London, 20 February 2014
EMA/CHMP/57346/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Firazyr

International non-proprietary name: icatibant

Procedure no. EMEA/H/C/000899/II/0024/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II and group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Shire Orphan Therapies GmbH submitted to the European Medicines Agency on 5 December 2012 an application for a group of variations including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name**	**Presentations:**
Firazyr	ICATIBANT	See Annex A

The following variations were requested in the group:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or Pharmacovigilance data	II

The MAH applied for an extension of the indication for the treatment of ACE-inhibitor induced angioedema. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8 and 5.1 of the SmPC and consequential changes to sections 1, 2 and 3 of the Package Leaflet.

In addition, the MAH proposed to update section 5.1 of the SmPC to include the results of the open-label extension phase of study FAST-3 (HGT-FIR-054).

In addition the MAH has taken the opportunity to make minor editorial changes throughout the PI.

The group of variations proposed amendments to the SmPC and Package Leaflet.

On 14 February 2014, on the basis of the GCP inspection findings and that additional data were required the MAH withdrew the following variation:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of the indication for the treatment of ACE-inhibitor induced angioedema. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8 and 5.1 of the SmPC and consequential changes to sections 1, 2 and 3 of the Package Leaflet.

Firazyr was designated as an orphan medicinal product EU/3/03/133 on 17 February 2003. Firazyr was designated as an orphan medicinal product in the following indication: treatment of angioedema.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0282/2012 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur:	Kristina Dunder	Co-Rapporteur:	Greg Markey

Submission date:	5 December 2012
Start of procedure:	21 December 2012
Rapporteur's preliminary assessment report circulated on:	11 February 2013
Co-Rapporteur's preliminary assessment report circulated on:	11 February 2013
PRAC RMP advice and Assessment Overview:	7 March 2013
Joint Rapporteur's updated assessment report circulated on:	15 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
A GCP inspection was requested by the CHMP. The final integrated Inspection Report was issued on 31 July 2013.	31 July 2013
MAH's responses submitted to the CHMP on:	18 September 2013
Rapporteur's and Co-Rapporteur's preliminary joint assessment report on the MAH's responses circulated on:	30 October 2013
PRAC RMP advice and Assessment Overview:	7 November 2013

Joint Rapporteur's updated assessment report circulated on:	15 November 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 November 2013
MAH's responses submitted to the CHMP on:	18 December 2013
Rapporteur's and Co-Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 January 2014
PRAC RMP advice and Assessment Overview:	6 February 2014
Joint Rapporteur's updated assessment report circulated on:	13 February 2014
MAH withdrawal letter submitted to the CHMP on:	14 February 2014
CHMP opinion:	20 February 2013

2. Scientific discussion

2.1. Introduction

About the product

Icatibant, the active substance in Firazyr, is a selective competitive antagonist of the bradykinin type 2 (B2) receptor. In hereditary angioedema (HAE), increased bradykinin concentrations are the key mediator in the development of the clinical symptoms. Icatibant was shown to be a competitive antagonist of bradykinin and to help symptoms to resolve during acute HAE attacks.

Firazyr was granted a Marketing Authorisation in the EU on 11 July 2008. It is indicated for the treatment of acute attacks of HAE in adults. Its approval was supported by clinical data from two Phase III studies: studies FAST-1 (JE049#2103) and FAST-2 (JE049#2102), which were randomised, double-blind, controlled studies and had identical designs except for the comparator (one with oral tranexamic acid as the comparator and the other placebo controlled).

Problem statement

The MAH submitted a grouping of two type II variations according to Article 7.2 (b) of Commission Regulation (EC) No 1234/2008 for the medicinal product Firazyr (icatibant). The purpose of the first type II variation was to extend the indication for Firazyr (icatibant) in the treatment of ACE-inhibitor induced angioedema.

Furthermore, the purpose of the second type II variation was to update section 5.1 of the SmPC to include the results of the open-label extension phase of study FAST-3 (HGT-FIR-054).

The new ACE-inhibitor induced angioedema indication is supported by the AMACE study, published literatures in ACE-I induced angioedema, the Phase III clinical studies (known as the FAST 1-3 studies) and post-marketing information in hereditary angioedema (HAE) subjects. The results from the AMACE trial are supported by the 3 FAST studies (FAST-1, FAST-2 and FAST-3) and by the open label extension phase of study FAST-3 (HGT-FIR-054). The final data for FAST-1 (JE049-2103-D) and FAST-2 (JE049-2102-D) have already been submitted and assessed as part of Firazyr FUM 027 and variation II/06. The interim data for FAST-3 (HGT-FIR-054) reflects data from the controlled phase only, up to the 1st of October 2010 cut-off date. This data has also already been submitted and assessed as part of variation II/015.

The update of section 5.1 of the SmPC is supported by the results of the recently completed open-label extension phase of the FAST-3 study.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical pharmacology

2.3.1. Pharmacokinetics

The pharmacokinetics (PK) of SC administered icatibant has been thoroughly characterized in healthy subjects and in patients with HAE. A PK analysis was not conducted in patients during the AMACE study. There is no indication from existing data or physiologically-based expectation that the PK of SC icatibant overall would differ significantly between healthy subjects, HAE patients or ACE-I-induced angioedema patients.

2.3.2. Pharmacodynamics

Pathophysiology of the disease

The pathophysiology of angioedema resulting from ACE inhibitor use resembles that of HAE due to C1 inhibitor deficiency, in that it is mainly mediated by bradykinin-induced activation of vascular bradykinin B2 receptors. Bradykinin is a potent vasodilator and increases vascular permeability, leading to rapid accumulation of fluid in the interstitial tissues. ACE inhibitors block angiotensin-converting enzyme, the main bradykinin-inactivating peptidase in humans along with aminopeptidase P, reducing the catabolism of bradykinin. There is experimental evidence that ACE inhibitors induce angioedema by increasing the availability of bradykinin. There may also be an endogenous anomaly in the degradation of bradykinin in patients with ACE-I-induced angioedema, further suggesting that its pathophysiologic mechanism lies in the catabolic side of kinin metabolism. Additionally, with ACE inhibitor administration, aminopeptidase P becomes the primary enzyme responsible for inactivating bradykinin. Individuals with low plasma concentrations of aminopeptidase P also appear to be predisposed to developing angioedema in association with ACE inhibitor therapy.

ACE-I-induced angioedema is not caused by an allergic or parallergic mechanism and while bradykinin plays a critical role, complement protein concentrations and C1 inhibitor function are normal in the case of ACE-I-induced angioedema. This is in contrast to other forms of angioedema, most notably HAE, resulting from mechanisms that alter bradykinin production. In HAE, the lack of C1 inhibitor results in excessive activation of complement as well as of the contact system (including factor XII, plasmin, and to a lesser degree factor XI). Activation of kallikrein follows resulting in the overproduction of bradykinin. Thus, it is the overproduction of bradykinin in HAE and not the reduced degradation of bradykinin as in ACE-I-induced angioedema, which causes the angioedema in patients with HAE. Due to this difference, treatment with purified C1 inhibitor, although effective in treating HAE, is unlikely to be effective in reversing or preventing the angioedema associated with ACE inhibitor as levels of C1 inhibitor are normal. Treatments including recombinant human C1 INH and recombinant human plasma kallikrein inhibitor (i.e. ecallantide) that have been shown to be effective at treating HAE may also be effective at treating ACE-I-induced angioedema. Some case reports have shown C1 INH concentrate to be efficacious in ACEI-induced angioedema.

Mechanism of action

Icatibant is a selective competitive antagonist of the bradykinin type 2 (B2) receptor. It is a synthetic decapeptide with a structure similar to bradykinin, but with 5 non-proteinogenic amino acids.

As summarised above, the pathophysiology of ACE-I-induced angioedema is most likely decreased due to degradation of bradykinin and therefore, direct antagonism of the bradykinin receptor by icatibant could be a relevant therapeutic approach.

2.3.3. Discussion on clinical pharmacology

It is agreed by the CHMP that it is not expected that PK parameters would differ between HAE patients or ACE-I-induced angioedema patients.

No pharmacodynamic studies have been performed. Since the pathophysiology of ACE-I-induced angioedema most likely is based on decreased degradation of bradykinin, it is agreed that direct antagonism of the bradykinin receptor by icatibant could be a relevant therapeutic approach.

The rationale for not conducting additional PK/PD and dose finding studies has been reviewed by the CHMP. Despite the similarities in pathophysiology of angioedema attacks in HAE or ACE-1 inhibitor induced settings, there are several distinct features which should be accounted for during clinical evaluation.

Firstly, the kinetics and levels of bradykinin can differ between HAE and ACE-1-angioedema. The MAH was requested during the evaluation to discuss the details on how levels of bradykinin vary between these groups of patients. Limited efforts were apparently made to measure bradykinin levels consistently and this remains one of the lacunae of the trial and development programme. The issue of different bradykinin levels and pathophysiological basis for the differences were satisfactorily addressed by the MAH. There are challenges in measuring bradykinin levels but this would have been feasible within a relatively small study such as AMACE trial where patients are confined for several days in the hospital and investigators are familiar with treatment and laboratory diagnosis of angioedema. The MAH was requested during the evaluation to justify why bradykinin measurements were not carried out. It is understood that C1 inhibitor (C1-INH) and complement levels are not routinely performed in the ED for suspected cases of ACE-I-induced angioedema and it is agreed that the inclusion and exclusion criteria in the study reflects clinical practice. However, in a clinical trial setting, especially considering the one pivotal trial situation, a more objective diagnosis would have been adequate, even if the final diagnosis would have been achieved after treatment initiation. The fact that this was not performed constitutes a weakness of the study. However, the non-responsiveness of the control patients to conventional therapy in the study may support that these patients indeed had bradykinin-mediated angioedema. The MAH made some efforts to discuss the issues relating to inclusion/ exclusion criteria and used clinical guidelines for emergency treatment of suspected angioedema as a guide to include ACE-I induced angioedema. While this approach is seemingly logical in the context of emergency treatment, it introduces certain difficulties; one availability of history of previous attacks, patient's ability to detail all the relevant points and thus arrive at a diagnosis of exclusion.

Secondly, ACE-1-angioedema cases should be well defined not only on the premise of medical history of taking ACE-1 inhibitor but also using panel of tests such as C1 inhibitor, complement levels and IgE. Levels of these biomarkers are not expected to be considerably affected in ACE-1 angioedema. It was noted that one of the study investigators Dr Bas has published on the role of bradykinin genetic polymorphisms and potential correlation between low levels of serum ACE and ACE-I-induced angioedema. However it is unclear why no attempt was made by the same investigator to carry out the

analysis of these biomarkers. Namely, the ACE levels were determined but no formal discussion or analysis of the data were included in the report. Thirdly, following the most commonly employed algorithm of management in emergency settings and namely, the diagnosis of exclusion, ACE-1 angioedema episodes might be more protracted and often may resolve themselves. The MAH did not provide the discussion on the pattern of angioedema attacks in HAE and ACE-1 induced circumstances and how the duration and / or recurrence in symptoms timely relate to the half-life of icatibant in order to justify the same posology as for HAE. For instance, the current posology suggests that 3 doses are rarely required and not more than 8 doses were employed in the HAE studies. Hence the MAH was requested during the evaluation to discuss the relevance of this posology to the clinical pattern of ACE-1 angioedema attacks (as per reliable epidemiological data) and what is the likely number of doses that will be required (as justified by AMACE data). There is limited data to support either the same posology as in HAE or a different posology. Based on the small dataset available, it seems logical and pragmatic to use the same posology as in HAE in the absence of any signal of lack of effectiveness.

2.4. Clinical efficacy

2.4.1. Introduction

The new ACE-I indication is supported by the AMACE study, published literatures in ACE-I induced angioedema and the Phase III clinical studies in HAE (FAST 1-3 studies).

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Since the new indication is supported by a single pivotal study and taking into account the relatively small size of the AMACE study and noted deviations in its conduct, both a study-specific GCP inspection of the main site and of the sponsor was requested. Namely, the following observations were made:

- In at least 4 subjects the evaluation of patients was carried out by unblinded investigators. It is of concern how the double-dummy design and masking of efficacy evaluations were maintained at each site and how the unblinding compromised overall results.
- The fact that 4 subjects from the control group were lost for follow-up in such a small study is of concern. Specifically, 3 subjects out of 4 recruited into the control group at site 1 (site 1) were lost for follow-up.
- The study database was altered with some additional data entries after the official date of the data-lock and therefore the sponsor's site needed to be inspected and the impact of these changes on the credibility of study findings should be verified.

A request for GCP inspection was adopted for the AMACE clinical study by the CHMP.

Outcome of the GCP inspection

The AMACE trial was planned as an investigator initiated trial, which was financially supported by Shire Deutschland GmbH. The trial conduct was delegated from the sponsor, the Technical University of München, to the Coordinating Investigator (Leiter der klinischen Prüfung, LKP). He in turn delegated most of the sponsor functions to two institutes belonging to the Technical University of München. According to the trial staff, the trial was classified by the sponsor as 'low priority trial'. After the clinical conduct was finished and the decision was made that the trial data will be used by Shire Deutschland

GmbH to extend the indication for Firazyr, major parts of data management, statistics and medical writing were outsourced to a CRO.

