually a tingling sensation), and approximately a third are accompanied by erythema marginatum, a non-pruritic rash that presents gradually. The swelling classically worsens slowly but relentlessly over the first 24 hours, then gradually subsides over the subsequent 48 to 72 hours.

Optimal management of HAE includes treatment of acute attacks, short-term prophylaxis to prevent an attack following a trigger such as a surgical or dental procedure, and long-term prophylaxis to minimise the frequency and severity of recurrent attacks.

The prevalence of HAE has been estimated between 1 in 10,000 and 1 in 50,000 of the population. This equates to between 1,075 and 5,373 people in England and Wales with the condition. On average, patients experience 12 attacks per year each lasting 2–5 days if left untreated. In 2005/6, there were 1,257 hospital admissions with a primary diagnosis of angioneuritic oedema (acquired and hereditary) and 5 deaths were recorded in 2008 (National Horizon Scanning Centre Ruconest).

Prophylaxis

Short-term prophylactic treatment to prevent attacks of hereditary angioedema is useful in patients with planned exposure to a situation likely to trigger an attack, such as substantial dental work, invasive medical procedures, and surgical procedures. Consensus guidelines based on uncontrolled studies recommends that patients with HAE be protected from severe swelling by means of prophylactic treatment with C1-INH (500 to 1500 units given 1 hour before the provoking event) or, when C1-INH is not available, by means of temporarily increasing plasma C1-INH levels through treatment with high-dose 17α-alkylated androgens (e.g., danazol at a dose of 200 mg orally three times a day) for 5 to 10 days before the provoking event or through administration of 2 units of fresh-frozen plasma 1 to 12 hours before the event. Tranexamic acid is the preferred option for the prophylaxis of HAE attacks in children due to the adverse effects of androgens on growth.

Long term prophylaxis should be considered in patients who experience more than one severe HAE event per month.

Treatment

In terms of management of acute attacks, purified C1-INH therapy (such as Berinert®) has been the main treatment for acute attacks of HAE, and attacks typically begin to resolve within 30 to 60 minutes after intravenous injection of C1-INH (500 to 2000 units). Targeting the bradykinin pathway during an acute attack may also be an option, and icatibant, a synthetic decapeptide, functions as a highly specific and extremely potent antagonist of the bradykinin-2 receptor (BK2R). Optimal strategies for managing acute attacks still need to be defined, and the place in therapy of icatibant and Berinert® need to be established, whilst several new treatments are now available.

Drugs used for the treatment of acute attacks of hereditary angioedema

Berinert®

Berinert® is a purified, human C1-INH, derived from plasma. It is licensed for the treatment of acute episodes of HAE, administered by slow iv injection or infusion, at a dose of 20 units per kilogram body weight. It regulates clotting and inflammatory reactions that, when impaired, can lead to local tissue swelling.

The manufacturing of Berinert® includes multiple steps to decrease the risk of viral transmission, including pasteurisation and nanofiltration. Donors for pooled plasma are carefully screened and donations are analysed for hepatitis A, B and C, HIV and parvovirus 19. After separation of C1-INH from cryodepleted human plasma adsorption and precipitation, the purified material is pasteurised by heat treatment for 10 hours at 60°C, then further purified by precipitation and chromatography, nanofiltration, sterile filtration and lyophilisation without preservatives.
In the UK, Berinert is licensed for the treatment of acute episodes of HAE in adults and adolescents. Berinert® may be used in pregnancy and is also licensed for use in children.5

Icatibant (Firazyr®)
In the UK, icatibant is licensed for the symptomatic treatment of acute attacks of HAE in adults with C1-INH deficiency. It is a synthetic decapeptide, similar in structure to bradykinin, which functions as a highly specific and extremely potent antagonist of the bradykinin-2 receptor (BK2R). Therefore, given that BK2R is thought to mediate most of the key activities of bradykinin, including the vasodilation associated with HAE, inhibition of this receptor should antagonise these effects.7

Icatibant is not licensed for use in pregnant women or in children.6

Following a re-submission after an initial rejection in 2008, the Scottish Medicines Consortium (SMC) has now accepted the use of icatibant acetate (Firazyr®) within NHS Scotland for the symptomatic treatment of acute attacks of hereditary HAE in adults with C1-esterase-inhibitor deficiency. The positive SMC recommendation takes into account the benefits of a Patient Access Scheme and is contingent upon its continuing availability in NHS Scotland.

Similarly, the All Wales Medicines Strategy Group (AWMSG) has approved the use of icatibant (Firazyr) as a treatment option for use within NHS Wales for the symptomatic treatment of acute attacks of HAE in adults (with C1 esterase inhibitor deficiency). As with the SMC approval, the recommendation applies only in circumstances where the approved Wales Patient Access Scheme is utilised.

CINRYZETM
CINRYZETM is a heat-treated, nanofiltered C1-INH, purified from human plasma. It is presented as a lyophilised powder and solvent for solution for injection.10

CINRYZETM is licensed for use in adults and adolescents for the following indications:
- Treatment and pre-procedure prevention of angioedema attacks in adults and adolescents with hereditary angioedema
- Routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of hereditary angioedema, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment
- CINRYZETM may be used in pregnancy.

Conestat alfa (Ruconest®)
Conestat alfa (Ruconest®, rhC1INH) is a recombinant human C1-INH that regulates early activation steps of the classical complement and contact pathways. It is licensed in the UK for the treatment of acute angioedema attacks in adults with HAE due to C1-INH deficiency. Conestat alfa is administered intravenously at a recommended dose of 50U/kg with a maximum dose of 4,200U.11

Conestat alfa is derived from milk of transgenic rabbits and contains traces of rabbit protein. Before initiating treatment with conestat alfa, patients should be tested for the presence of IgE antibodies against rabbit allergens using a validated test for IgE antibodies against rabbit epithelium (dander) e.g. ImmunoCap system, Phadia, Sweden. Only patients who have been shown to have negative results for such a test, should be treated with conestat alfa. IgE antibody testing should be repeated once a year or after 10 treatments, whichever occurs first.11

In the absence of a submission from the holder of the marketing authorisation, the Scottish Medicines Consortium (SMC) does not recommend conestat alfa (Ruconest) for use within NHS Scotland.12

One unit of conestat alfa activity is defined as the equivalent of C1 esterase inhibiting activity present in 1 mL of pooled normal plasma.11

Ecallantide (Kalbitor®)
Ecallantide is a selective, reversible inhibitor of plasma kallikrein, and inhibits plasma kallikrein-mediated production of bradykinin. The US Food and Drug Administration (FDA) has approved ecallantide (Kalbitor®) subcutaneous injection for the treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.

