European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT
FOR
Firazyr

International Nonproprietary Name:
icatibant
Procedure No. EMEA/H/C/899

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 Submission of the dossier

The applicant Jerini AG submitted on 27 July 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Firazyr, which 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 hereditary angioedema. The calculated prevalence of this condition was 2 - 3 per 10.000 EU population.

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication: treatment of hereditary angioedema

Protocol Assistance:
The applicant received Protocol Assistance from the CHMP on 24 July 2003, 24 March 2004, 29 July 2004 and 16 September 2004. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: Bengt Ljungberg Co-Rapporteur: Ian Hudson

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 27 July 2007.
- The request for Accelerated Assessment procedure was accepted by the CHMP on 19 July 2007 subject to review at time of discussion of the List of Questions.
- The procedure started on 15 August 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 1 November 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 2 Novemeber 2007.
- During the meeting on 10-13 December 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 13 December 2007.
- The Accelerated Assessment was reviewed considering the consolidated List of Questions and during the meeting on 10-13 December 2007, the CHMP decided to continue the assessment under "normal" centralised timetable.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 January 2008 and supplementary information was provided on 25 February 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 February 2008.
- During the CHMP meeting on 17–19 March 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 March 2008.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues on 7 April 2008.

- During the meeting on 21–24 April 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Firazyr on 24 April 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 April 2008.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 11 July 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease caused by either a quantitative (Type I) in about 85% of patients or qualitative (Type II) deficiency of C1 esterase inhibitor (C1-INH) caused by mutations of the C1-INH gene. The exact prevalence of HAE is unknown but estimates suggest that 1:10,000 to 1:50,000 persons are affected.

Clinically, HAE is characterised by unpredictable, recurring attacks of oedema at various body sites. Swelling of the skin is most often located on the lips and face, hands or feet. If angioedema occurs in the gastrointestinal tract, it can be very painful and may be mistaken for appendicitis, diverticulitis, or mesenterical ischemia. Swellings in the upper airways, particularly when involving the larynx, are life-threatening. Most patients with symptomatic untreated HAE experience at least one acute exacerbation per month. Each attack typically lasts a few days before spontaneously subsiding (2 to 5 days). If undiagnosed, life-time mortality from HAE can be as high as 33% mostly due to laryngeal oedema and upper airway obstruction.
A deficiency of C1-INH is accompanied by an increased release of bradykinin (BK), which is probably the key mediator responsible for the increased vascular permeability during angioedema formation and the theory behind development of icatibant, a bradykininantagonist.

Current treatment options are divided into long-term prophylaxis to prevent attacks, short-term prophylaxis before elective surgical procedures, and treatment for acute attacks. Long-term prophylactic treatments include attenuated androgens (e.g. danazol or stanozolol), which may reduce the number of HAE attacks, but with safety and tolerability problems, including weight gain, virilisation, menstrual irregularities, hypertension, and, potentially, hepatotoxicity/hepatocellular adenoma with long-term use. Other prophylactic treatments include tranexamic acid (TA) and C1-INH concentrate, both of which are only approved for use in certain countries. The efficacy of TA is lower than with attenuated androgens and, being an antifibrinolytic agent, the drug may carry a risk of causing thromboembolic events. Acute attacks can be successfully treated with C1-INH concentrate (i.v. infusion), approved in some countries.

Firazyr contains the active substance icatibant, which is a selective competitive antagonist at the bradykinin type 2 (B2) receptor. It is a synthetic decapeptide with a structure similar to bradykinin, but with 5 nonproteinogenic amino acids.

The proposed indication for Firazyr is for the symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency). The proposed dose is one subcutaneous injection of 30 mg administered, preferably in the abdominal area. In case of insufficient relief or recurrence of symptoms, a second injection can be administered after 6 hours and if needed, a third injection, after a further 6 hours could be given. No more than 3 injections should be administered in a 24 hour period.