The GCP inspection was performed at investigator site no. 1 (Coordinating Investigator) from 21 May until 24 May 2013, at the sponsor site (Techn. University München) from 3 June until 5 June 2013 and at the CRO from 5 June until 7 June 2013.

The involvement of Shire Deutschland GmbH in the conduct of the AMACE trial was not clear to the inspectors and was not adequately covered by the agreements available. During the three inspections performed in connection with the trial it turned out that Shire Deutschland GmbH did not only financially support the conduct of the trial, but was also involved in the preparation of the statistical analyses plan (SAP), gave instructions which WHO medical dictionary was to be used for data management, provided the template for the clinical study report and contributed to the preparation of the clinical study report for the trial.

Summary of Inspection Findings

At the inspection of investigator site no. 1 there were 2 critical, 8 major and 5 minor findings. At the inspection of the sponsor of the trial, Technical University München, Medical Faculty, there were 1 critical, 9 major and 6 minor findings. At the inspection at the CRO, there were no critical, 1 major and 11 minor findings.

In relation to the observations (1.-3.), which were made by the CHMP and which are listed in the scope of the inspection request, the following was verified during the inspection:

(1) The blinding system established in the clinical trial protocol and implemented at the inspected investigator site turned out to be not robust enough to ensure blinding of the investigators.

(2) At investigator site no. 1, only 2 patients were actually lost to follow-up, for 1 patient the follow up visit was performed, but, by mistake, not entered in the Case Report Form.

(3) It was verified at the CRO that there were no changes to the database other than as described for the database unlock in the Clinical Study Report.

In relation to all findings at the GCP inspection the inspectors concluded the below.

Given the critical and major findings, this casts substantial doubt on the reliability of the trial data. The main reasons for this are:

- Firstly, it was not possible to reconstruct, which patient received which treatment at the investigator site inspected (documentation was missing and documentation which was available was contradictory). It is likely that a reconstruction of drug accountability is also not possible at the other investigator sites, because the same deficient instructions for documentation were given to all sites.

- Secondly, the system of conduct of the trial implemented at the inspected investigator site was not robust to ensure blinding of the investigators who performed the primary and secondary objective assessments. Actually, unblinding was very likely to occur due to the local side effects of icatibant and due to the insufficient preventive measures to keep the investigators blinded of the trial and as there is the probability that the same system was used at the other investigator sites, because it was established in the protocol, it is likely that the entire trial is affected.

- Finally, the results reported in the CSR for 'Complete Oedema Restitution' were not exclusively based on a systematic collection at specific time points (visits) as defined in the protocol, but also on ad hoc assessments between the visits. The reported results are therefore not correct. However, bias towards a positive result for icatibant seems, according to a preliminary evaluation presented by the CRO during the inspection, unlikely. The new evaluation using the predefined timepoints from the protocol

will be provided by the sponsor of the trial with a revised and amended clinical study report after the inspection for assessment.

Evaluation by the Inspectors of the Response from the Investigator/Sponsor

The responses of the inspectees and the sponsor of the trial to the inspection reports did not change the grading of any of the findings of the three inspection reports. They did also not change the conclusions made in the three reports.

2.4.2. Dose response studies

The pathophysiology and mechanism of action of HAE (currently approved indication) and ACE-inhibitor induced angioedema are similar, and therefore, the currently approved dose for HAE was used for investigation of efficacy and safety of Firazyr in the treatment of patients with ACE-induced angioedema.

2.4.3. Main studies

2.4.3.1. Extension of indication for the treatment of ACE inhibitor induced angioedema

AMACE study (AMelioration of Angiotensin Converting Enzyme Inhibitor Induced Angioedema Study)

Methods

The AMACE study was a multicentre, two-armed, double-blind, randomised phase II study in parallel group design for the assessment of the treatment concept of ACE inhibitor-induced angioedemas with icatibant.

Study participants

Patients aged between 18 and 95 years with an acute angioedema attack of the upper air and food passageways caused by ACE inhibitors (ACEI) were to be enrolled into this study. Patients arrived at the emergency room of the clinic with acute angioedema of the head and neck area. A prerequisite for recruiting the patient was concomitant intake of an ACEI. The diagnosis was based on the patient's medical history. For this, other differential diagnostics that came into question (allergy, insect bite, trauma, abscess, tumor, post-radiogenic or post-operative swellings, ranula, and other salivary gland processes) were excluded. The inclusion and exclusion criteria were checked and the patient was randomized after obtaining their written informed consent.

Main inclusion criteria

- Aged 18 and < 96 years
- Patients being treated with ACEI
- Patient with acute angioedema attack caused by ACEI
- Treatment administered within 10 hours after onset of the angioedema
- Patients with angioedema of the head and/or neck (face, lips, cheeks, tongue, soft palate/uvula, pharynx and larynx)
- Male participants and female participants not capable of bearing children or who use a method of contraception that is medically approved by the health authority of the respective country.

Main exclusion criteria

- Diagnosis of angioedema of other genesis: e.g. hereditary angioedema, C1-inhibitor deficiency, allergic edema, anaphylaxis, insect bite, trauma, abscess, local inflammation, local tumor, post-operative or post-radiogenic edema, salivary gland disorders
- Participation in a clinical study in the past 30 days
- Patients with simultaneous itchiness of skin (acute urticaria)
- Patients with a history of angioedema before taking ACEI
- Unstable pectoral angina or acute myocardial ischemia
- Acute cardiac insufficiency with an New York Heart Association (NYHA)-classification of 3-4
- History of hypersensitivity to any of the study medications or medicine with a similar chemical structure
- Pregnancy and/or breastfeeding
- Mental retardation of the patient with restriction of general judgment and awareness
- History of drug abuse (including alcohol and alcoholic liver disorders)
- Potentially unreliable patients
- Patients not suitable for the study in the opinion of the Investigator.

Treatments

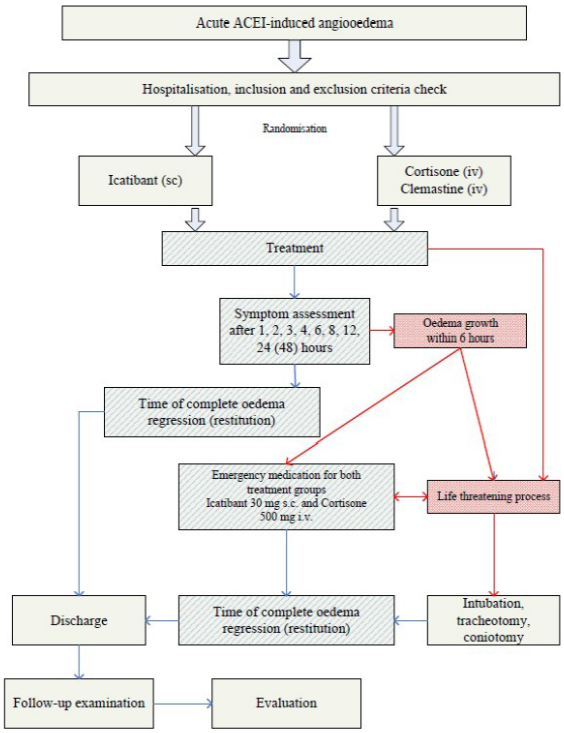
Subjects were randomized at a 1:1 ratio to one of the following treatment arms:

- Arm 1 (“Icatibant group”): Icatibant 30 mg sc
- Arm 2 (“cortisone group”): Solu-Decortin H (prednisolone)/Tavegil (clemastin) intravenous.

If no improvement of the symptoms had occurred within 6 hours after the first administration of study treatment, (irrespective of the randomized treatment group), a second "rescue" administration of 30 mg icatibant dose with 500 mg Solu-Decortin H was possible. In life-threatening situations, the treating physician could implement medicinal and invasive treatment measures (i.e. "rescue" procedures).

The in-patient monitoring phase of the study lasted for at least 18 to 24 hours after administration of study medication, with all patients presenting themselves at the clinic 14 days (+/- 2 days) after end of treatment for re-examination.

Figure 1. AMACE study design



Objectives

The primary objective was to assess the efficacy of the subcutaneously-administered bradykinin B2-receptor antagonist icatibant in comparison to the previous standard treatment consisting of intravenous administration of 500 mg Solu- Decortin H and 2 mg Tavegil in ACE inhibitor-induced angioedema of the upper air and food passageway.

The secondary objectives were to assess the efficacy of the test treatment, icatibant, at different time intervals, and to investigate its safety profile.

Outcomes / endpoints

The primary endpoint was time to complete edema resolution (COR).

At discharge, the time to COR was documented by the second investigator (trained ENT specialist) who was blinded with regard to the actual treatment allocation. The assessment of whether a COR took place (documented as “yes/no” in the CRF) was to be made by the investigator based on the symptom score (investigator and patient; “Composite investigator-assessed symptom score” and “Composite VAS or Patient Perception Scale score”) and the assessment of the severity of the angioedema (“Composite investigator-assessed angioedema score”).

Based on the time of COR and on the timing of the first study drug administration, the time to COR was calculated for each patient.

Composite investigator-assessed symptom score

Attack symptoms were evaluated by the investigator (swallowing disorder, voice changes, sensation of foreign body, shortness of breath, pain, sensation of pressure) using a 4 point scale: (0 = no complaints, 1 = mild complaints, 2 = moderate complaints, 3 = severe complaints). The composite symptom score was calculated as the average of these 6 symptom scores.

Laryngeal Severity Scores

No standard scale for measurement of edema exists in the literature. The principal investigator of the AMACE study developed severity measurements, using an ascending 5-point scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms and 4 = very severe symptoms), which were followed during the study.

Composite investigator-assessed angioedema score

The investigator assessed severity of the angioedema at selected locations (lips and cheeks, tongue, oropharynx, and hypopharynx/larynx), using a 5-point scale: (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms and 4 = very severe symptoms). The composite angioedema score was calculated as the average of these 4 symptom scores.

Composite VAS (or Patient Perception Scale) score

Each subject assessed the intensity of symptoms (pain, shortness of breath, dysphagia, change in voice, foreign body sensation, and feeling of pressure) at pre-treatment and at 1, 2, 3, 4, 6, 8, 12, 18, 24, and 48 hours post-treatment using a Visual Analog Scale (VAS). Due to printing problems, the VAS scale in the subject questionnaire is not 10 cm long, which means that the raw VAS data needed rescaling before analysis. To ensure comparability, all raw VAS measurements were thus divided by a factor determined by data management before analysis and prior to database lock. Composite VAS scores were calculated as the average of VAS measurements for these 6 symptoms.

Secondary Endpoints

- Proportion of patients with COR at 4 hours post-treatment
- Time to onset of symptom relief (defined as the first of three consecutive non-missing assessments in which there was at least a 50% reduction from the pre-treatment composite score) for composite investigator-assessed symptom score [calculated as the average of 6 symptom scores (swallowing disorder, voice changes, sensation of foreign body, shortness of breath, pain, and sensation of pressure) evaluated by the investigator using a 4-point scale]
- Composite investigator-assessed symptom scores and change from pre-treatment at each protocol defined time point, and area under the curve (AUC) at 12 hours post-treatment
- Individual investigator-assessed symptom scores by time point
- Time to onset of symptom relief (defined as the first of three consecutive non-missing assessments in which there was at least a 50% reduction from the pre-treatment composite score) for composite investigator-assessed angioedema score [calculated as the average of 4 angioedema scores (lips and cheeks, tongue, oropharynx, and hypopharynx/larynx) evaluated by the investigator using a 5-point scale]
- Composite investigator-assessed angioedema scores and change from pre-treatment at each protocol defined time point, and AUC at 12 hours post-treatment
- Individual investigator-assessed angioedema scores by time point
- Investigator-assessed laryngeal severity scores by time point
- Time to onset of symptom relief (defined as the first of three consecutive non-missing assessments in which there was at least a 50% reduction from the pretreatment composite score) for composite VAS score [calculated as the average of 6 VAS scores (pain, shortness of breath, dysphagia, change in voice, foreign body sensation, and feeling of pressure) evaluated by the subject using a VAS with a scale of 0 to 10, with a score of 10 being the worst]

- Composite VAS (or patient perception scale) scores and change from pre-treatment at each protocol defined time point, and AUC at 12 hours post-treatment
- Individual VAS scores by time-point
- Proportion of treatment failures.

Sample size

A total of 30 patients (15 patients per treatment arm) in 4 centers were planned for enrolment into the study. Of the 30 subjects enrolled in the study, 3 subjects were not randomized and, therefore by definition, were excluded from the ITT population which consequently consisted of 27 subjects. Because 2 patients in the ITT population did not re-consent to have their individual data be used for submission, a total of 25 subjects were included in the r-ITT population.