Ecallantide is not currently licensed in the UK, and an EU marketing authorisation application was withdrawn in November 2011.13

Clinical Evidence

1. Icatibant (Firazyr®)
Three phase III trials evaluating icatibant for HAE have been published – For Angioedema Subcutaneous Treatment (FAST)-1 conducted in North and South America, FAST2 conducted in Europe and Israel, and FAST3 conducted across 11 countries. All three trials had a randomised, double-blind, controlled phase for the treatment of the first post-enrollment attack (except where there was laryngeal oedema), followed by an open-label extension phase.

The studies enrolled patients aged 18 years or older with a diagnosis of HAE, and a current angioedema...
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Clinically significant relief of the index symptom. A phase were not reported.

Data from the open-label extension studies for FAST1 and FAST2, all patients were given open-label icatibant to treat subsequent attack of sufficient severity to necessitate treatment was included in an open-label extension phase, and received icatibant.

In the extension studies for FAST1 and FAST2, all patients were given open-label icatibant to treat second and subsequent attacks and more than one injection during an attack was permitted (up to a maximum of 90mg/day). Based on the highest score on the visual analogue scale before study-drug administration, one of the three main symptoms (cutaneous swelling, cutaneous pain or abdominal pain) was defined in each patient as the index symptom for assessing the primary endpoint. For attacks with a combination of these symptoms, abdominal pain was considered the index symptom. Data from the open-label extension phase were not reported.

In the double-blind phase of FAST2 (n=74), the median time to onset of symptom relief was statistically significantly shorter in patients given icatibant than in those on tranexamic acid (2.0 vs. 12.0 hours, p<0.001). In both studies the time to patient-reported symptom improvement statistically favoured icatibant (see table 1). Rescue medication (including C1 inhibitor concentrate/attenuated androgens) was permitted in both studies and was given within 12 hours to three (11%) and 13 (45%) patients on icatibant and placebo, respectively, in FAST1, and to five patients (13%) on tranexamic acid in FAST2.

In the double-blind phase of FAST1 (n=56) the median time to onset of symptom relief was shorter in the icatibant group than in the placebo group (2.5 vs. 4.6 hours; P=0.142). This was not statistically significant.

In the double-blind phase of FAST2 (n=74), the median time to onset of symptom relief was statistically significantly shorter in patients given icatibant than in those on tranexamic acid (2.0 vs. 12.0 hours, p<0.001). Both studies included patients with a combination of cutaneous, abdominal, and laryngeal symptoms. In FAST3, these symptoms were not randomised, but were treated with open-label subcutaneous icatibant 30mg. Each patient only had their first HAE attack involving the skin, abdomen or larynx of moderate to severe intensity (for cutaneous and abdominal symptoms this was indicated by a score of ≥30 on a visual analogue scale of 0 to 100mm, where 0 = no symptoms and 100 = worst possible symptoms).

FAST3 was conducted at 67 centres across 11 countries (North America, South America and Europe). The trial was conducted to evaluate the safety and efficacy of icatibant compared to placebo in patients with a diagnosis of HAE type I or type II, confirmed by decreased C4 levels and/or antigenic or functional C1-INH deficiency (<50% of normal levels). Similar to FAST1 and FAST2, FAST3 involved 93 patients aged 18 years or older with a diagnosis of HAE, and a current angioedema attack involving the skin, abdomen or larynx of moderate to severe intensity (for cutaneous and abdominal symptoms this was indicated by a score of ≥30 on a visual analogue scale of 0 to 100mm, where 0 = no symptoms and 100 = worst possible symptoms).

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Please see table 1 (copied from reference 25) for results from the FAST1 and FAST2 studies, and table 2 for results from the FAST3 study. No data on the open-label extension phase of these studies have been reported.

The primary efficacy endpoint was the median time to clinically significant relief of the index symptom. A clinically significant symptom relief was defined as a minimum decrease in the score on the visual-analogue scale of 20 to 30mm (range 0-100mm), depending on the initial symptom severity. This decrease had to have been sustained for three consecutive measurements on the visual-analogue scale, with the first measurement being the time point at which clinically significant relief was achieved. Secondary efficacy endpoints included the median times to first symptom improvement according to the patient and according to the investigator; the median time to almost complete relief of symptoms (i.e. the end of an attack), defined as the time point at which the score on the visual-analogue scale was 0 to 10mm for at least three consecutive measurements for all symptoms. Safety was evaluated by means of adverse-event reporting, documentation of local tolerability (i.e. injection-site reactions), measurement of vital signs, electrocardiography, clinical laboratory testing, urinalysis, and assessment of complement activation.

Exclusion criteria included diagnosis of angioedema other than HAE, serious concomitant illness, and pregnancy and lactation. Additionally, patients were excluded if they had received pain medication for the current attack, a C1 esterase inhibitor within 3 days of the attack, or tranexamic acid within a week before the attack or if they were receiving angiotensin-converting-enzyme inhibitors.

In the double-blind phase of FAST1 (n=56) and FAST3 (n=93) and with tranexamic acid (1g three times a day for two days) in FAST2 (n=74). In FAST1 and FAST2, patients with laryngeal oedema received open-label icatibant for their first attack. In both trials, any patient having a subsequent attack of sufficient severity to necessitate treatment was included in an open-label extension phase, and received icatibant.