2.2 Quality aspects

Introduction

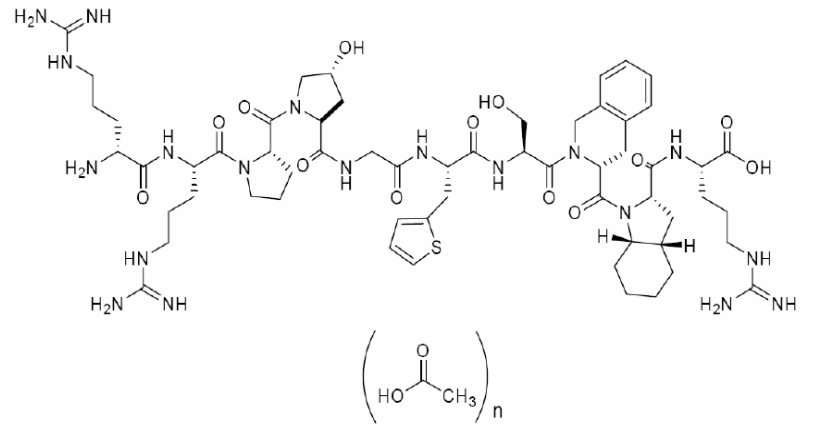
Firazyr is presented as solution for injection for subcutaneous administration, containing 30 mg of icatibant (active substance) in 3 ml (10 mg/ml). The excipients used in the preparation of Firazyr are those typically used in injectable preparations. It contains sodium chloride as a tonicity agent, acetic acid and sodium hydroxide for pH adjustment and water for injections as a vehicle.

The solution is a clear and colourless. It is supplied in single dose, pre-filled clear glass syringe (3 ml of solution in a 5 ml syringe) with plunger stopper (bromobutyl coated with fluorocarbon polymer) and a Luer-lock adaptor (polycarbonate).

Active Substance

Icatibant, which is a selective competitive antagonist at the bradykinin type 2 (B2) receptor, is a synthetic decapeptide with a structure similar to bradykinin, but with 5 nonproteinogenic amino acids. It consists of ten amino acids in the following sequence: H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH. All the chiral amino acids of icatibant are in the L-configuration with the exception of arginine (position 1) and 1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid (position 8).

The active substance is chemically designated as D-Arginyl-L-arginyl-L-prolyl-L[(4R)-4-hydroxyprolyl]-glycyl-L[3-(2-thienyl)alanyl]-L-seryl-D-(1,2,3,4-tetrahydroisoquinolin-3-ylcarbonyl)-L[(3aS,7aS)-octahydroindol-2-ylcarbonyl]-L-arginine, acetate salt (CAS) or H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate salt (IUPAC Three-Letter Code) and has the following structure:



Icatibant acetate is a white to almost white amorphous powder isolated by lyophilisation and existing as an acetate salt (1-4 moles of acetic acid present). It is hygroscopic, freely soluble in water, phosphate buffer pH 7.4, isotonic saline solution, acetate buffer pH 3.5, ethanol and methanol. Only amorphous form of icatibant acetate exists and no other polymorphic forms, including crystalline forms, are known.

Since the medicinal product is a solution, solid-state and bulk properties of the active substance have no impact on the product performance.

- Manufacture

Icatibant is synthesised in a solid phase peptide synthesis (SPPS) process. It is synthesized from the appropriate protected L- and D-amino acids and protected glycine. The suitable coupling and cleavage methods have been selected to minimize isomerisation of both starting materials and the growing

peptide chain. A detailed description of the manufacturing process including process flow diagram and in process controls was provided in the restricted part of the Active Substance Master File (ASMF). Initially icatibant acetate was manufactured by different ASMF Holder by synthesis in solution (SIS) and some of these batches were used in non-clinical and clinical studies. However it has been proven that the active substance manufactured by SPPS process is comparable to the active substance produced by SIS process.

The ASMF Holder adequately characterised the chemical structure, enantiomeric purity, the amino acid sequence, the chemical impurities and residual solvents of the active substance.
The structure of icatibant acetete was confirmed by amino acid analysis, elemental analysis, IR-spectroscopy, nanospray ionization-mass spectrometry (NSI-MS), nanospray ionization-mass spectrometry-collision activated dissociation-mass spectrometry (NSI-MS-CAD-MS) (sequence analysis), ^{1}H- and ^{13}C-NMR spectroscopy and GC-MS (analysis of enantiomeric purity).
The assessment of possible polymorphism has been performed using X-ray powder diffraction. It has been demonstrated that the active substance was amorphous in nature and over time it retains its amorphous nature.

- Specification

The active substance specification includes tests for appearance, appearance of solution, identification (ESI-MS, IR, HPLC), related substances, assay, water content, acetic acid content, trifluoroacetic acid content, residual organic solvents, heavy metals, bacterial endotoxins and bioburden.