Randomisation

Randomization was performed online and was completed once the patient signed the informed consent form to participate in the study. Randomization applied no dynamic allocation of treatment.

Randomization lists were generated beforehand by the statistics department of the Sponsor according to existing standard operating procedures using the randomization software Rancode Professional 3.6 (idv-Datenanalyse und Versuchsplanung, Krailling, Germany; www.idvgauting.com). Randomization lists were stratified by centre and used permuted blocks with a fixed block length only known to the study statistician and the random operator (the study protocol describes variable block length; this was not implemented) and then uploaded onto a secure server.

The randomized allocation of a patient into one of the two treatment groups took place after enrolment of the patient into the study (fulfilment of inclusion criteria and no violation of the exclusion criteria, informed consent form personally signed and dated by the patient) through an online randomization process. The Munich study site then received a recruitment form via FAX when a randomization occurred.

Blinding (masking)

To avoid identification of a patient's treatment due to local injection site effects of icatibant (red skin, pain, burning, itchiness), one investigator only randomized and treated the patient. A second investigator was responsible for monitoring the patient, to assess safety and efficacy parameters as required by the study protocol, and to document them in the case report form (CRF); the second investigator was blinded with regard to the treatment, i.e. he had no information about the randomization and the local injection-site effects.

The first investigator had access to the actual treatment of each randomized patient via the online randomization tool for 7 hours after each randomization. The "7-hour rule" was implemented because a "rescue" dose of treatment (30 mg icatibant dose with 500 mg Solu-Decortin H, irrespective of the randomized treatment group) was possible after assessment of the edema at 6 hours after the initial treatment. Since the two treatment arms had different forms of administration, for the purpose of patient blinding, patients in the icatibant group received placebo treatment intravenously and patients in the Solu-Decortin H / Tavegil group received placebo via subcutaneous injection.

Statistical methods

The statistical analysis was performed twice for the following reason: Only after all patients were enrolled and had been treated in the study it was considered to transfer and submit study results to regulatory agencies. A second informed consent was to be obtained from each patient that explicitly allowed the use of data for submission purposes. However, for 2 patients this re-consent could not be obtained.

Efficacy analyses using the ITT population considered patients as belonging to the treatment group to which they were randomised, regardless of the treatment actually received. For analyses using the as-treated (AT) population and for analyses using the per-protocol population, however, patients were analysed according to the treatment actually received; in the case of the AT population, which could include patients in the control arm who subsequently received icatibant as a rescue medication, patients were analysed according to the first treatment received. The datasets of re-consented patients were named as r-AT and r-ITT.

To assess the impact of baseline attack severity and age on the primary endpoint, time to COR was analysed using a Cox proportional hazards model which included covariates for treatment and either baseline severity of the attack or age group. No imputation strategy was employed for subjects that required rescue therapy, instead the time to COR as observed was used. Because all subjects eventually achieved COR, no subject was censored. The hazard ratio (icatibant vs. control), corresponding 95% confidence interval and p-value assessing differences in the time to COR between the treatment groups for the r-ITT population was presented. In addition, the p-value from the stratified Peto-Peto Wilcoxon test was presented.

Since a skewed distribution of time until complete oedema restitution is to be expected, the comparison between intervention and control groups was done using the Mann-Whitney-U Test. For the calculation of sample size of this non-parametric test the area under the ROC-Curve (receiver-operating-characteristic curve): a quantitative parameter (time till the complete oedema restitution) vs. treatment group affiliation can be drawn on as a measurement of effect. This area can be interpreted as probability of observing a smaller value in one of the two groups when compared to the other (P(X<Y)). As there were disjointed distributions with regard to oedema restitution times between icatibant-treated and cortisone/clemastine-treated patients in the off-label administration observations, this probability can be set with P(X<Y) = 0.90 so that 11 patients per group will be required to prove the distribution differences to be expected with a power of 90% to a two-sided significance level of 5%.

Baseline Attack Severity

Subjects were classified into two groups based on their baseline attack severity. Two measures of attack severity were considered; one based on the composite investigator-assessed symptom score at pre-treatment and the other based on the composite VAS score at pre-treatment.

Classification groups were created based on the median value at pre-treatment for each measure.

Composite investigator-assessed symptom score:

- 0 to 1
- >1.

Composite VAS score:

- 0 to 2 cm
- >2 cm.

Age Group

Subjects were classified into two groups based on their age at baseline.

- 18-65 years
- >65 years.

Time to Onset of Symptom Relief for Individual Symptoms

Each subject assessed the intensity of attack symptoms (pain, shortness of breath, dysphagia, change in voice, foreign body sensation, and feeling of pressure) using a VAS. Additionally, attack symptoms were evaluated by the investigator (swallowing disorder, voice changes, sensation of foreign body, shortness of breath, pain, sensation of pressure) using a 4 point scale: 0 = no complaints, 1 = mild complaints, 2 = moderate complaints, 3 = severe complaints. Time to onset of symptom relief for individual symptoms was calculated from the time of study drug administration to the onset of symptom relief. Symptom relief was determined retrospectively as the earliest of three consecutive non-missing measurements in which there is at least a 50% reduction in the individual pre-treatment score. Subjects that did not achieve symptom relief were censored at the time of their last assessment. The median time to onset of symptom relief for individual symptoms was estimated by treatment group for the r-ITT population using the Kaplan-Meier method.

The following changes in the conduct of the study were performed:

- The statistical analysis was performed twice for the following reason: Only after all patients were enrolled and had been treated in the study was it considered to transfer and submit study results to regulatory agencies. A second informed consent was to be obtained from each patient that explicitly allowed the use of data for submission purposes (re-consent). However, for 2 patients this re-consent could not be obtained.

- The study database was locked on 31-Jul-2012 and unblinding took place on the same day. The study database was unlocked on 2-Aug-2012 in order to correct an erroneously entered value for a patient: In the comment field on the adverse event page the date of tracheostomy in local anesthesia was changed from 28-Oct-2012 to 08-Oct-2010. No further data were changed and the database was locked again on 2-Aug-2012.

The following deviations from the analysis as planned in the protocol were performed:

- The proportion of patients with complete oedema restitution 4 hours after treatment was added to the list of secondary endpoints. No additional data was needed in order to analyse this endpoint. Further efficacy analyses were performed using the VAS and symptom score measures at the 4 hours after treatment time point, and achievement of COR was also analysed at the 4 hour post-treatment time point. These analyses were not specified in the original protocol, but were documented in the final version of the SAP prior to the unblinding of study results.

- The statistical analysis was performed twice for the following reason: Only after all patients were enrolled and had been treated in the study it was considered to transfer and submit study results to regulatory agencies. A second informed consent was to be obtained from each patient that explicitly allowed the use of data for regulatory submissions (re-consent). However, for 2 patients this re-consent could not be obtained. Patient listings are therefore provided twice, once containing all patients for non-submission purposes and once excluding those patients with missing re-consent. The statistical analysis was also performed twice: once containing all patients and once excluding those 2 patients with missing second informed consent. The submitted report refers mainly to all patients who received study medication regardless of whether the re-consent could be obtained.

- In addition to the ITT and PP analysis populations the AT ("as treated") population was included in the SAP. The AT population is essentially a new name for the safety population and was used for safety and efficacy analyses.

- Due to the fact that 2 patients did not provide a second informed consent, so called "re-consented" analysis populations were defined, excluding these 2 patients: r-ITT, r-PP, r-AT.

Results

Participant flow

In the ITT population, 4 subjects, all in the control group, discontinued the study. All 4 subjects were lost to follow-up. These patients received complete treatment and were discharged from hospital with COR but did not perform the last visit that was scheduled 14 days after the admission to hospital. Similarly, in the r-ITT population, 3 subjects, all in the control group, discontinued the study; all were lost to follow-up.

Table 1. Summary of Patient Disposition by Actual Treatment Group and Overall - AT Population

	Icatibant		Control		Total	
Disposition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Informed consent*	15	(100.0%)	15	(100.0%)	30	(100.0%)
Patient status						
Discontinued study	0	(0.0%)	4	(26.7%)	4	(13.3%)
Completed study	15	(100.0%)	11	(73.3%)	26	(86.7%)
Reason for discontinuation						
Adverse Event	0	(0.0%)	0	(0.0%)	0	(0.0%)
Withdrawal of consent	0	(0.0%)	0	(0.0%)	0	(0.0%)
Protocol violation	0	(0.0%)	0	(0.0%)	0	(0.0%)
Lost to follow-up	0	(0.0%)	4	(26.7%)	4	(13.3%)
Death	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other reason	0	(0.0%)	0	(0.0%)	0	(0.0%)

Source: Table 10.1.1.1

*For 2 patients, 1 in the Icatibant group and 1 in the Control group, re-consent could not be collected to allow transfer of individual data for regulatory purposes.

Conduct of the study

As part of quality assurance the study site was visited by a monitor at regular intervals to:

- Evaluate valuation the progress of the study
- Check compliance with the study protocol
- Discuss problems including AEs
- Verify the pCRF for accuracy and completeness
- Compare data of pCRF against original data
- Verify handling of the study preparation.

A total of 4 audits were performed: 2 on-site audits, 1 audit of the Sponsor and 1 audit of the data management and biostatistics CRO Metronomia. No local authority inspections took place at any investigational site during the study period.

Baseline data

Table 2. Subject Demographics and Baseline Characteristics- AMACE

Baseline Characteristics	ITT Population		r-ITT Population	
	Icatibant (N=13)	Control (N=14)	Icatibant (N=12)	Control (N=13)
Age [n(%)]				
18-65 years	9 (69.2)	3 (21.4)	8 (66.7)	3 (23.1)
>65 years	4 (30.8)	11 (78.6)	4 (33.3)	10 (76.9)
Age (years)				
n	13	14	12	13
Mean (Std. Dev.)	62.4 (9.7)	69.4 (16.6)	62.3 (10.2)	68.8 (17.1)
25th percentile	63.0	66.0	58.0	66.0
Median [Min, Max]	63.0 [42.0,75.0]	75.0 [28.0,86.0]	63.5 [42.0, 75.0]	73.0 [28.0, 86.0]
75th percentile	70.0	81.0	70.0	81.0
Gender [n (%)]				
Male	9 (69.2)	8 (57.1)	8 (66.7)	7 (53.8)
Female	4 (30.8)	6 (42.9)	4 (33.3)	6 (46.2)
Family history of angioedema				
Yes	0	0	0	0
No	13 (100.0)	14 (100.0)	12 (100.0)	13 (100.0)
Previous episode of angioedema [n (%)]				
Yes	5 (38.5)	5 (35.7)	4 (33.3)	5 (38.5)
No	8 (61.5)	9 (64.3)	8 (66.7)	8 (61.5)

Approximately one-third of patients in both groups experienced a prior history of angioedema. Although subjects with urticaria and previous angioedema prior to taking ACE inhibitors were excluded from the study, these subjects were permitted to be enrolled in the study because the angioedema was reported while subjects were receiving ACE inhibitors.

A total of 3 patients in the icatibant group and 4 in the control group had various allergies to drugs and animals. In both groups, the most common medical history was hypertension, in 14/15 (93.3%) patients. For concomitant medications, see the table below.

Table 3. Concomitant Medications by Either Treatment Group - As- Treated Population

ATC2 Name Base Substance	Icatibant (N=15) n	 (%)	Control (N=15) n	 (%)
Agents acting on the renin-angiotensin system	15	(100.0%)	15	(100.0%)
Benazepril	1	(6.7%)	0	(0.0%)
Candesartan	0	(0.0%)	1	(6.7%)
Capozide	1	(6.7%)	0	(0.0%)
Captopril	1	(6.7%)	1	(6.7%)
Enalapril	5	(33.3%)	2	(13.3%)
Lisinopril	0	(0.0%)	3	(20.0%)
Olmesartan	1	(6.7%)	1	(6.7%)
Prinzide	1	(6.7%)	0	(0.0%)
Quinapril	1	(6.7%)	0	(0.0%)
Ramipril	5	(33.3%)	9	(60.0%)
Renin-angiotensin system, agents acting on	1	(6.7%)	0	(0.0%)
Salutec	0	(0.0%)	1	(6.7%)
Valsartan	0	(0.0%)	1	(6.7%)
Analgesics	4	(26.7%)	7	(46.7%)
Antibacterials For Systemic Use	2	(13.3%)	4	(26.7%)
Antiepileptics	0	(0.0%)	2	(13.3%)
Antigout Preparations	4	(26.7%)	2	(13.3%)
Antihistamines For Systemic Use	2	(13.3%)	0	(0.0%)
Antihypertensives	3	(20.0%)	4	(26.7%)
Antithrombotic Agents	2	(13.3%)	2	(13.3%)
Beta Blocking Agents	6	(40.0%)	7	(46.7%)
Calcium Channel Blockers	10	(66.7%)	7	(46.7%)
Corticosteroids For Systemic Use	4	(26.7%)	1	(6.7%)
Diuretics	6	(40.0%)	8	(53.3%)
Drugs For Acid Related Disorders	5	(33.3%)	4	(26.7%)
Drugs For Obstructive Airway Diseases	0	(0.0%)	3	(20.0%)
Drugs Used In Diabetes	4	(26.7%)	3	(20.0%)
Lipid Modifying Agents	6	(40.0%)	6	(40.0%)
Thyroid Therapy	1	(6.7%)	3	(20.0%)

Baseline severity of ACE-I-induced angioedema was assessed by the composite symptom score, composite angioedema score, composite VAS score and individual VAS score for the ITT and r-ITT populations. The severity of angioedema at baseline was comparable across the two treatment groups by the composite symptom score, the composite angioedema score and the composite VAS Score. Based on the composite symptom score, attacks tended to be mild in nature (a score of 0 indicates no symptoms, while a score of 3 indicates severe symptoms).