Fast3 was conducted at 67 centres across 11 countries (North America, South America and Europe). The trial was conducted to evaluate the safety and efficacy of icatibant compared to placebo in patients with a diagnosis of HAE type I or type II, confirmed by decreased C4 levels and/or antigenic or functional C1-INH deficiency (<50% of normal levels). Similar to FAST1 and FAST2, FAST3 involved 93 patients aged 18 years or older with a diagnosis of HAE, and a current angioedema attack involving the skin, abdomen or larynx of moderate to severe intensity (for cutaneous and abdominal symptoms this was indicated by a score of ≥30 on a visual analogue scale of 0 to 100mm, where 0 = no symptoms and 100 = worst possible symptoms).

Eligible patients presented to the study site within 6 hours after an acute HAE attack became at least moderate (abdominal and/or cutaneous) or mild (laryngeal) in severity, and within 12 hours of attack onset. Patients were randomised to a single injection of either icatibant 30mg or placebo (isotonic, acetate-buffered solution). Patients with severe laryngeal symptoms were not randomised, but were treated with open-label subcutaneous icatibant 30mg. Each patient only had their first HAE attack treated in the randomised phase; all patients could subsequently receive open-label icatibant for subsequent attacks during the open-label extension phase of the study. Only results of the controlled-phase of FAST3 have been published. The primary efficacy endpoint for patients presenting with cutaneous and/or abdominal attacks was patient-assessed time to 50% reduction in symptom severity of the cutaneous and/or abdominal attack by the visual analogue scale (defined as a 50% reduction from the pretreatment score in the 3-symptom composite visual
analogue scale score i.e. a mean of scores for skin swelling, skin pain, abdominal pain, VAS-3), maintained at three consecutive time-points. For laryngeal attacks, the primary efficacy was assessed as median time to a 50% reduction from pre-treatment score in the 5-symptom composite VAS score (VAS-5, skin swelling, skin pain, abdominal pain, difficulty swallowing and voice change).

A total of 88 patients with non-laryngeal first attacks received icatibant (n=43) or placebo (n=45); of 5 patients with mild to moderate laryngeal attacks 3 patients received icatibant and 2 patients received placebo. Five patients with severe laryngeal attacks received open-label icatibant. Table 3 shows efficacy results reported for the FAST3 study.

Overall, 41.3% of patients (19/46) who received icatibant and 52.2% of patients (24/46) who received placebo specifically experienced study drug-related adverse effects. Of these, 5 patients receiving icatibant and 3 patients receiving placebo experienced adverse effects. Dizziness, infections, gastrointestinal disorders (such as abdominal pain, distension, diarrhoea, and nausea), and pyrexia occurred more frequently in patients on icatibant, whilst headaches occurred more frequently in patients on placebo.

C1-esterase inhibitor (Berinert®)

There have been two phase III studies, IMPACT-1 and -2, which have evaluated the safety and efficacy of purified, human C1-esterase inhibitor (derived from plasma) – Berinert® for the management of moderate to severe HAE attacks16,17.

The International, Multiple Prospective, Angioedema, C1-INH (IMPACT-1) trial was a double-blind, parallel-group, randomised, placebo-controlled three-arm trial designed to assess the safety and efficacy of Berinert® at doses of 10 units/kg (n=40) and 20 units/kg (n=43) vs. placebo (n=42) for the management of abdominal or facial attacks of HAE16,17. Patients were eligible if they were at least 6 years of age and had laboratory-confirmed C1-INH deficiency (type I and type II). Patients were treated on presentation of an acute attack attaining moderate to severe intensity (as assessed by the patient and confirmed by the investigator). For each patient, only a single abdominal attack (gastrointestinal colic, not cutaneous) or facial attack (not laryngeal) was treated and evaluated. Patients received a single intravenous infusion of either Berinert® at a dose of 10units/kg or 20units/kg, or placebo. Patients were observed for a minimum of 4 hours after the start of treatment, after which they could be discharged if they had reported onset of relief of symptoms. After 4 hours, patients who reported insufficient or no symptom relief received a second dose of double-blind treatment called “rescue study medication” as follows:

- Berinert 20 units/kg for patients who first received placebo
- Berinert 10 units/kg for patients who initially received 10 units/kg
- Placebo for patients who received Berinert 20 units/kg

The primary endpoint was the time from the start of treatment to the onset of symptom relief, as determined by patient responses to a standard question posed at various time intervals for as long as 24 hours after the start of treatment. Secondary endpoints were the time to complete resolution of all HAE symptoms, the proportion of patients with worsened intensity of HAE symptoms between 2 and 4 hours after the start of treatment compared with baseline for at least 1 HAE symptom present at baseline, and the number of vomiting episodes within 4 hours after the start of treatment. Other endpoints included were adverse events occurring as long as 9 days after treatment (serious adverse events as long as 12 weeks after treatment), vital signs (blood pressure, heart and respiratory rate, body temperature) before and as long as 24 hours after treatment, and viral safety (HIV types 1 and 2, hepatitis virus, and human B19 virus) before and as long as 12 weeks after treatment.

For the primary efficacy analysis, the time to onset of symptom relief was set to 24 hours if the patient received rescue study medication or analgesics, antiemetics, open-label Berinert, or fresh frozen plasma after 4 hours.