All specification parameters except, acetic acid content by HPLC, trifluoroacetic acid content by IC, residual organic solvents by GC are tested according PhEur.
For the non-compendial analytical methods appropriate validation studies were performed with regards to relevant guidelines. Validation studies were performed for the following methods: identification by ESI-MS, identification by amino acid analysis, assay and related substances by HPLC, water content by Karl Fischer titration, acetic acid content by HPLC, trifluoroacetic acid content by IC, residual organic solvents by GC, heavy metals by ICP-OES, bacterial endotoxins (LAL), microbial limit test.

The same HPLC method is used for the identification, assay and related substances. The validation studies included specificity, linearity, accuracy, precision and intermediate precision, limit of detection and limit of quantification as appropriate.
The GC method for residual has been validated. The validation included specificity, linearity, accuracy, precision and intermediate precision, limit of detection and limit of quantification.

In general, analytical methods proposed are suitable to control the quality of the active substance.

Data provided on six batches of icatibant acetate produced by the current ASMF Holder were provided. All results complied with the requirements of the active substance specification.

- Stability

Stability studies have been performed on three commercial scale batches after storage at less than - 15 °C and 5 °C for up to 24 months and for storage at 25 °C/60 % RH for up to 6 months, to cover short-term changes in the proposed storage conditions. The batches have been tested according to ICH requirements Q1A(R2). Additionally, data from forced degradation studies (exposure to elevated temperature, presence of moisture or oxidative, alkaline or acidic conditions) has been provided to characterise the degradation pathways of icatibant acetate.

The stability data provided for the active substance confirmed the proposed re-test period.

Medicinal Product

- Pharmaceutical Development

The formulation used in late-stage clinical studies, including Phase III clinical trials was identical to the intended commercial formulation. Initially the product was packaged in 5 ml glass ampoules. After switching to disposable syringes, compatibility studies were performed.

In early development stage a number of formulation factors including solution pH, buffer types and concentrations were tested. The obtained results indicated that the development of aqueous formulations was possible. Three formulations were used during the clinical development of the medicinal product. All formulations employed acetate buffer systems targeted to a fixed pH value with sodium chloride as the tonicity modifying agent. The pH value and osmolality were fixed in a physiologically compatible range. The respective formulations differed in the concentration of icatibant and were administered under selected intravenous infusion regimens and as single and multiple subcutaneous injections. Based on results from the tolerability of different concentrations of subcutaneous injections and the bioavailability of subcutaneous injection against intra-venous infusion in healthy subjects one of the tested formulations was selected as the commercial formulation.

- Adventitious Agents

None of the excipients used in the formulation are of animal or human. Only chemically modified amino acids sourced from non-human (animal) materials are used in the manufacturing process of the medicinal product.

- Manufacture of the Product

The manufacturing process of Firazyr solution for injection comprises (1) removal of the active substance from refrigerated storage and weighing after equilibration, (2) preparation of a formulation, (3) filtration, (4) filling, (5) terminal sterilisation, (6) labelling and packaging. Bioburden is tested prior to the filtration step and prior to the terminal sterilisation. The medicinal product is terminally sterilised according to the method specified in the PhEur. Terminal sterilisation of the filled syringes employs a validated steam sterilisation cycle (121.5°C, 20 min). Sterility is assured through the validation of the sterilisation process and by final product sterility testing of each batch manufactured.

A detailed manufacturing process description was provided. Although full validation of the manufacturing process was not performed the key components of the manufacturing process including filter extractables and maximum filtration time have been validated. Critical steps of the manufacturing process have been identified and are sufficiently controlled by in-process control testing.

Batch analysis data on three production scale batches manufactured at the proposed manufacturing site indicate satisfactory uniformity and compliance with the proposed specifications.

- Product Specification

The specification for Firazyr solution for injection includes test for appearance, identification (HPLC), impurities (HPLC), sterility, bacterial endotoxins, content, pH, osmolality, particulate matter visible particles and subvisible particles, and uniformity of dosage units.

Adequate method descriptions were provided for all methods. Validation data was provided for the HPLC method and for the pharmacopoeial methods for sterility and bacterial endotoxins. The HPLC method used for identification, potency and organic impurities has been validated including specificity, determination of response factors, linearity and range ; purity: limit of detection (LOD) and limit of quantification (LOQ), precision repeatability and intermediate (for assay and purity) accuracy (for assay and purity) and robustness.