Table 4. Baseline Severity of ACE-I-Induced Angioedema by Composite Scores (AMACE)

	ITT Population		r-ITT Population	
	Icatibant (N=13)	Control (N=14)	Icatibant (N=12)	Control (N=13)
Composite Investigator-Assessed Symptom Score				
Mean (Std. Err.)	1.1 (0.2)	1.2 (0.2)	1.0 (0.2)	1.1 (0.2)
Median [Min, Max]	1.2 [0.0, 2.2]	1.1 [0.2, 2.5]	1.1 [0.0, 1.8]	1.0 [0.2, 2.5]
Composite Investigator-Assessed Angioedema Score				
Mean (Std. Err.)	1.1 (02)	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)
Median [Min, Max]	0.8 [0.5, 2.3]	0.9 [0.5, 2.5]	0.8 [0.5, 2.3]	0.8 [0.5, 2.0]
Composite Subject- Assessed VAS Score				
Mean (Std. Err.)	2.9 (0.6)	3.5 (0.6)	2.5 (0.6)	3.2 (0.5)
Median [Min, Max]	2.0 [0.2, 7.1]	3.1 [0.6, 7.6]	1.8 [0.2, 6.5]	3.1 [0.6, 6.6]
Individual Subject-Assessed VAS Scores				
Dysphagia				
Mean (Std. Err.)	3.9 (1.1)	4.9 (1.0)	3.4 (1.1)	4.5 (1.0)
Median [Min, Max]	2.9 [0.0, 9.7]	5.0 [0.0, 9.7]	2.2 [0.0, 9.7]	4.8 [0.0, 9.7]
Change in Voice				
Mean (Std. Err.)	3.0 (1.0)	3.8 (0.8)	2.5 (0.9)	3.4 (0.8)
Median [Min, Max]	0.9 [0.0, 9.6]	4.2 [0.0, 8.9]	0.6 [0.0, 9.6]	3.1 [0.0, 7.7]
Pain				
Mean (Std. Err.)	1.0 (0.5)	1.9 (0.6)	0.6 (0.4)	1.8 (0.6)
Median [Min, Max]	0.1 [0.0, 5.2]	1.8 [0.0, 6.3]	0.1 [0.0, 4.0]	1.7 [0.0, 6.3]
Shortness of Breath				
Mean (Std. Err.)	1.1 (0.5)	1.7 (0.5)	1.1 (0.5)	1.4 (0.4)
Median [Min, Max]	0.1 [0.0, 4.8]	1.1 [0.0, 6.0]	0.1 [0.0, 4.8]	0.4 [0.0, 3.5]
Foreign Body Sensation				
Mean (Std. Err.)	4.0 (0.1)	4.7 (0.9)	3.6 (1.0)	4.4 (0.9)
Median [Min, Max]	2.7 [0.0, 9.8]	4.2 [0.4, 9.9]	2.5 [0.0, 9.8]	3.5 [0.4, 9.9]
Feeling of Pressure				
Mean (Std. Err.)	4.4 (0.9)	4.2 (0.9)	4.0 (0.9)	3.8 (0.8)
Median [Min, Max]	3.4 [0.1, 9.7]	4.2 [0.0, 9.4]	3.4 [0.1, 9.7]	3.8 [0.0, 9.0]

max = maximum, min = minimum, Std. Err. = standard error

Numbers analysed

The primary population for efficacy analyses was the Intent-to-Treat (ITT) subject population. The ITT population is defined as all randomized subjects who received at least one dose of study medication. In the ITT population, subjects were analysed according to randomized treatment. The ITT population was used for all primary and secondary efficacy analyses.

Two of the subjects enrolled in the study did not consent to provide individual data for submission for registration in this trial. These subjects were excluded from the ITT population to form the re-consented ITT (r-ITT) population. All analyses performed for the ITT population were repeated in the r-ITT population.

The per-protocol (PP) population consisted of all patients in the ITT population except for those who received additional study medications or procedures due to edema worsening and patients with major protocol violations. Three patients, all from the Control group received additional study medication (rescue medication) and were therefore excluded from the PP. The PP consisted consequently of 24 patients; 13 patients were in the icatibant group and 11 patients in the Control group.

The as-treated (AT) population consisted of all patients who received at least one dose of study medication, with results attributed to the treatment they received first. Analysis of the secondary safety endpoints were performed on the AT population. In addition, all primary and secondary efficacy analyses were repeated for the AT population as sensitivity analyses.

The AT population consisted of 30 patients, 15 patients in the icatibant group and 15 patients in the Control group.

Outcomes and estimation

Table 5. Time to Complete Oedema Restitution (hours)

	ITT Population		r-ITT Population	
	Icatibant (N=13)	**Control (N=14)**	**Icatibant (N=12)**	**Control (N=13)**
Number (%) subjects with worsening oedema	0	3 (21.4)	0	3 (23.1)
Time to Complete Oedema Restitution				
n	13	14	12	13
Mean (Std. Dev.)	15.4 (18.8)	33.2 (18.0)	16.4 (19.3)	34.2 (18.4)
Median	8.0	27.1	8.1	30.3
[Min, Max]	[2.8, 61.2]	[11.3, 61.2]	[2.8, 61.2]	[11.3, 61.2]
P-value[b] (Wilcoxon rank-sum test)	0.002		0.006	
P-value (Van Elteren's test)	0.025		0.050	
Hodges-Lehmann estimate (95% CI)	-17.3 (-32.9, -8.3)		-17.2 [-33.1,-6.0]	

These results are based on an imputed time to COR for the 3 patients in the Control group who had a worsening of edema after the initial treatment with study medication and received a rescue treatment. No patient in the icatibant group received a second injection. As pre-defined for the primary analysis, the missing time to COR was replaced by the highest time to COR from the whole analysis population. For these patients, a time to COR of 61.2 hours was thus imputed, which was the highest time to COR that was observed for a patient in the Icatibant group.

A more conservative approach was defined by imputing the time to COR using the highest time from the opposite treatment. In this study this approach led to exactly the same result.

Table 6. Time (in hours) to Complete Edema Restitution (COR) by Treatment Group - Primary Endpoint, Supportive Analysis Using the Original Time to COR

Parameter	ITT Population		PP Population		AT Population	
	Icatibant (N=13)	Control (N=14)	Icatibant (N=13)	Control (N=11)	Icatibant (N=15)	Control (N=15)
Number of patients with worsening edema	0 (0.0%)	3 (21.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (20.0%)
Time to COR[a] (in hours)						
n	13	14	13	11	15	15
Mean (SD)	15.4 (18.8)	23.2 (11.0)	15.4 (18.8)	25.6 (11.2)	14.1 (17.7)	24.4 (11.6)
25th percentile	3.0	14.0	3.0	17.8	3.0	14.0
Median (Range)	8.0 (2.8-61.2)	21.2 (10.5-48.0)	8.0 (2.8-61.2)	23.7 (11.3-48.0)	8.0 (2.8-61.2)	22.0 (10.5-48.0)
75th percentile	16.0	30.3	16.0	35.9	16.0	35.9
P-value[b] (Wilcoxon rank-sum test)	0.016		0.012		0.004	
P-value (Van Elteren's test)	0.093		0.089		0.039	
Hodges-Lehman estimate (95% CI)	-10.5 (-19.1, -3.0)		-14.8 (-21.0, -4.0)		-12.3 (-20.7, -5.3)	

In the ITT population all patients reached COR, therefore no patient was censored in the first Kaplan-Meier analysis. The median time to onset of COR for the patients treated with icatibant was 8.0 hours (range: 2.8 - 61.2 hours) versus 27.1 hours (range: 11.3 - 61.2 hours), and the p-value was 0.0002 (Peto-Peto-Prentice).

Figure 2. Kaplan-Meier Plot of Time (in hours) to Complete Edema Restitution (COR) by Randomized Treatment Group - Censoring Patients who did not Obtain COR - ITT population

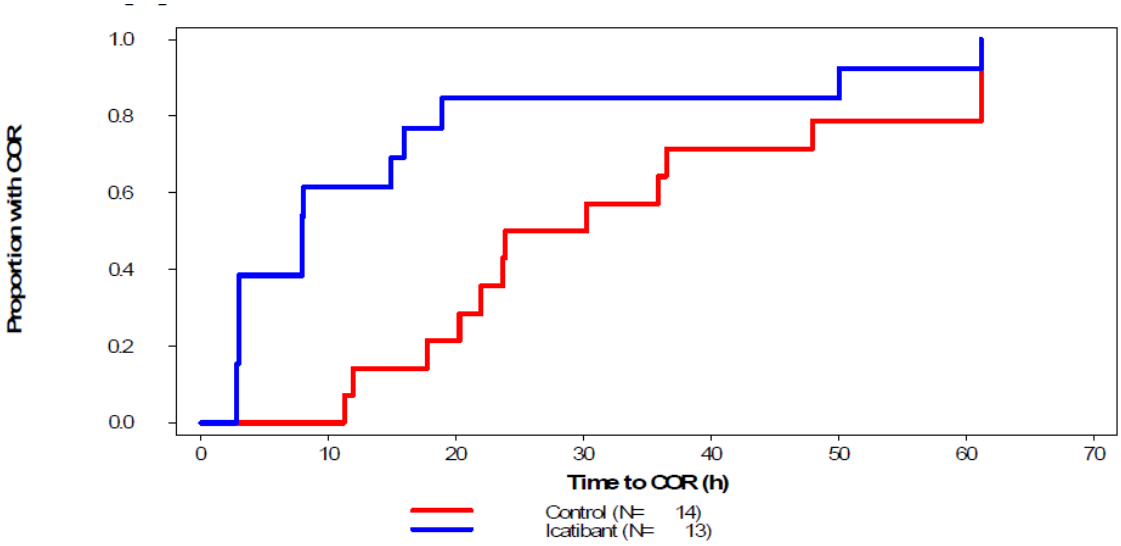


Table 7. Results, secondary endpoints– ITT Population

Endpoint	Statistic	Icatibant	Control	p-value
Secondary Endpoints		(n = 13)	(n=14)	
Proportion of Patients with Complete Edema Resolution at 4 Hours Post-Treatment	n (%)	5 (38.5)	0 (0.0)	0.016
Change in Composite Investigator-Assessed Symptom Score				
At 2 hrs After Treatment	Mean (SE)	-0.7 (0.2)	0.0 (0.1)	0.002
At 4 hrs After Treatment	Mean	-0.9 (0.2)	-0.1 (0.2)	0.004
Time to Onset of Symptom Relief for Composite Investigator-Assessed Symptom Score (hrs)	Median [95% CI]	2.0 [1.0, 8.1]	11.7 [8.0, 18.0]	0.031
Change in Composite Investigator-Assessed Angioedema Score				
At 2 hrs After Treatment	Mean (SE)	-0.6 (0.1)	0.1 (0.1)	<0.001
At 4 hrs After Treatment	Mean (SE)	-0.7(0.1)	0.0 (0.1)	<0.001
Time to Onset of Symptom Relief for Composite Investigator-Assessed Angioedema Score (hrs)	Median [95% CI]	2.0 [2.0, 12.0]	12.0 [11.3, n.e.]	<0.003
Change in Composite Patient-Assessed VAS Score				
At 2 hrs After Treatment	Mean (SE)	-2.0 (0.6)	-0.6 (0.3)	0.063
At 4 hrs After Treatment	Mean (SE)	-2.4 (0.7)	-0.8 (0.4)	0.074
Time to Onset of Symptom Relief for Composite Patient-Assessed VAS Score (hrs)	Median [95% CI]	2.0 [2.0, 6.3]	7.9 [1.2, 11.8]	0.356
Proportion of Treatment Failures (patients who required the use of rescue medications)	n (%)	0	3 (21.4)	0.222

Patient-assessed symptom scores

In the r-ITT population, the median time to symptom relief based on the individual VAS score of dysphagia was 1.9 hours for the icatibant group and 7.0 hours for the control group (p=0.078); for change in voice was 2.2 hours for the icatibant group and 3.7 hours for the control group (p=0.923); for pain the score change was 4.7 hours for the icatibant group and 3.0 hours for the control group (p=0.817); for shortness of breath was 9.1 hours for the icatibant group and 11.8 hours for the control group (p=0.684); for foreign body sensation was 2.0 hours for the icatibant group and 4.0 hours for the control group (p=0.579); the feeling of pressure was 2.5 hours for the icatibant group and 12.0 hours for the control group (p=0.164).