The following results were reported:

- The numbers of patients with values set to 24 hours were 17 of 42 (40.5%) for placebo, 11 of 39 (28.2%) for Berinert 10 U/kg, and 6 of 43 (14.0%) for Berinert 20 U/kg.
- The median time to onset of symptom relief was statistically significantly shorter with C1-INH 20 U/kg (0.5 hours) than with placebo (1.5 hours; P=0.0025), whilst time to onset of symptom relief with C1-INH 10U/kg was 1.17 hours, which was only slightly shorter than time to onset of relief with the placebo patients (p not statistically significant).
- The median time to complete resolution of all HAE symptoms (including pain) was 7.79 hours (range 0.33 to 1486.17) for patients on placebo, 20.00 hours (range 0.47 to 1486.17) for patients on C1-INH 10U/kg and 4.92 hours (range 0.47 to 1486.17) for patients on C1-INH 20U/kg (p<0.0237 compared to placebo).
- The proportion of patients with worsened intensity of HAE symptoms between 2 and 4 hours after the start of treatment for at least 1 of the HAE symptoms present at baseline was also statistically event, significantly lower with C1-INH 20 U/kg (4.7%) than with placebo (31.0%; P=0.0014).
Drugs used in the management of hereditary angioedema

- The mean number of vomiting episodes within the first 4 hours after treatment was also significantly lower with C1-INH 20 U/kg (0.1) than with placebo (0.8; P=0.0329).
- The percentage of patients experiencing an adverse event within 4 hours was lower with C1-INH 20 U/kg (19.6%) and C1-INH 10 U/kg (25.6%) compared to placebo (43.9%).
- In patients with abdominal or facial attacks treated with C1-INH 20 U/kg, no new attacks occurred before the complete resolution of the previous attack, indicating an absence of rebound angioedema.
- No seroconversions were observed for HIV, hepatitis virus or human B19 virus.

The researchers conclude that whilst C1-INH 20U/kg has demonstrated to be a reliable and effective treatment for rapidly alleviating the symptoms of abdominal and facial HAE, efficacy of the lower C1-INH dose of 10 U/kg was not statistically significant compared to placebo. The recommended dose of C1-INH concentrate in the treatment of acute HAE attacks is therefore 20 U/kg.

Subsequently, IMPACT2 was conducted as an extension of the IMPACT1 trial to assess the efficacy and safety of long-term treatment of successive HAE attacks at any body location, including the larynx. Patients were eligible for inclusion in IMPACT2 if they had any type of HAE attack and had previously participated in IMPACT1. No restrictions were specified for the time between the onset of an attack and the start of C1-INH replacement therapy. After enrolment, patients received a single intravenous dose of 20U/kg for each attack. The primary endpoint was the time from the start of treatment to onset of symptom relief, as determined by the patients’ responses to a standard question posed at pre-determined intervals. The secondary endpoint was the patient-reported time to complete resolution of HAE symptoms. Additionally, adverse events were recorded for up to 9 days after treatment of each attack. A total of 1085 HAE attacks in 57 patients (aged between 10 years and 53 years) were treated with C1-INH concentrate. Patients were in the study for a median duration of 24 months (range 0-51 months), during which time they received C1-INH concentrate for a median of 7 attacks (range: 1-184 attacks). The predominant type of HAE attack was abdominal, followed by peripheral, facial and laryngeal attacks. The following results were reported:

- The median time to onset of symptom relief was 0.46 hours.
- The individual average time to onset of symptom relief was <1 hour in 89.5% of patients.
- The median time to complete resolution of HAE symptoms was 15.5 hours.
- The individual average time to complete resolution of HAE symptoms was <24 hours in 71.9% of patients.
- A single dose of 20U/kg of C1-INH concentrate was sufficient to effectively treat 1073 to 1085 HAE attacks (99%). Additional doses of C1-INH concentrate (up to a total dose of 60U/kg per attack) were administered for 12 abdominal attacks in 6 patients for worsening of the HAE attacks.
- A total of 25 patients (43.9%) experienced at least one adverse event, with most adverse events being of mild to moderate intensity. One patient experienced a serious adverse event leading to withdrawal from study medication.

The researchers conclude that C1-INH 20U/kg appears to provide a safe and reliable option for the long-term treatment of successive HAE attacks at any body location.

C1-esterase inhibitor (CINRYZE™)

The LEVP 2005-1 study was a phase III randomised, double-blind, placebo-controlled trial which evaluated the safety and efficacy of CINRYZE™ for the treatment (Part A) and prevention (Part B) of HAE.

Participants in both studies were required to be at least 6 years of age and to have confirmed diagnosis of hereditary angioedema.

For the acute-attack treatment study, a total of 71 patients were enrolled, and randomised to receive either C1-INH 1000 units in 10mL sterile water or placebo (10mL of saline). Patients were asked to return to the study site within 4 hours of the onset of an acute attack. Attacks of laryngeal angioedema were excluded, and patients with such attacks were treated with open-label CINRYZE™. Patients were asked to rate their angioedema symptoms as “none”, “mild”, “moderate” or “severe” for each affected site (extremities, throat, abdomen, face and external genitalia). The site of the most severe symptoms was designated the defining site. Symptom severity was assessed every 15 minutes, beginning with the initial injection and continuing until the subject reported unequivocal relief at the defining site, with unequivocal relief defined as three consecutive reports of improvement at that site. If 4 hours elapsed without unequivocal relief, the assessments were discontinued, and rescue therapy with open-label C1-INH (CINRYZE™) was offered. Patients were subsequently contacted by telephone to confirm the complete resolution of symptoms and were asked to return for a follow-up office visit at 3 months. The primary end point was the time from administration of the study drug to unequivocal relief of symptoms at the defining site (i.e., the first of three consecutive reports of improvement). Secondary efficacy end points included the percentage of subjects who had an onset of unequivocal relief within 4 hours after treatment, the time to complete resolution of the attack (i.e., all symptoms of swelling absent), and the effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels. Safety was evaluated by assessing adverse events, changes in clinical laboratory values,
physical findings, and vital signs before and after the injection.

Efficacy analysis was conducted for 68 patients, as 3 patients were considered not to have true HAE. The following results were reported:

- The estimated median time to onset of unequivocal relief was 2 hours in the CINRYZE™ group, compared with more than 4 hours in the placebo group (estimated success rate ratio 2.41; 95% CI 1.17 to 4.95; p=0.02)
- The onset of unequivocal relief occurred within 4 hours in 21 of the 35 patients in the CINRYZE™ group, and 14 of the 33 patients in the placebo group (60% vs. 42%, p=0.06)
- Both antigenic and functional levels of C1 inhibitor increased during treatment in the group given CINRYZE, but not in the group given placebo (p<0.001).