- Stability of the Product

The stability studies included evaluation of long-term storage under ICH conditions. Results were presented for primary stability batches produced at the proposed manufacturer and supported by stability data on three pilot scale batches. Further long-term stability data were provided on batches of the medicinal product used in clinical trials.

The stability testing will be further performed on the first three production scale validation batches. Also, as per GMP requirements, one batch per year will be tested for stability at long term conditions.

- Comparability Exercise for Medicinal Product

Compatibility of the formulation with the proposed container closure system was demonstrated by the ongoing stability studies. Product specific leachables studies demonstrated low and acceptable levels of leachables when the proposed container closure system is used.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and the medicinal product have been appropriately characterised and generally satisfactory documentation has been provided. The excipients used in the preparation of the medicinal product and manufacturing process selected are typical for injectable preparations. The results indicate that the active substance and the medicinal product can be reproducibly manufactured.

At the time of the CHMP opinion, there ere minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

2.3 Non-clinical aspects

Introduction

Most safety-pharmacology and pharmacokinetic studies are not GLP-compliant. Pivotal toxicity and toxicokinetic studies were conducted in compliance with GLP.

Pharmacology

- Primary pharmacodynamics

Icatibant has been considered for several clinical indications besides the current (HAE) and the pharmacological programme reflects this fact. Consequently, many of the studies on primary and secondary pharmacodynamics are not very relevant for the current application. Nevertheless, they demonstrate that icatibant is a selective bradykinin type 2 (B_2) receptor antagonist, both *in vitro* and *in vivo*. The affinity of icatibant to the B_2 receptor (IC_{50} values in the 1-10 nM range in various models) was comparable to that of bradykinin itself, while the affinity to the analogous bradykinin type 1 (B_1) receptor was at least 100 times lower.

An interesting finding in several studies was that icatibant acted as a bradykinin agonist at high concentrations. However, the only clinical situation where such concentrations are likely to occur is locally at the injection site, contributing to an inflammatory reaction; the clinical systemic exposure (C_{max}) is deemed to be far too low to trigger the agonist activity.

- Secondary pharmacodynamics

Screening against a wide variety of other receptors (other than bradykinin type 2 receptor), ion channels, and enzymes did not reveal any remarkable interactions.

- Safety pharmacology programme

Icatibant was tested in a variety of disease models (few of these having any direct bearing on hereditary angioedema). The overview of safety pharmacology studies is shown in the table below.

Table 1 - Overview of Safety Pharmacology Studies

Study number GLP compliant	Type of study Test system	Noteworthy findings
CNS effects		
JE049-001 Non-GLP	Behavioural observation (IRWIN) Mice	Icatibant doses: 0.01, 0.1, 1, and 10 mg/kg, i.v. ≤ 0.1 mg/kg: no effect ≥ 1 mg/kg: motor activity ↓, body temperature ↓, ptosis No deaths occurred
JE049-001 Non-GLP	Spontaneous motor activity Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 6 h recording No effect
JE049-001 Non-GLP	Electroshock convulsions Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 0.2 sec, 12 mA, 50 Hz AC No effect
JE049-001 Non-GLP	Pentetrazol convulsions Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 125 mg/kg s.c. pentetrazol No effect
JE049-001 Non-GLP	Tetrabenazine ptosis Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 40 mg/kg, i.p. tetrabenazine No effect.
JE049-001 Non-GLP	D,L-5-HT head twitches Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v ; 200 mg/kg i.p. D,L-5-HT No potentiation of twitches during 90 min
JE049-001 Non-GLP	Hexobarbital sleeping time Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 55 mg/kg hexobarbital, i.v. Icatibant did not affect sleeping time
JE049-001 Non-GLP	Apomorphine-induced climbing Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 1.5 mg/kg apomorphine, s.c., 15 min after icatibant. No antagonism of climbing (no neuroleptic-like effect)
JE049-001 Non-GLP	Sodium nitrite hypoxia Mice	Doses: 0.01, 0.1, 1 mg/kg, i.v.; 250 mg/kg, s.c., 15 min after icatibant. No prolongation of survival
JE049-001 Non-GLP	Scopolamine-induced amnesia Mice	Mice were trained to avoid a dark chamber and were subsequently injected with scopolamine (2 mg/kg, s.c.). They were tested 24 h later. Icatibant (3, 10, or 30 μg/kg) on training and test days had no effect on the amnesia
Cardiovascular effects		
JE049-0202 Non-GLP	hERG channel inhibition Xenopus oocytes	Icatibant (10, 30, 100 μM) did not inhibit I_{Kr} (hERG)
JE049-0203 GLP	hERG-channel inhibition CHO cells	Icatibant (≤ 308 μM) did not inhibit I_{Kr}
JE049-0204 Non-GLP	Mean arterial blood pressure (MAP) Anaesthetised rats	Icatibant was administered i.v. (0.13, 1.3 mg), s.c. (1.3, 13 mg/kg, or nasally (36 μg/kg). Intravenous administration, but not the others, decreased MAP for 3 min. The effect was deemed due to partial agonist activity of icatibant on the vascular endothelium.