Supportive data

Efficacy in Subjects with Laryngeal HAE Attacks (FAST Studies)

The final data for FAST-1 and FAST-2 have been submitted and assessed as part of FUM 027 and variation II/006. The interim data for FAST-3 reflecting data from controlled phase only, up to 1 October 2010 cut-off date was assessed as part of variation II/015. These trials were performed in subjects with Type I or Type II HAE. FAST-1 and FAST-2 were randomized, double-blind, controlled trials and had identical designs except for the comparator (one with oral tranexamic acid as the comparator and one placebo controlled). A total of 130 patients were randomized to receive either a 30 mg dose of icatibant (63 patients) or comparator (either tranexamic acid, – 38 or placebo – 29 patients). Patients with symptoms of laryngeal angioedema received open label treatment with icatibant. The primary efficacy endpoint was the time to onset of symptom relief using a visual analogue scale (VAS).

FAST-3 was a randomized, placebo-controlled, parallel-group study of 98 adult patients. Patients were randomized to receive either icatibant 30 mg or placebo by subcutaneous injection. The primary endpoint was time to onset of symptom relief assessed using a 3-item composite visual analogue score.

Methods

Efficacy data from laryngeal HAE attacks from these studies in have been provided based on the similar symptomatology of laryngeal HAE attacks compared with ACE-I-induced angioedema. A dataset pooling the first laryngeal attacks of subjects in the FAST studies has been created to support the efficacy seen with icatibant in ACE-I-induced angioedema.

Similar to the AMACE study, investigator-assessed symptom scores and VAS scores were used to assess the severity of HAE; however different attack symptoms were assessed.

Table 8. Summary of Clinical Measures in the FAST Studies for Laryngeal HAE Attacks (FAST Studies)

Clinical Measure	Symptoms include:	Rating
Investigator Assessed Symptom Score	Difficulty swallowing* Voice change* Breathing difficulties Stridor Asphyxia Skin swelling Erythema (skin redness) Skin pain Abdominal pain Nausea Abdominal tenderness Vomiting Diarrhea	No symptoms Mild symptoms Moderate symptoms Severe symptoms
Patient-Assessed Visual Analog Score (VAS)	Difficulty swallowing* Voice change* Skin pain Skin swelling Abdominal pain	Patient draws a line indicating the severity of a symptom along a 100 mm line.

Clinical Measure	Symptoms include:	Rating

[a] indicates a symptom that is directly comparable to one that was collected in AMACE

The most analogous endpoint in the FAST studies to the primary endpoint used in the AMACE study (time to COR after the administration of study medication) is the time from treatment administration to almost complete symptom relief (TACSR). However, the TACSR endpoint was based on the Visual Analog Scale (VAS) and the time to COR endpoint in the AMACE study was based on direct clinical observation by the ENT specialist. Almost complete symptom relief was determined retrospectively as the earliest of three consecutive non-missing measurements for which all VAS scores are less than 10 mm.

Study population

The laryngeal treated population consisted of 66 subjects with an icatibant-treated laryngeal attack. The analyses focused on the subject's first icatibant-treated laryngeal attack. Fifty-five of 66 (83.3%) subjects completed assessments to Day 14, with the remaining 11 subjects having missing data (1 subject) or discontinuing (10 subjects) due to additional HAE attack (6 subjects), lost to follow up (1 subject), or other (3 subject). Sixty-one of 66 subjects (94.2%) were treated with one 30 mg SC icatibant injection each for this laryngeal attacks, while 5 of 66 subjects (7.6%) received a second injection of icatibant.

The median age was 38.5 years for the laryngeal treated population. Overall the majority (42 subjects, 63.6%) of subjects were female. Most subjects were white (57 subjects, 86.4%).

Results

The median time to almost complete symptom relief (TACSR) based on the subject-assessed VAS was 6.4 hours. Almost complete symptom relief was achieved by 24 of the 27 subjects (96%) with evaluable data in the laryngeal treated population. FAST 1 and 2 did not collect VAS scores for laryngeal symptom and thus symptom relief could not be determined.

The median times to onset of symptom relief based on the composite investigator-assessed symptom score and the composite subject-assessed VAS score were 2.0 hours (based on 37 of 40 subjects with evaluable data). Most individual investigator-assessed symptom scores for laryngeal-related symptoms were mild or absent by 4 hours after treatment. Individual subject-assessed VAS scores for difficulty swallowing and voice change showed similar results to that of the individual symptoms scores, with symptoms decreasing rapidly over the first 5-6 hours of treatment.

Table 9. Time to Almost Complete Symptom Relief- Laryngeal Treated Population (FAST Studies)

	FAST 2 (N=12)	FAST 1 (N=27)	FAST 3 (N=27)
Time to Almost Complete Symptom Relief			
Number of subjects with almost complete symptom relief	NA	NA	24 (96.0%)
Censored[a]			1 (4.0%)
Kaplan-Meier Estimates (hours)			
Median (hours)			6.4
95% CI			3.1, 24.3

Almost complete symptom relief is defined as all VAS scores <10 mm.

Published Case Reports in ACE-I-Induced Angioedema

- In a case series described in 2010 in the Annals of Emergency Medicine, Bas et al conducted a study of 8 patients with ACE-I-induced angioedema who presented to the emergency department. All patients had an acute angioedema attack of the head or neck (face, lips, cheeks, tongue, soft palate/uvula/ pharynx, and larynx) of less than 10 hours' duration, and had previously received ACE inhibitor therapy of varying duration between 12 and 132 months. Each patient received a single SC injection of icatibant 30 mg, and the outcome was assessed by the time to first improvement of symptoms, complete symptom relief, and safety. First symptom improvement after icatibant administration occurred at a mean time of 50.6 minutes (± 21 minutes) and complete relief of symptoms at 4.4 hours (± 0.8 hours). No patient underwent tracheal intubation, other drug treatment, tracheotomy, or received a second icatibant injection. No adverse events were reported except for erythema at the injection site.
- In a case report presented at the European Academy of Allergy and Clinical Immunology Congress in 2011, Reksten described an episode of acute angioedema in a 72-year old woman, who had been receiving therapy with ramipril for 5 years, that occurred 3 months after an increase in her prescribed dosage. The patient awoke with severe breathing difficulties, dysphagia and severe tongue swelling, and was admitted to the hospital with severe oropharyngeal swelling. She showed little to no response to treatment with antihistamines and glucocorticoids. ACE-I-induced angioedema was suspected, and a single SC injection of icatibant 30 mg was administered approximately 4.5 hours after the initial development of angioedema symptoms. Within 30 minutes of icatibant administration, the severe tongue swelling had receded and the patient's breathing had eased. Submandibular swelling persisted over the next few hours, but declined progressively and was barely present after 24 hours. No systemic or serious adverse reactions were observed, and no injection site reactions were recorded. The patient was able to return home after 48 hours.
- In an abstract presented at the American Academy of Allergy, Asthma, and Immunology scientific meeting in 2011, Perez, et al. presented 2 cases of ACE-I induced angioedema, both caused by lisinopril. One patient developed angioedema of the lower lip, tongue and uvula, accompanied by dysphagia and dysphonia. She did not respond to corticosteroid and antihistamine therapy, and her condition worsened over 2 hours. Icatibant was administered, and angioedema resolved over 30 minutes. The second patient developed lip, tongue, and uvular angioedema, and was found to have airway involvement by laryngoscopy. Icatibant was administered and the edema resolved within 2 hours.
- In 2010, Schmidt, et al presented a case report in the Journal of the American Academy of Dermatology of a 42-year-old man who developed angioedema of the tongue and larynx, presumed to be associated with treatment with fosinopril. Angioedema worsened despite treatment with corticosteroids, antihistamines, and inhaled epinephrine. 30 mg of icatibant was administered and edema began to resolve within 15 minutes, averting the need for emergency tracheotomy.
- In another case report by Manders et al, a 45-year-old woman was presented to emergency department with progressive swelling of the tongue for several hours. Medication use consisted of chlorthalidone, metoprolol, methotrexate, omeprazole, simvastatin, and lisinopril, the dose of which was recently raised from 10 to 20 mg daily. Before presentation, she had already been repeatedly treated, without response, with adrenaline 0.5 mg intramuscularly (IM), DAF (Di-Adreson-F) 25 mg intravenously and clemastine 0.5 mg IM. After admission to emergency department, subcutaneous icatibant 30 mg was administered. Within a few minutes, the

swelling of the tongue decreased and she was able to speak and articulate more clearly. There was no need for intubation. The total duration of hospital stay was two days.

- Iling et al reported no immediate benefit when icatibant was administered in a 62-year old male presenting with severe oral, pharyngeal and laryngeal oedema while on an ACE inhibitor.

Icatibant outcome survey

IOS is a MAH sponsored registry of patients taking commercially administered icatibant in 8 countries in the EU, which has accumulated data from 457 subjects since 2009. While this is intended to be a registry of patients using icatibant for its approved used in HAE, it records "real world" use, and thus a small number of patients whose providers used icatibant "off-label" for other indication are included.

IOS includes data for 3 patients (all from a single site in Denmark) with a diagnosis of ACE-I-induced angioedema, each of whom received treatment with a single SC injection of icatibant 30 mg after also having received rescue medications (antihistamines, corticosteroids, epinephrine).

Two of the patients, a 71-year-old female and a 57-year-old male, presented with acute attacks of ACE-I-induced angioedema characterized by severe to very severe tongue involvement. Treatment with icatibant produced resolution of the attacks in these patients within 2.0 and 7.0 hours, respectively. The third patient, a 79-year-old female with very severe laryngeal edema, was not treated with icatibant until 13.8 hours after the onset of symptoms and experienced resolution of the attack 23.2 hours after receiving a single icatibant injection of 30 mg.

2.4.3.2. Open-label extension phase of the FAST-3 study (HGT-FIR-054)

FAST-3 study (HGT-FIR-054*)*

FAST-3 was a randomized, placebo-controlled, parallel-group study of 98 adult patients. Patients were randomized to receive either icatibant 30 mg or placebo by subcutaneous injection. The primary endpoint was time to onset of symptom relief assessed using a 3-item composite visual analogue score.

The interim report for FAST 3 included data from 76 subjects treated with icatibant across 198 attacks of HAE in the completed blinded phase and the open label phase, which was ongoing at the time of the interim data cut-off. The interim data for FAST-3 reflecting data from controlled phase only, up to 1 October 2010 cut-off date was assessed as part of variation II/015 and information was included in the SmPC.

The final FAST 3 report incorporates the complete data from the open-label extension phase from 88 subjects treated with icatibant across 489 attacks of HAE. Data not previously included in the interim report consist of 291 additional icatibant attacks, originating from 12 subjects with a first-icatibant treated attack, 42 subjects with additional icatibant-treated attacks (ie, subjects were previously reported in the interim report, but experienced additional attacks), and 6 subjects with a first icatibant-treated laryngeal attack.

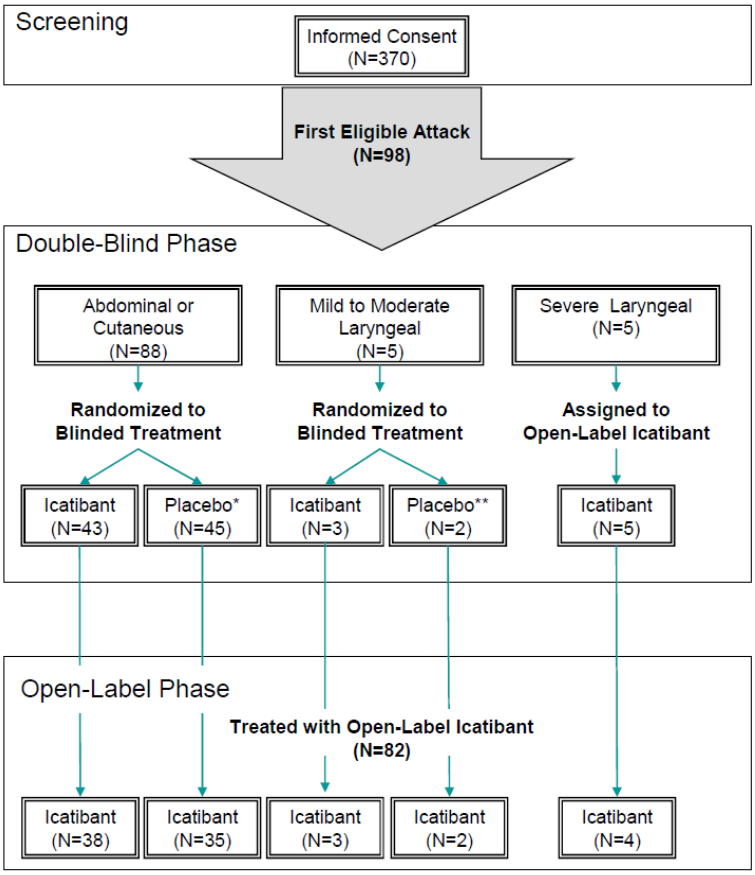
Study Design

This was a phase III randomized double-blind, placebo-controlled multicenter study of icatibant for Subcutaneous Injection in Patients with Acute Attacks of Hereditary Angioedema. The primary objective was to compare the efficacy of icatibant with placebo on the time to symptom relief using a composite visual analog scale (VAS) during moderate to very severe acute cutaneous and/or abdominal attacks in patients with type I or type II hereditary angioedema (HAE).