Conestat alfa (Ruconest®)

According to the SPC for conestat alfa (Ruconest), evidence to support the licensing/use of the drug is based on two double-blind, randomised, placebo controlled, phase III trials, both of similar design (C1-1205 RCT and C1-1304 RCT) and four open label clinical studies. The phase III studies have been described below: Study C1-1205 was conducted in North America and Canada, while study C1-1304 was conducted in Italy, Spain, Romania, UK and Israel. Inclusion criteria were age (12 years or older in the North American study, and 16 years or older in the “European study”), and a functional C1INH in plasma of <50% of the normal. Exclusion criteria included a history of allergy against rabbits, and acquired C1-INH deficiency. Patients were eligible for randomisation if they presented with symptoms of an attack within 5 hours, and an overall severity VAS >/= 50mm. Patients with an eligible attack were randomised to receive 50 to 100U/kg rhC1INH or placebo in the North American study, or 100U/kg rhC1INH or saline in the European study.

The doses of conestat alfa evaluated in the clinical studies ranged from a single vial of 2100 units (corresponding to 18 40 units/kg), to 50 and 100 units/kg. Patients receiving the lower dose of conestat alfa had the option of receiving a second dose up to 4 hours after the first. The primary outcome measure was the time taken to an improvement in symptoms, which was measured by the patients rating the severity of their symptoms on the VAS symptom scale from 0 to 100mm (with 0mm meaning no symptoms at all, and 100mm meaning extremely disabling). The score was recorded at the time of evaluation (-1 hour), at the start if infusion (baseline), and at various time intervals thereafter. The table below shows the results (primary and secondary endpoints) of the two randomised controlled trials (taken directly from the SPC):

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Time (minutes) to beginning of relief median (95% CI)</th>
<th>Time (minutes) to minimal symptoms median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-1205 RCT</td>
<td>100 U/kg (n =13)</td>
<td>68 (62 to 132) p = 0.001</td>
<td>245 (125 to 270) p = 0.04</td>
</tr>
<tr>
<td></td>
<td>50 U/kg (n =12)</td>
<td>122 (72 to 136) p &lt; 0.001</td>
<td>247 (243 to 484)</td>
</tr>
<tr>
<td></td>
<td>Saline (n = 13)</td>
<td>258 (240 to 720)</td>
<td>1101 (970 to 1494)</td>
</tr>
<tr>
<td>C1-1304 RCT</td>
<td>100 U/kg (n =16)</td>
<td>62 (40 to 75) p = 0.003</td>
<td>480 (243 to 723) p = 0.005</td>
</tr>
<tr>
<td></td>
<td>Saline (n = 16)</td>
<td>508 (70 to 720)</td>
<td>1440 (720 to 2885)</td>
</tr>
</tbody>
</table>
The most commonly reported adverse effect was headache, occurring in between 1 to 10% of patients receiving conestat alfa (Ruconest®).

In a pooled analysis of the two randomised, controlled, phase III studies, the primary efficacy endpoint was the time to the beginning of relief of symptoms i.e. the interval during which the VAS score at any eligible location had decreased by >20 mm compared with baseline for 2 consecutive VAS recordings19. The following results were presented for the pooled analysis:

- Treatment with conestat alfa 100units/kg (n=29) and 50units/kg (n=12) achieved the primary endpoint with statistically significant reduction in time to beginning of relief of symptoms, median, 66 minutes (95% CI, 61-122) with 100units, and 122 minutes (range 72-136) with the 50 units dose, compared with saline (n=29), 495 minutes (range 245-520), P < 0.001 and P = 0.013, respectively.
- Treatment with conestat alfa 100units/kg and 50 units/kg also resulted in a statistically significant reduction of time to minimal symptoms, median, 266 (range 242-490) minutes and 247 minutes (range 243-484), respectively, compared with treatment with saline, median, 1210 minutes (range 970-1500) minutes, P < 0.001 and P=0.001, respectively.
- A total of 59% of patients in the saline group had a therapeutic failure compared to 0% in the conestat alfa 50units/kg group and 10% in the 100units/kg group.
- Treatment-emergent adverse effects (TEAEs) occurred less frequently in the conestat alfa groups (27 TEAEs in 7 patients treated with 100 U/kg and 6 TEAEs in 4 patients in the 50 U/kg group) than in the saline group (33 TEAEs in 14 patients).
- Events that were assessed as related to study treatment in the patients receiving the conestat alfa were headache, injection site swelling, epistaxis and hypotension.

The authors of the pooled analysis discuss that recombinant human C1-INH was developed to offer an alternative to plasma-derived C1-INH for the treatment of acute HAE attacks. It may therefore reduce the risk of transmission of human pathogens associated with the alternative plasma derived products.

Ecallantide (Kalbitor®)
Two phase III studies evaluating ecallantide have been published – EDEMA3 and EDEMA420,21. The objectives of these studies were to assess the safety and efficacy of 30mg subcutaneous ecallantide versus placebo in the treatment of moderate-to-severe acute attacks of HAE. Both studies were randomised, double-blind, placebo-controlled trials of similar design. Patients were eligible if they were aged over 10 years. Exclusion criteria were pregnancy, breast-feeding, or receipt of an investigational drug other than ecallantide within 7 days before enrollment. Prophylactic androgen therapy was permitted.

Moderate attacks were defined as those for which intervention was highly desirable for symptoms and that impede activities of daily living; severe attacks were defined as those necessitating treatment or intervention and that result in patients’ inability to perform activities of daily living.

Patients received either 30mg subcutaneous ecallantide (n=36) or placebo (n=36) and were observed for at least 4 hours after drug administration. Symptoms were assessed every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, and finally, at 24 hours. An open-label dose of 30mg ecallantide was allowed for cases involving severe upper-airway compromise. The primary endpoint was the treatment outcome score (TOS) at 4 hours after study-drug administration. The treatment outcome score was a composite, patient reported outcome measure based on the site or sites of symptoms, the symptom severity at baseline, and the response to treatment. Values for the composite treatment outcome score ranged from +100 (designated in the protocol as significant improvement in symptoms) to −100 (significant worsening of symptoms).

The principal secondary endpoint was the change from baseline in the mean symptom complex severity (MSCS) score at 4 hours (this score is a patient-reported outcome measure incorporating the symptom or site and symptom severity at a single point in time of an acute attack, both versus after treatment). Values for the mean symptom complex severity score range from 0 (no symptoms) to 3 (severe). An additional secondary endpoint was the time to significant improvement in overall response.

The following results were reported in the EDEMA3 trial20:
- At 4 hours after study-drug administration, the median TOS was 50.0 (interquartile range [IQR] 0.00 to 100.0) for the ecallantide group, and 0.0 (0.00 to 100.0) for the placebo group (p=0.004).
- At 4 hours after study-drug administration, the median change in the MSCS score was −1.00 (-1.50 to 0.00) in the ecallantide group, and −0.50 (-1.00 to 0.00) in the placebo group (p=0.01).
- The median time to significant improvement in overall response was 165.0 minutes with ecallantide, and >240 minutes with placebo (p=0.14, not significant).
- The median time to sustained improvement in overall response was 67.0 minutes (37.0 to > 240 minutes) in the ecallantide group and 165.0 minutes (49.0 to >240 minutes) in the placebo group (p=0.08, not significant).
- Adverse events were experienced by 20 patients (56%) in the ecallantide group, and 12 patients (33%) in the placebo group.
The most common adverse events occurring more often with ecallantide than with placebo included headache, diarrhoea, pyrexia, and nasal congestion.

A total of 41 of the 72 patients (57%) (20 of the 36 [56%] receiving ecallantide and 21 of the 36 [58%] receiving placebo) had at least one acute attack of angioedema during the 90-day follow-up period. Serious adverse events, all of which were acute attacks of angioedema, were reported in 3 ecallantide-treated patients (8%) and 2 placebo-treated patients (6%).

The EDEMA4 trial had a similar trial design to EDEMA3, and involved a total 95 patients. The primary efficacy endpoint was change from baseline in MSCS score at 4 hours after dosing (the MSCS score provides a comprehensive, patient-reported assessment of symptom burden at a single point in time during an acute attack – a decrease in the MSCS score indicates improved symptoms). The principle secondary efficacy endpoint was the TOS 4 hours after dosing. The following results were reported:

- Four hours after dosing, a statistically significantly greater improvement (mean [SD] change from baseline) in the MSCS score was seen after ecallantide treatment (-0.8[0.6]) vs. placebo use (-0.4 [0.8]); p=0.01.
- Ecallantide was also associated with a statistically significantly greater mean (SD) TOS 4 hours after dosing, indicating improvement, vs. placebo (53.4 [49.7] vs. 8.1 [63.2]; p=0.003).
- During double-blind treatment, at least 1 treatment-emergent adverse event was experienced by 8 ecallantide patients (17%) and 19 (40%) placebo-treated patients.

In a separate pooled analysis of EDEMA3 and EDEMA4, the researchers reported the following results:

- In the integrated analysis, the change from baseline MSCS score at 4 hours after dosing was statistically significantly greater for the ecallantide group than for the placebo group (p<0.01).
- By 4 hours, 74.3% of ecallantide-treated patients experienced a reduction in symptom severity at least as great as the minimally important difference (-0.30) compared with 49.3% of placebo-treated patients (p=0.003).
- The TOS at 4 hours after dosing was statistically significantly higher for ecallantide-treated patients than for placebo-treated patients (p<0.001).
- The proportion of patients who achieved improvement in overall response within 4 hours after dosing was greater in the ecallantide-treated group (51/70 [72.9%]) than in the placebo-treated group (42/73 [57.5%]) although this difference did not reach statistical significance (p=0.79).
- The incidence of adverse events was similar between ecallantide-treated (36.0%) and placebo-treated (34.6%) patients – the most commonly reported adverse events reported in the ecallantide group were headache (8.0%), nausea (5.0%), diarrhoea (4.0%), pyrexia (4.0%), and nasopharyngitis (3.0%) vs. headache (7.4%), diarrhoea (3.7%) and vomiting (3.7%) in the placebo group.

- No patients withdrew from the study due to adverse events.

**Prophylaxis of HAE**

The LEVP 2005-1 study was a phase III randomised, double-blind, placebo-controlled trial which evaluated the safety and efficacy of CINRYZE™ for the treatment (Part A) and prevention (Part B) of HAE.

For the prophylaxis study (Part B), CINRYZE™ was compared with placebo for preventing attacks of angioedema during a 24-week crossover period. This part of the study involved patients who had been randomly assigned to a study drug in the acute-attack treatment study, and who also had a history of at least 2 attacks per month. The study consisted of two consecutive 12-week treatment periods during which patients received prophylactic injections every 3 to 4 days. Patients were randomly assigned to receive either CINRYZE™ (1000 units) or placebo (10mL of saline) during the first period. During the second period, they received the study medication that had not been assigned during the first period. Patients were asked to keep a daily diary of symptoms throughout both study periods, and all patients with acute attacks of angioedema were eligible for rescue treatment with open-label C1-INH. Prophylaxis study injections were delayed for at least 24 hours after open-label rescue treatment for an acute attack. The primary efficacy end point for the prophylactic study was the number of attacks of angioedema during each treatment period, which was normalised for the number of days the patient participated during that period. Secondary endpoints, reported for each period included the average severity of attacks, average duration of attacks, number of open-label injection of C1 inhibitor, and the total number of days of swelling. Safety assessments included the extent of exposure, the number and severity of adverse events, and changes in clinical laboratory values.