A total of 88 patients who had previously been screened and presented with moderate to very severe cutaneous and/or abdominal symptoms were to be randomized to receive a single, double-blind treatment of icatibant (30 mg) or placebo, with approximately equal numbers assigned to each study arm. Patients experiencing severe laryngeal attacks were to receive open-label icatibant.

After the first attack, patients could continue to receive open-label icatibant for the treatment of subsequent attacks until such time as the study was discontinued by the sponsor or the investigational product became commercially available. There were 70 subjects with icatibant-treated second attacks, 55 subjects with treated third attacks, 37 subjects with -treated fourth attacks, and 31 subjects with treated fifth attacks.

Figure 3. Disposition of Subjects



Results open label extension phase

The median time to onset of symptom relief based on the 3-symptom composite VAS score and time to onset of primary symptom relief based on the primary VAS score were consistent across the first 5 icatibant-treated attacks (range: 1.9 to 2.1 hours).

There were 435 attacks treated in the open-label phase; of those, 19 attacks (4.4%) required a second icatibant injection and 1 attack (<1%) required a third icatibant.

2.4.4. Discussion on clinical efficacy

The pathophysiology of ACE-I-induced angioedema is most likely based on decreased degradation of bradykinin. Thus, the mechanism of action (direct antagonism of the bradykinin receptor) supports the theory that icatibant may be a relevant treatment of ACE-I-induced angioedema.

The pivotal trial for this new indication is the AMACE trial which was a multicenter, randomized, rater-blinded, double-dummy, parallel-group, two-arm, comparative Phase II study. The primary objective was to assess the efficacy of the subcutaneously-administered bradykinin B2-receptor antagonist Icatibant in comparison to standard treatment consisting of intravenous administration of 500 mg Solu- Decortin H and 2 mg Tavegil in ACE inhibitor-induced angioedema of the upper air and food passageway.

The same posology as currently approved for HAE indication was used in the study although it was not supported by data. However, based on the small dataset available, it seems logical and pragmatic to use the same posology as in HAE in the absence of any signal of lack of effectiveness.

Patients aged between 18 and 95 years with an acute angioedema attack caused by ACEI presenting at the emergency ward were to be enrolled into this study. A prerequisite for recruiting the patient was concomitant intake of an ACEI. The diagnosis was based on the patient's medical history. For this, other differential diagnostics that came into question (allergy, insect bite, trauma, abscess, tumor, post-radiogenic or post-operative swellings, ranula, and other salivary gland processes) were excluded as assessed based on patient history.

At study entry, no assessments of laboratory markers, e.g. measuring complement, IgE and bradykinin levels were performed. It is accepted that these evaluations are difficult to carry out routinely but taking into account the fact that the study was carried out at centres specialised in treating patients, and acknowledging various up-to-date EU guidelines on diagnostic algorithms for angioedema, the lack of these evaluations in the study are considered as a drawback, albeit not pivotal for the interpretation of the results.

The patient population enrolled into the AMACE study, as originally presented, was characterised by relatively mild-to-moderate severity of symptoms and only 3 patients (all from the control group) required rescue re-treatment and a single patient from control group required tracheotomy. However, the fact that patients who participated in the AMACE study were those who were severe enough to seek medical attention for their ACE-I-induced angioedema attack supports that they represent the population who would be considered for icatibant treatment in the emergency department. This is further supported by the approach to examine the maximum severity score across all symptoms or all angioedema locations. In this analysis, the majority of patients in the AMACE study (82.1% by angioedema scores and 64% to 82.1% by symptom scores) experienced ACE-I-induced angioedema attacks that were either moderate or severe in intensity.

Primary (time to complete edema resolution) and secondary endpoints are in general acceptable. The primary endpoint was based on both investigator and patient assessments which seems reasonable. It is acknowledged that most likely no validated scores are available for this orphan condition. However, the components of the scores are rather similar to scores used in the HAE-studies. Further, investigations were performed by trained ENT specialists and examination was standardized through training at an Investigators Meetings, including training on scales for rating oropharyngeal and laryngeal edema.

The study was blinded using a double-dummy design. However, at least 4 subjects became unblinded due to “unavailability of the blinded study investigator”. In addition, the treatment administration was carried out by unblinded investigators as local injection reactions are well recognised with icatibant. Still, it is unclear what measures were in place in order to prevent interaction between blinded and unblinded investigators as the evaluation overlapped in the first 7 hours at the same site. The MAH has conducted additional analyses indicating that the time to COR in both patients with and without injection site reactions was similar. It is not possible to rule out that the unblinding has biased the results however it is accepted that the analyses provided give some reassurance and that it is unlikely

that the unblinding has introduced a substantial bias. However, considering the overall conclusion of the GCP inspection, this is still a concern.

4 subjects were lost to follow-up from the comparator group including 3 subjects from a single centre. It is of concern that the loss of patients occurred at a single site in such a small study. The dataset has been also affected by some patients being randomised but assigned in the icatibant group as opposed to the control arm. The MAH has provided further sensitivity analyses that show evidence of a treatment effect regardless of how these patients are treated in the analysis. The median time to COR in the icatibant group was 8.0 hours compared to 21.2 hours in the control group. The difference was statistically significant using the Wilcoxon rank-sum test, and is of clinical relevance. However, the range of time to COR was wide in the icatabant group, with a max of 61.2 hours (longer than the max time in the control group).

There were 2 "outliers" in the icatibant group with long duration until COR. However, based on the narratives, both had rapid symptom relief after treatment and only minor symptoms remained. Demographics and baseline characteristics did not differ between those with COR ≤ 8 hours versus those with COR > 8 hours after treatment with icatibant. No major differences in severity of attacks were detected.

During the triggered GCP inspection, it was found that the results reported in the CSR for 'Complete Oedema Restitution' were not exclusively based on a systematic collection at specific time points (visits) as defined in the protocol, but also on ad hoc assessments between the visits. The MAH has performed a sensitivity analysis which only used the scheduled times of the visits. In this analysis, the median time to COR in the icatibant group was 8.0 hours compared to 24 hours in the control group, i.e very similar to the original results. However, as mentioned above, considering the overall conclusion of the GCP inspection, this is still a concern.

Overall, icatibant provided an approximately 2.5-fold greater probability that the oedema would subside quicker than when using control treatments. For the investigator-assessed symptom scores statistically significant differences were seen for all symptoms except for foreign body sensation and sensation of pressure but the duration to symptom severity reduction was numerically better with icatibant for all symptom components.

The MAH has performed analyses indicating a positive concordance between the investigator and subject assessments of symptom severity. Further, there were similar trends across the investigator- and subject-assessed scores for the individual symptoms. It is recognized that treatment comparisons at the 1, 2, 3, 4, and 6 hour assessments are statistically significant for the investigator-assessed symptom scores but not for the subject-assessed VAS scores. However, considering the small sample size, statistical significance cannot be expected for all analyses. It is true that the effect size was larger in the investigator assessed outcomes, but considering the similar trends over time for both investigator and patient assessed outcomes, the results are considered as supportive of an effect of icatibant.

From a mechanistic point of view, results from patients with laryngeal HAE attacks may be considered as supportive for the proposed indication and the MAH has provided pooled data from the FAST studies. However, the endpoints were not the same and data for the most similar endpoint (time to almost complete symptom relief) is only available for 24 patients. Even if the median time is similar (6.4 compared to 8.0 hours) the strength of the data is questionable.

The MAH has identified 28 publications through a PubMed search. The majority of the publications have been published during the recent years. Five of the publications were written by Dr Bas who was involved in the AMACE study. Nine publications refers to case reports or case series while the rest are mainly review articles covering the treatment of angiooedema including those with bradykinin

mediated ethiology. Concerning the case reports, all except one seems to be supportive of a beneficial effect of icatibant in the treatment of ACE-I-induced angioedema. There are no controlled studies reported.

Concerning the open label phase of the FAST 3 study, data not previously included in the interim report consist of 291 additional icatibant attacks, originating from 12 subjects with a first-icatibant treated attack, 42 subjects with additional icatibant-treated attacks (ie, subjects were previously reported in the interim report, but experienced additional attacks), and 6 subjects with a first icatibant-treated laryngeal attack. The proposed changes to section 5.1 of the SmPC are acceptable.

2.4.5. Conclusions on clinical efficacy

In summary, whilst there is good clinical and pathophysiological rationale for the use of icatibant in treatment of ACE-I-induced angioedema, and the results of the AMACE study may indicate a support for this rationale, the critical and major findings at the GCP inspection cast substantial doubt on the reliability of the trial data. The CHMP concluded that the robustness of the results needs further justification and confirmation. The MAH therefore withdrew the extension of indication.

Concerning the open label phase of the FAST 3 study, data not previously included in the interim report consist of 291 additional icatibant attacks, originating from 12 subjects with a first-icatibant treated attack, 42 subjects with additional icatibant-treated attacks (ie, subjects were previously reported in the interim report, but experienced additional attacks), and 6 subjects with a first icatibant-treated laryngeal attack. The proposed changes to section 5.1 of the SmPC are acceptable.

2.5. Clinical safety

2.5.1. Introduction

The new proposed indication is angiotensin converting enzyme-inhibitor (ACE-I) -induced angioedema, for which this type II variation is submitted. The MAH refers to efficacy and safety data from the AMACE study as well as the experience with icatibant in the treatment of HAE patients, a bradykinin-mediated condition. The HAE data presented have been generated from three controlled Phase III studies (known as the FAST studies). Published case reports in ACE-I-induced angioedema and post-marketing experience in HAE are also provided as supportive information.

AMACE is a multicenter, two-armed, double-blind, randomised, parallel group trial. The study evaluated the safety and efficacy of icatibant compared to standard of care (in this trial defined as corticosteroid and clemastine), enrolling 30 patients (15 patients per arm) suffering from an acute attack of ACE-I-induced angioedema. The study population consisted of 30 adult subjects, 18 to 86 years of age, who presented with an ACE inhibitor-induced acute angioedema attack of the head and/or neck. Eligible subjects were enrolled into the study within 10 hours of an attack onset, and randomised 1:1 to receive either SC administered icatibant (30 mg) or IV administered corticosteroid and clemastine as a control. The safely evaluation consisted of:

- Evaluation of laboratory data (routine blood)
- Evaluation of vital signs
- Evaluation of adverse events
- Evaluation of necessity of additional medicines
- Evaluation of necessity of implementation of invasive procedures (intubation, tracheostomy).

Patient exposure

In the AMACE study, 30 subjects were recruited. Three subjects were never randomised, and were excluded from the ITT population (=27 subjects). Further, two subjects in the ITT population did not follow through with the data submission, and a total of 25 subjects were included (reconsented-ITT population).

As a result of the above, 12 subjects in the icatibant group required one injection, and three of the 13 subjects in the control group received an injection of icatibant along with IV cortisone as rescue therapy. Therefore, the total exposure for icatibant is 15 subjects. For the three subjects who received rescue therapy, it was administered within 6-6.9 hours after initial treatment.

Adverse events

In the AMACE study, 30 subjects were recruited.

Treatment-emergent adverse events:

In the as treated (AT) population, no subjects discontinued from the AMACE study due to AEs; however, four subjects, all in the control group, were discontinued from the study because they were lost to follow-up. These subjects received complete treatment and were discharged from hospital with complete oedema restitution but did not perform the last visit that was scheduled 14 days after admission to the hospital.

In the AMACE study, six AEs were reported by five subjects, one of whom (subject 2) was not included in the re-consented population (r-ITT). One subject in the icatibant group reported a mild AE of pain that was probably related to study drug. All other AEs occurred in subjects in the control group. One of these AEs (blood glucose increased) was considered by the investigator to be probably related to study medication, two AEs (COPD and fatigue) were considered to be unlikely related to study drug, and all other AEs were not related to study drug. There was one severe AE of dyspnoea, reported by a subject in the control group, all other AEs were mild.

Subject No.	Treatment	SOC/Preferred Term	Serious	Severity	Relatedness
1	Icatibant	General disorders and administration site conditions/Pain	No	Mild	Probably
2*	Control	Respiratory, thoracic, and mediastinal disorders/COPD	No	Mild	Unlikely
3	Control	Investigations/Blood glucose increased	No	Mild	Probably
4	Control	General disorders and administration site conditions/Fatigue	No	Mild	Unlikely
5	Control	Respiratory, thoracic, and mediastinal disorders/Dyspnea	Yes	Severe	Not related
5	Control	General disorders and administration site conditions/Influenza like illness	No	Mild	Not related

Patient No. 1., in the Icatibant group, experienced mild pain on the day of first treatment application. This AE was considered as probably related to study medication. The patient was given an NSAID, the AE resolved and the patient recovered.