In the prophylaxis trial, 24 patients were enrolled and randomly assigned to receive either CINRYZE™ 1000 units (n=12) or placebo (10mL saline, n=12). During the first 12-week period, one patient from each group withdrew from the study.
The following results were reported for the remaining 22 patients:

- The average normalised attack rates for all 22 patients during the two 12-week crossover periods were 6.26 and 12.73 attacks for the CINRYZE™ and placebo treatments, respectively. The estimated average difference in attack rates between patients receiving CINRYZE™ and those receiving placebo was 6.47 attacks over 12 weeks (95% CI 4.21 to 8.73; P<0.001), and there was no evidence of a significant sequence effect (P = 0.54) or period effect (P = 0.42).
- The mean (±SD) score for the severity of attacks (on a 3-point scale, with 1 indicating mild, 2 moderate, and 3 severe) was statistically significantly lower with CINRYZE™ prophylaxis than with placebo (1.3±0.85 vs. 1.9±0.36, P<0.001).
- The total duration of attacks was statistically significantly shorter with CINRYZE™ prophylaxis than with placebo (2.1±1.13 vs. 3.4±1.39 days, P = 0.002). A total of 11 subjects receiving Cinryze prophylaxis required open-label rescue therapy, as compared with 22 patients receiving placebo. CINRYZE™ prophylaxis was associated with fewer open-label injections (4.7±8.66 vs. 15.4±8.41, P<0.001) and fewer days of swelling (10.1±10.73 vs. 29.6±16.9, P<0.001).
- During the acute-attack treatment trial, 6 of the 36 patients assigned to CINRYZE™ (17%) and 7 of the 35 patients assigned to placebo (20%) had adverse events.
- In the prophylaxis trial, 21 of 24 patients (88%) had one or more adverse events. Three adverse events (pruritus and rash, lightheadedness, and fever) were classified as possibly related to the study drug.

**Health economics / budget impact model**

The table below describes approximate costs for various treatment strategies (table copied from reference 7):

<table>
<thead>
<tr>
<th>Cost of relevant comparators drug</th>
<th>Dose regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icatibant (Firazyr)</td>
<td>30mg subcutaneous injection</td>
<td>£1,395 per dose²⁴</td>
</tr>
<tr>
<td>Tranexamic acid oral</td>
<td>1 to 1.5grams orally two to three times daily</td>
<td>£1.00 to £2.15/day²⁴</td>
</tr>
<tr>
<td>Berinert®</td>
<td>20 units/kg for adults and children</td>
<td>Based on an average body weight of 70kg for an adult, the dose would be 1400 units ≡ £1,650 per dose²⁴</td>
</tr>
<tr>
<td>Conestat alfa (Ruconest)</td>
<td>Adults &lt; 84 kg body weight – One iv injection of 50 U/kg body weight. Adults &gt;/= 84 kg body weight - One iv injection of 4200 U (2 vials).</td>
<td>Based on an average weight of 70kg, a dose of 3500 units would be required (2 vials). The cost of 2 vials is £2800²³</td>
</tr>
<tr>
<td>Cinryze</td>
<td>Adults and adolescents, 1000 units</td>
<td>£1336 per 1000 unit dose (2 vials)</td>
</tr>
<tr>
<td>Ecallantide</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

These costs are for single doses, and do not take into account multiple doses for a single attack.

Short term prevention of attacks with danazol, tranexamic acid or C1-INH (C1-INH given 1 hour prior to the provoking event) may be considered in patients with planned exposure to a situation likely to trigger an attack.

**Table of costs for prevention strategies in anticipation of an HAE attack:**

<table>
<thead>
<tr>
<th>Cost of relevant comparators drug for prevention of HAE</th>
<th>Dose regimen</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tranexamic acid</td>
<td>30mg subcutaneous injection</td>
<td>£1,395 per dose²⁴</td>
</tr>
<tr>
<td>Danazol</td>
<td>200mg tds for 5 to 10 days</td>
<td>£33.10 per 10 day course</td>
</tr>
<tr>
<td>Berinert®</td>
<td>500 to 1000 units given once 1 hour before the provoking event</td>
<td>£550 to £1650 per course</td>
</tr>
</tbody>
</table>
Prophylaxis with CINRYZE™ using the doses mentioned in the LEVP part B study would require approximately 22 doses of CINRYZE™ 1000 units over a period of 90 days for patients who experience at least 2 attacks of angioedema per month, equating to approximately £30,000 per patient.

Points for consideration

- There are no head-to-head studies to determine which is more effective for the treatment of an acute attack: Targeting the bradykinin pathway (using icatibant) or the administration of a C1-esterase inhibitor such as Berinert or CINRYZE™.
- Many of the studies included small numbers of patients, which may reflect the low incidence of HAE.
- There is only one study comparing one of these new products with currently used therapy (icatibant vs. tranexamic acid) for the prevention of a HAE attack. All other studies have been placebo-controlled.
- The only evidence to support use of an agent for routine prevention of HAE attacks is with CINRYZE™, which showed a 50% reduction in the average normalised attack rates with CINRYZE™ treatment, compared with placebo.

References

2. Angioedema. www.patient.co.uk
5. Berinert SPC (C1-esterase inhibitor, human); Date of revision = 2 Dec 2011
6. Icatibant SPC (Firazyr); Date of revision = 28 Feb 2011
10. Human plasma-derived C1 inhibitor SPC (Cinryze); Date of revision = 15 June 2011
11. Conestat alfa (Ruconest – recombinant C1-esterase inhibitor) SPC; Date of revision = August 2011
Drugs used in the management of hereditary angioedema


23. Personal communication – ViroPharma
26. National Horizon Scanning Centre Conestat alfa for acute hereditary angioedema. (June 2012). www.nhsc-healthhorizons.org.uk/files/downloads/1222/1727.76aa026184b11be808db92a0851a4ff7.pdf&sa=U&ei=cTuQT468DpPg8QZku22BA&ved=0CBYQFjAB&usg=AFQjCNFQ1j5G2gXz2ecR2eP-SeJC4AAOw

The document reflects the views of LNDG and may not reflect those of the reviewers.

The LNDG would like to thank:
Dr Clive Grattan, Consultant Dermatologist, Guy’s & St Thomas Hospitals NHS Foundation Trust for his comments on this review. Pharmaceutical companies have also commented on this review.