Patient No. 2., in the Control group, experienced mild chronic obstructive disease one day after the first study drug administration. This AE was considered as unlikely related to study medication. The patient was given cefuroxim; the AE resolved and the patient recovered.

Patient No. 3., in the Control group, experienced a mild blood glucose increase one day after the first study drug administration. This AE was considered as probably related to study medication. No action was taken, the AE resolved and the patient recovered.

Patient No. 4., in the Control group, experienced mild fatigue on the first day of study drug administration. This AE was considered as unlikely related to study medication. No action was taken, the AE resolved and the patient recovered. However, this patient received a second treatment application/rescue medication (i.e. icatibant and cortisone).

Patient No. 5., in the Control group, experienced mild influenza-like illness 15 days after the first study drug administration. This AE was considered as not related to study medication. The patient was given cefuroxim; the AE resolved and the patient recovered with sequelae. This patient also experienced an SAE (dyspnoea).

Injection Site Reactions:

Injection site reactions occurred in a majority of subjects in the icatibant group, including redness (80%), swelling (53.3%), pain (46.7%), itching and burning (26.7% each). These symptoms resolved within four hours of dosing. Fewer subjects in the control group reported injection-site reactions; however, those reported resolved within two hours of dosing.

Serious adverse events and deaths

As related above, there was one subject who described an SAE: (subject No. 5), dyspnoea: The subject received rescue therapy with icatibant and IV cortisone six hours after initial treatment in the study, and had a tracheostomy 25 minutes after receiving rescue therapy. COR (complete oedema restitution) was achieved 14 hours after the initial treatment. The SAE of dyspnoea was not considered related to the study medication. The subject completely recovered from the event.

There were no reports of fatal cases.

Laboratory findings

Laboratory data (blood count, inflammation parameter, coagulation parameters, electrolytes, liver parameters, renal parameters, other parameters) were collected at baseline, 12 hours post-treatment, and 14 hours post-treatment. ACE activity was reported as U/l. Actual values and change from pre-treatment were summarised by study time point and treatment group for the AT population.

ACE activity:

Observed Values at Scheduled Time Points by Treatment Group - AT Population:

	Observed Value					
	Baseline		12 hours		14 days	
Laboratory Parameter	Icatibant	Control	Icatibant	Control	Icatibant	Control
ACE-activity [U/L]						
n	9	12	4	8	9	8
Mean (SD)	15.1 (20.6)	9.4 (10.0)	36.3 (28.2)	10.6 (7.2)	39.1 (18.3)	49.3 (17.8)

Change from Pre-Treatment at Scheduled Time Points by Treatment Group - AT Population:

	Change from Pre-Treatment			
	12 hours		14 days	
Laboratory Parameter	Icatibant	Control	Icatibant	Control
ACE-activity [U/l]				
n	3	6	6	7
Mean (SD)	4.67 (4.04)	4.52 (4.17)	35.10 (16.59)	38.39 (11.43)

Vital signs

Vital signs were generally normal for all subjects. In the icatibant group, a total of 3 subjects presented with above-normal systolic blood pressure; one patient with above-normal temperature and three subjects with below normal temperature. In the control group, two subjects presented with above- and two with below- normal temperature.

Table 10. Proportion of Subjects Experiencing at Least One Abnormal Change in a Vital Sign Parameter by Treatment Group - AT Population

	Proportion of Subjects[a]	
Infusion Vital Sign Parameter	Icatibant	Control
Pulse Rate (bpm)		
Above Normal	0 / 14 (0)	0 / 12 (0)
Below Normal	0 / 14 (0)	0 / 12 (0)
Systolic blood pressure (mmHg)		
Above Normal	3 / 14 (21.4)	0 / 12 (0)
Below Normal	0 / 14 (0)	0 / 12 (0)
Diastolic blood pressure (mmHg)		
Above Normal	0 / 14 (0)	0 / 13 (0)
Below Normal	0 / 14 (0)	0 / 13 (0)
Temperature (°C)		
Above Normal	1 / 5 (20.0)	2 / 6 (33.3)
Below Normal	3 / 5 (60.0)	2 / 6 (33.3)

Safety in special populations

There was a majority of males in the study (70% of the icatibant group and 60% in the control group). In the ITT group overall, the patients in the control group were older than those in the treatment group.

Immunological events

N/A.

Safety related to drug-drug interactions and other interactions

N/A.

Discontinuation due to AES

N/A.

Post marketing experience

Supportive post-marketing information on icatibant as a treatment for ACE-I-induced angioedema is provided in the following:

- The Firazyr Risk Management Plan
- A comprehensive assessment of safety and efficacy of Firazyr in both clinical development and the post-marketing setting was submitted on 11 Jul 2012, as part of the EU 5-year renewal
- The Periodic Safety Update Report (PSUR)
- The Icatibant Outcome Survey (IOS)
- Case reports from the published literature.

Despite the rarity of HAE, a clinical safety dataset was created to establish the safety of icatibant. Based on the marketing data the estimated patient exposure is 20,720 patient exposures for the reporting period 12 July 2011 through 11 July 2012 and 33,841 patient exposures cumulatively.

Three reports from the Icatibant Outcome Survey (IOS) concerning reports on treating ACEi induced oedema with icatibant

IOS is a MAH sponsored registry of patients taking commercially administered icatibant in 8 countries in the EU, which has accumulated data from 457 subjects since 2009. While this is intended to be a registry of patients using icatibant for its approved used in HAE, it records “real world” use, and thus a small number of patients whose providers used icatibant “off-label” for other indication are included. IOS includes data for three patients with a diagnosis of ACE-I-induced angioedema, each of whom received treatment with a single SC injection of icatibant 30 mg after also having received rescue medications (antihistamines, corticosteroids, epinephrine).

Two of the patients, a 71-year-old female and a 57-year-old male, presented with acute attacks of ACE-I-induced angioedema characterised by severe to very severe tongue involvement. Treatment with icatibant produced resolution of the attacks in these patients within 2 and 7 hours, respectively. The third patient, a 79-year-old female with very severe laryngeal oedema was not treated with icatibant until 13.8 hours after the onset of symptoms and experienced resolution of the attack 23.2 hours after receiving a single icatibant injection of 30 mg.

Literature reports on treating ACEi induced oedema with icatibant

In a case series described in 2010 in the Annals of Emergency Medicine, Bas et al conducted a study of eight patients with ACE-I-induced angioedema who presented to the emergency department. All patients had an acute angioedema attack of the head or neck (face, lips, cheeks, tongue, soft palate/uvula/ pharynx, and larynx) of less than ten hours’ duration, and had previously received ACE inhibitor therapy of varying duration between 12 and 132 months. Each patient received a single SC injection of icatibant 30 mg, and outcome was assessed by the time to first improvement of symptoms, complete symptom relief, and safety. First symptom improvement after icatibant administration occurred at a mean time of 50.6 minutes (± 21 minutes) and complete relief of symptoms at 4.4 hours

(± 0.8 hours). No patient underwent tracheal intubation, other drug treatment, tracheotomy, or received a second icatibant injection. No adverse events were reported except for erythema at the injection site.

In a case report presented at the European Academy of Allergy and Clinical Immunology Congress in 2011, Reksten described an episode of acute angioedema in a 72-year old woman, who had been receiving therapy with ramipril for five years that occurred three months after an increase in her prescribed dosage. The patient awoke with severe breathing difficulties, dysphagia and severe tongue swelling, and was admitted to the hospital with severe oropharyngeal swelling. She showed little to no response to treatment with antihistamines and glucocorticoids. ACE-I-induced angioedema was suspected, and a single SC injection of icatibant 30 mg was administered approximately 4.5 hours after the initial development of angioedema symptoms. Within 30 minutes of icatibant administration, the severe tongue swelling had receded and the patient's breathing had eased. Submandibular swelling persisted over the next few hours, but declined progressively and was barely present after 24 hours. No systemic or serious adverse reactions were observed, and no injection site reactions were recorded. The patient was able to return home after 48 hours.

In an abstract presented at the American Academy of Allergy, Asthma, and Immunology scientific meeting in 2011, Perez, et al. presented two cases of ACE-I induced angioedema, both caused by lisinopril. One patient developed angioedema of the lower lip, tongue, and uvula, accompanied by dysphagia and dysphonia. She did not respond to corticosteroid and antihistamine therapy, and her condition worsened over two hours. Icatibant was administered, and angioedema resolved over 30 minutes. The second patient developed lip, tongue, and uvular angioedema, and was found to have airway involvement by laryngoscopy. Icatibant was administered and the oedema resolved within two hours.

In 2010, Schmidt, et al presented a case report in the Journal of the American Academy of Dermatology of a 42-year-old man who developed angioedema of the tongue and larynx, presumed to be associated with treatment with fosinopril. Angioedema worsened despite treatment with corticosteroids, antihistamines, and inhaled epinephrine. 30 mg of icatibant was administered and oedema began to resolve within 15 minutes, averting the need for emergency tracheotomy.

In another case report by Manders et al, a 45-year-old woman was presented to emergency department with progressive swelling of the tongue for several hours. Medication use consisted of chlorthalidone, metoprolol, methotrexate, omeprazole, simvastatin, and lisinopril, the dose of which was recently raised from 10 to 20 mg daily. Before presentation, she had already been repeatedly treated, without response, with adrenaline 0.5 mg intramuscularly (IM), DAF (Di-Adreson-F) 25 mg intravenously and clemastine 0.5 mg IM. After admission to emergency department, subcutaneous icatibant 30 mg was administered. Within a few minutes, the swelling of the tongue decreased and she was able to speak and articulate more clearly. There was no need for intubation. The total duration of hospital stay was two days.

In another patient who recently presented to the emergency department with swollen tongue and gums while being treated with fosinopril (since 2009) was not treated with icatibant and had to be admitted to the ICU for endotracheal intubation for 24 hours with a total hospital stay of four days.

Iling et al reported no immediate benefit when icatibant was administered in a 62-year old male presenting with severe oral, pharyngeal, and laryngeal oedema while on an ACE inhibitor, however the finding is inconclusive.

2.5.2. Discussion on clinical safety

The MAH stated that subcutaneously administered icatibant 30 mg provides a clinically meaningful and statistically significant improvement in the time to the resolution of symptoms as demonstrated by the blinded randomised AMACE trial and the HAE Phase III clinical trials. This is agreed for the HAE phase III trials that also were the foundation for the present indication.

The AMACE trial showed effect also in patients with ACEi-induced oedema, but the trial was small and as there was a limited number of patients included, making thorough assessment of safety difficult.

There was no different safety pattern, but also here it must be noted the small sample of patients in the study. No new safety data was retrieved in a recent renewal. Due to small sample size no subgroup analysis was meaningful. In the laboratory findings, there is a notable difference in values of ACE activity, but again, the number of patients is small, making the assessment difficult.

The AE of injection site reactions are well known in the already approved indication, and from earlier studies. Few cases are serious, and the majority resolve without treatment. It is an identified risk in the RMP.

Follow-up is important, although it is agreed that the exposure to these patients will be limited to one occasion, as the use of ACE inhibitors will be discontinued after an attack of angioedema.

From the cases from the literature, nor from the IOS registry, no new safety information can be drawn.

2.5.3. Conclusions on clinical safety

The safety profile of icatibant, when given under the indication of HAE, is established from trials, post-marketing reporting, and IOS registry. During recent PSURs and renewal procedures, no new safety concerns were identified, and the risk-benefit balance continued to be positive. The safety findings in the AMACE study seem similar to previously shown profile, but the number of patients is very limited. If approved, patients treated under the new indication must be followed-up rigorously, and e.g. registered in the IOS.

2.6. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.7. Risk management plan

2.7.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

The PRAC considered that the risk management system version 5.1.1 could be acceptable with revisions required as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

In the most recent version 5.1.1 of the RMP, the introduction section and section 2.2 have been revised, as requested, to amend the IOS protocol to monitor also the safety profile of ACE-I-induced angiooedema patients. However, also section 2.4 “Overview of study protocols for the

pharmacovigilance plan", and possibly also table 27 under section 2.6 "Summary of outstanding actions, including milestones" should be amended.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns	
Important identified risks	Injection site reactions
Important potential risks	Deterioration of cardiac function under ischemic conditions due to bradykinin antagonism Partial bradykinin agonism Antigenicity Lack of efficacy Self administration
Missing information	Use during pregnancy and in lactating women Use in children, and in adolescents.