Please direct any comments to Hina Radia, London & South East Medicines Information Service, Guy’s Hospital, Great Maze Pond, London SE1 9RT

June 2012

London New Drugs Group—APC/DTC Briefing
## Icatibant

### Table 1 - Double-blind controlled phases of FAST1 and FAST 2

<table>
<thead>
<tr>
<th>Ref No</th>
<th>Trial design</th>
<th>Inclusion and exclusion criteria</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| FAST 1 | Multi-centre (USA, Canada, Argentina and Australia), randomised, placebo controlled. | **Inclusion criteria:**  
- Age ≥ 18 years  
- Diagnosis of hereditary angioedema type I or II  
- Current moderate to severe attack involving cutaneous, abdominal or laryngeal areas  
- Able to start treatment within six hours of current attack becoming moderate  
- Visual Analogue Scale score of ≥30mm for cutaneous or abdominal symptom  
**Exclusion criteria:**  
- Diagnosis of other type of angioedema  
- Participation in other clinical trial in last month  
- Treatment with pain medication since onset of current attack  
- Treatment with C1 inhibitor concentrate or tranexamic acid within last three or seven days, respectively  
- Treatment with ACE inhibitor  
- Coronary heart disease or congestive heart failure (class 3/4)  
- Serum creatinine ≥250μmol/L  
- Pregnancy or breastfeeding  
- Serious concomitant illness  
Intention to treat (ITT) population n=56  
Icatibant as a single 30mg subcutaneous dose n=27  
Placebo n=29 | Intention to treat (ITT) population n=56  
Icatibant as a single 30mg subcutaneous dose n=27  
Placebo n=29 | **Primary**  
All attacks - median time (hrs) to onset of symptom relief  
<table>
<thead>
<tr>
<th>Icatibant</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>4.6</td>
<td>0.142 (NS)</td>
</tr>
</tbody>
</table>
| **Secondary**  
Cutaneous attacks - median time (hrs) to onset of symptom relief  
Abdominal attacks - median time (hrs) to onset of symptom relief  
Response rate 4 hours after start of treatment (%)  
Median time (hrs) to almost complete symptom relief  
Median time (hrs) to regression of symptoms according to patient  
Median time (hrs) to regression of visible symptoms according to doctor  
Median time (hrs) to overall patient improvement according to doctor  | Icatibant | Placebo | P value |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3.4</td>
<td>10.0</td>
<td>0.221 (NS)</td>
</tr>
<tr>
<td>2.0</td>
<td>3.0</td>
<td>0.159 (NS)</td>
</tr>
<tr>
<td>66.7</td>
<td>46.4</td>
<td>0.176 (NS)</td>
</tr>
<tr>
<td>8.5</td>
<td>23.3</td>
<td>0.069 (NS)</td>
</tr>
<tr>
<td>0.8</td>
<td>16.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6.5</td>
<td>14.0</td>
<td>0.240 (NS)</td>
</tr>
<tr>
<td>1.0</td>
<td>5.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| **Primary**  
All attacks - median time (hrs) to onsets of symptom relief  
Icatibant as a single 30mg subcutaneous dose n=36  
Tranexamic acid oral 1g three times a day, for 2 days n=38  | Icatibant | Tranexamic Acid | P value |
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>12.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| **Secondary**  
Cutaneous attacks - median time (hrs) to onset of symptom relief  
Abdominal attacks - median time (hrs) to onset of symptom relief  
Response rate 4 hours after start of treatment (%)  
Median time (hrs) to almost complete symptom relief  
Median time (hrs) to regression of symptoms according to patient  
Median time (hrs) to regression of visible symptoms according to doctor  
Median time (hrs) to overall patient improvement according to doctor  | Icatibant | Tranexamic Acid | P value |
<table>
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</thead>
<tbody>
<tr>
<td>2.5</td>
<td>16.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.6</td>
<td>3.5</td>
<td>0.026</td>
</tr>
<tr>
<td>80.0</td>
<td>36.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>10.0</td>
<td>51.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.8</td>
<td>7.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.7</td>
<td>8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.5</td>
<td>6.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Reference:

1. FAST 1
2. FAST 2
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Population</th>
<th>Inclusion and exclusion criteria as for FAST1 and FAST2</th>
<th>ITT population n=93</th>
<th>Icatibant as a single subcutaneous dose n=46</th>
<th>Placebo n=47</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST3</td>
<td>Multi-centre (North America, South America and Europe) randomised, placebo-controlled</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Table 2: Results of the double-blind controlled-phase of FAST3**

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
<th>Laryngeal attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaenous and abdominal attacks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Icatibant (n=43)</td>
<td>Placebo (n=45)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Median time to 50% reduction in symptom severity of pre-treatment VAS-3 score (the primary endpoint) - hours</td>
<td>2.0 (95% CI 1.5 to 3.0)</td>
<td>19.8 (95% CI 6.1 to 26.3)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Median time to onset of primary symptom relief (hours)</td>
<td>1.5 (1.0 to 2.0)</td>
<td>18.5 (3.6 to 23.9)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Median time to almost complete symptom relief (hours)</td>
<td>8.0 (8.0 to 42.5)</td>
<td>36.0 (29.0 to 50.9)</td>
<td>P=0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laryngeal attacks</td>
<td>Primary</td>
<td>Secondary</td>
<td>Open label icatibant</td>
</tr>
<tr>
<td>Icatibant (n=3)</td>
<td>Placebo (n=2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to 50% reduction in symptom severity of pre-treatment VAS-5 score (the primary endpoint) - hours</td>
<td>2.5 (1.3 to 3.0)</td>
<td>3.2 (1.0 to 5.4)</td>
<td>2.3 (1.5 to 4.0)</td>
</tr>
<tr>
<td>Median time to onset of primary symptom relief</td>
<td>2.5 (1.3 to 3.0)</td>
<td>2.7 (1.0 to 4.4)</td>
<td>2.3 (1.7 to 4.0)</td>
</tr>
<tr>
<td>Median time to almost complete symptom relief</td>
<td>6.0 (3.5 to 44.8)</td>
<td>4.0 (1.5 to 6.4)</td>
<td>4.5 (2.2 to 47.5)</td>
</tr>
</tbody>
</table>