Pharmacovigilance plans

Safety issues	**Agreed pharmacovigilance activities**	**Agreed risk minimisation activities**
Identified risk: • Injection site reactions	Routine pharmacovigilance	Routine risk minimisation activities
Potential risks: • Deterioration of cardiac function under ischemic conditions due to bradykinin antagonism • Partial bradykinin agonism • Antigenicity • Lack of efficacy • Self administration	Routine pharmacovigilance Safety data monitoring via the Icatibant Outcome Survey (IOS)	Routine risk minimisation activities
Missing information: • use during pregnancy and in lactating women • use in children and adolescents	Routine pharmacovigilance PIP (Paediatric use) Safety data monitoring via the Icatibant Outcome Survey (IOS)	Routine risk minimisation activities

Risk minimisation measures

Safety issues	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Identified risk: • Injection site reactions	Routine pharmacovigilance	Routine risk minimisation activities
Potential risks: • Deterioration of cardiac function under ischemic conditions due to bradykinin antagonism • Partial bradykinin agonism • Antigenicity • Lack of efficacy • Self administration	Routine pharmacovigilance Safety data monitoring via the Icatibant Outcome Survey (IOS)	Routine risk minimisation activities
Missing information: • use during pregnancy and in lactating women • use in children and adolescents	Routine pharmacovigilance PIP (Paediatric use) Safety data monitoring via the Icatibant Outcome Survey (IOS)	Routine risk minimisation activities

The CHMP endorsed this advice without changes.

Following the withdrawal of the variation related to the extension of indication for the treatment of ACE-inhibitor induced angioedema, RMP version 5.1.1 cannot be considered as approved.

2.8. Update of the Product information

- Extension of the indication for the treatment of ACE-inhibitor induced angioedema

The MAH initially proposed the update of sections 4.1, 4.2, 4.4, 4.5, 4.7, 4.8 and 5.1 of the SmPC and consequential changes to sections 1, 2 and 3 of the Package Leaflet. However following the withdrawal of this variation, these proposed changes are no longer pursued by the MAH.

- Update to section 5.1 of the SmPC to include the results of the open-label extension phase of study FAST-3 (HGT-FIR-054)

The MAH initially proposed the following changes to the Product Information (new text= underlined, deleted text= strikethrough) to which the CHMP agreed:

Section 5.1 Pharmacodynamic properties of the SmPC

Response was also consistent across repeated attacks in the controlled Phase III trials. A total of 237~~225~~ patients were treated with 1,386~~1,076~~ doses of 30 mg icatibant for 1,278~~987~~ attacks of acute HAE. In the first 15 Firazyr treated attacks (1,114 doses for 1,030 attacks), the median times to onset of symptom relief were similar across attacks (2.0 to 2.5 hours). 92.4 % of these attacks of HAE were treated with a single dose of Firazyr. ~~In an assessment of the first 5 icatibant-treated attacks (621 doses for 582 attacks) the time to onset of symptom relief was similar across attacks. 92.9 % of these attacks were treated with a single dose of icatibant.~~

[...]

~~126~~208 patients were treated in the open label extension (OLE) phase FAST-1~~,and~~ FAST-2 and FAST-3 for a total of ~~714~~1149 separate attacks. The efficacy results were similar to those seen in the controlled phase of the studies. The majority of attacks (88.2% in FAST-1~~,and~~ 89.8% in FAST-2 and 95.6% in FAST-3) required only a single dose of icatibant.

A total of ~~60~~66 patients with attacks of HAE affecting the larynx were treated in these controlled Phase III clinical trials. The results were similar to patients with non-laryngeal attacks of HAE with respect to time to onset of symptom relief.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

In addition the MAH has taken the opportunity to make minor editorial changes throughout the PI and to amend the Package Leaflet based on the results of user testing submitted and assessed as part of FUM 028 (the CHMP conclusions were adopted in April 2013).

3. Benefit-Risk Balance

Benefits

Beneficial effects

The pathophysiology of ACE-I-induced angioedema is most likely based on decreased degradation of bradykinin. Thus, the mechanism of action (direct antagonism of the bradykinin receptor) supports the theory that icatibant may be a relevant treatment of ACE-I-induced angioedema.

The pivotal trial supporting the new indication is the AMACE trial which was a multicenter, randomized, rater-blinded, double-dummy, parallel-group, two-arm, comparative Phase II study. The primary objective was to assess the efficacy of the subcutaneously-administered bradykinin B2-receptor antagonist icatibant in comparison to the previous standard treatment consisting of intravenous administration of 500 mg Solu- Decortin H and 2 mg Tavegil in ACE inhibitor-induced angioedema of the upper air and food passageway.

The median time to complete edema resolution (primary endpoint) in the icatibant group was 8.0 hours compared to 21.2 hours in the control group. The difference was statistically significant using the Wilcoxon rank-sum test, and is of clinical relevance. Results of secondary endpoints in general support the results for the primary endpoint. No patient in the icatibant group required rescue medications compared to 3 in the control group.

The MAH has submitted case reports which could be supportive of a beneficial effect of icatibant in the treatment of ACE-I-induced angioedema.

Uncertainty in the knowledge about the beneficial effects

Due to suspected deviations in the conduct of the AMACE trial, a triggered GCP inspection has been performed. At the inspection of investigator site no. 1 there were 2 critical, 8 major and 5 minor findings. At the inspection of the sponsor of the trial, Technical University München, Medical Faculty, there were 1 critical, 9 major and 6 minor findings. At the inspection at the CRO there were no critical, 1 major and 11 minor findings. The inspection report concludes that due to the number and kind of findings observed, a GCP-compliant conduct of the AMACE trial at the sponsor site and at investigator site no. 1 cannot be confirmed. Main areas of concern were the protocol design and its practical application at the investigator sites (e.g. blinding, assessment of Complete Oedema Restitution), the instructions given by the sponsor to the investigators (in particular in relation to IMP documentation),

the quality control (monitoring) and the escalation of issues (e.g. GCP and protocol deviations/violations). Concerning the assessment of COR, it was found that the results reported in the CSR were not exclusively based on a systematic collection at specific time points (visits) as defined in the protocol, but also on ad hoc assessments between the visits. The MAH has performed a sensitivity analysis which only used the scheduled times of the visits. In this analysis, the median time to COR in the icatibant group was 8.0 hours compared to 24 hours in the control group, i.e very similar to the original results.

There were 2 "outliers" in the icatibant group with long duration until COR. However, based on the narratives, both had rapid symptom relief after treatment and only minor symptoms remained. Demographics and baseline characteristics did not differ between those with COR ≤ 8 hours versus those with COR > 8 hours after treatment with icatibant.

EU consensus on angioedema diagnosis recommends the use of laboratory parameters in assisting the differential diagnosis of ACE-I-induced angioedema. It is understood that C1 inhibitor (C1-INH) and complement levels are not routinely performed in the emergency department for suspected cases of ACE-I-induced angioedema and it is agreed that the inclusion and exclusion criteria in the study reflects clinical practice. However, in a clinical trial setting, especially considering the one pivotal trial situation, a more objective diagnosis would have been adequate, even if the final diagnosis would have been achieved after treatment initiation. The fact that this was not performed constitutes a weakness of the study. However, the non-responsiveness of the control patients to conventional therapy in the study may support that these patients indeed had bradykinin-mediated angioedema.

Symptomatically, based on mean values, most of patients had mild-to-moderate severity of the disease. However, the fact that patients who participated in the AMACE study were those who were severe enough to seek medical attention for their ACE-I-induced angioedema attack, supports that they represent the population who would be considered for icatibant treatment in the emergency department. This is further supported by the approach to examine the maximum severity score across all symptoms or all angioedema locations. In this analysis, the majority of patients in the AMACE study (82.1% by angioedema scores and 64% to 82.1% by symptom scores) experienced ACE-I-induced angioedema attacks that were either moderate or severe in intensity and could be considered to represent patients in clinical practice.

It is recognized that treatment comparisons at the 1, 2, 3, 4, and 6 hour assessments are statistically significant for the investigator-assessed symptom scores but not for the subject-assessed VAS scores. However, considering the small sample size, statistical significance cannot be expected for all analyses. It is true that the effect size was larger in the investigator assessed outcomes, but considering the similar trends over time for both investigator and patient assessed outcomes, the results are considered as supportive of an effect of icatibant.

Risks

Unfavourable effects

Some unfavourable effects are known, and already addressed in the RMP:

Identified risk: Injection site reactions

Potential risks: Deterioration of cardiac function under ischemic conditions due to bradykinin antagonism, partial bradykinin agonism, antigenicity, lack of efficacy, and self administration

Missing information: Use during pregnancy/lactation, use in children and adolescents.

Immunogenicity has been given special interest due to the potentially severe/fatal outcome; after initial exposure to icatibant in controlled Phase III studies, and after repeated treatment for multiple attacks of acute HAE over time, immunogenicity generally remained negative in subjects for up to 82 attacks over two years. This will be followed also for ACE-I-induced angioedema.

Overall, for the HAE indication the most frequent acute or observation period adverse event reported by subjects in controlled Phase III studies was worsening or recurrence of HAE.

In the pivotal study for the proposed indication, six AEs were reported by five subjects, one of whom were treated with icatibant. This subject reported a mild AE of pain that was probably related to study drug.

Injection site reactions occurred in a majority of subjects in the icatibant group, including redness (80%), swelling (53.3%), pain (46.7%), itching and burning (26.7% each). The AE of injection site reactions are well known in the already approved indication and is an identified risk in the RMP.

One patient reported an SAE, a subject from the control group, given icatibant as rescue therapy. The symptom was dyspnoea, and even after the patient had received rescue therapy, tracheostomy was needed. Later, this was resolved.

In the laboratory findings, there is a notable difference in values of ACE activity, but again, the number of patients is small, making the assessment difficult.

Uncertainty in the knowledge about the unfavourable effects

The safety profile of icatibant, when given under the indication of HAE, is established from trials, post-marketing reporting, and IOS registry. During recent PSURs and renewal procedures, no new safety concerns were identified, and the risk-benefit balance continued to be positive. The safety findings in the AMACE study seem similar to previously shown profile, but the number of patients is very limited.

The current open risks according to the current RMP for icatibant are: identified risk injection site reactions, and potential risks of deterioration of cardiac function under ischemic conditions, partial bradykinin agonism, antigenicity, lack of efficacy and self-administration. Important missing information is paediatric use and use in pregnancy and lactation.

The most important safety concern should be the risk of lack of efficacy in patients developing laryngeal oedema.

The uncertainty overall, regarding this new indication, is due to the low number of patients included in the AMACE trial.

The potential risk “Deterioration of cardiac function under ischemic conditions due to bradykinin antagonism” (and possibly also other risks) may be of higher relevance for the proposed indication compared to the approved one, considering that patients with ACE-I induced angioedema in general are older compared to patients with acute attacks of hereditary angioedema (mean age 38 and 65 years respectively in pivotal trials).

Benefit-risk balance

Importance of favourable and unfavourable effects

ACE-I-induced angioedema is a rare but potentially lethal condition. In clinical practice, this is a diagnosis of exclusion and patients presenting at the emergency ward are in general initially given anti-allergic treatment. However, this treatment is generally not effective for patients with

ACE-I-induced angioedema. Thus, there is a medical need for an efficient treatment to be used in ACE-I-treated patients with angioedema not responding to initial treatment. The pathophysiology is most likely based on decreased degradation of bradykinin. Thus, the mechanism of action (direct antagonism of the bradykinin receptor) supports the theory that icatibant may be a relevant treatment of ACE-I-induced angioedema. In the pivotal study, there was a statistically significant shortening of median time to complete edema resolution with icatibant compared to standard of care which is also considered to be of clinical relevance. These findings were in general supported by results for secondary endpoints.

Since only 15 patients were treated with icatibant in the pivotal study, very limited safety data is available for the proposed target population and safety would have to be extrapolated from the currently approved indication.

Benefit-risk balance

The potential effect of Firazyr in the treatment of ACE-I-induced angioedema is supported by the mechanism of action of icatibant, the results of the AMACE study and case reports. However, the critical findings at the triggered GCP inspection cast doubt on the reliability of the results of the AMACE study especially with respect to blinding, IMP documentation and the assessment of the primary endpoint. Even though the MAH has provided justifications for some of the findings including new analyses, the overall conclusion that the study was not GCP compliant warrants further justification and confirmation of the study results. According to clinicaltrials.gov, a multicenter phase III trial is planned with intended starting date September 2013. The need to provide these results before or after a possible approval should be further discussed.

Thus, additional justification is needed to ensure that the results of the AMACE study are robust enough to support the indication.

The overall B/R of Firazyr in the new indication for the treatment of ACE-inhibitor induced angioedema was considered negative at the time of the MAH's withdrawal of the extension of indication.

The proposed update to section 5.1 of the SmPC to include the results of the open-label extension phase of study FAST3 were considered acceptable by the CHMP.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		**Type**
C.I.4	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or Pharmacovigilance data	II

Update to section 5.1 of the SmPC to include the results of the open-label extension phase of study FAST-3 (HGT-FIR-054).

In addition the MAH has taken the opportunity to make minor editorial changes throughout the PI and to amend the Package Leaflet based on the results of user testing submitted and assessed as part of FUM 028.

Furthermore, the PI is being brought in line with the latest QRD template version 9.0.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.