Study number GLP compliant	Type of study Test system	Noteworthy findings
JE049-001 Non-GLP	Blood pressure and heart rate Dogs	Icatibant (0.01-1 mg/kg, i.v.) was administered at 90 min intervals, measuring blood pressure and heart rate (HR) with an ultrasonic monitor positioned onto the dog's tail. Icatibant doses ≤ 0.1µg/kg had no effects 0.6 mg/kg caused a pronounced drop in blood pressure/HR for 5-10 min 1 mg/kg caused a drastic drop, resulting in immeasurable levels for the first 3 min and a marked effect for at least 30 min; DAP at 1 mg/kg also caused a blood pressure drop but no details are presented in the report. High dose icatibant and DAP were accompanied by symptoms like pain reaction, restlessness and hyper salivation. It was concluded that the effects of high dose icatibant and DAP might be due to residual BK-agonist activity.
JE049-0205 Non-GLP	Haemodynamics and ECG during exercise Dogs	The dogs were exercised on a tread-mill (7 km/h, 13% inclination) and each animal received 3 doses of icatibant (0.1, 0.3, 0.5 mg/kg, i.v.), usually on three consecutive days. As expected, exercise caused increases in heart rate (HR) and blood pressure, as well as a shortened QT interval. Icatibant (0.5 mg/kg) transiently increased HR by about 20% and had a marginal accentuating effect on post exercise vasodilatation. Two animals had signs of catheter-induced ventricular endothelial damage post mortem and these animals had an increased frequency of ventricular ectopic activity, including episodes of ventricular tachycardia. However, icatibant did not appear to affect the intensity or severity of ectopic activity in these animals.
JE049-001 Non-GLP	Acute renal hypertension Anaesthetised rats	The left renal pedicle was clamped for 4 h; following unclamping, there was a rapid and persisting increase in blood pressure. Icatibant (40 µg) or saline was infused during 30 min, starting 5 min before unclamping. Icatibant had no effect in this model
JE049-001 Non-GLP	Post-ischaemic arrhythmias Isolated rat hearts	Hearts were perfused for 20 min (control period), regional ischaemia was produced by clamping the left anterior descending coronary artery for 15 min (ischaemic period), and the clip was than opened for an additional 30 min perfusion (reperfusion period). Icatibant (0.1-10 nM) ± BK (0.1 or 1 nM) were added to the perfusion medium. Control period: 1 nM icatibant decreased LPV, LV dP/dt max and CF, while 10 nM had the opposite effect. Ischaemic period: occlusion caused a marked reduction of LPV, LV dP/dt max and CF. There was also an increase in LDH and CK activities. These changes were aggravated by 1 nM, and improved by 10 nM, icatibant. Reperfusion period: the main finding was ventricular fibrillation that occurred in 100% of the control hearts (mean duration 17.2 min). Icatibant (0.1 and 1 nM) prolonged the fibrillations (mean duration 20.6 and 27.6 min, respectively), while 10 nM shortened them (mean duration 7.4 min). BK at 10 nM by itself increased CF and it reversed the effects of icatibant.

Study number GLP compliant	Type of study Test system	Noteworthy findings
JE049-0207 Non-GLP	Ischemia-induced arrhythmias Anaesthetised rats	Rats were anaesthetised and ischemia was caused by clamping the left main coronary artery. One group of animals was 'preconditioned' by clamping for 3 min, followed by 10 min reperfusion, prior to 30 min occlusion. The other group was subjected to 30 min occlusion directly. Icatibant (40, 400, 4000 µg/kg, i.v.) was administered 10 min before the experimental procedure, which caused a dose-dependent reduction in mortality and a trend towards a reduction in arrhythmias. Preconditioning reduced arrhythmia and this reduction was not influenced by icatibant.
JE049-0206 Non-GLP	Myocardial infarction model Anaesthetised dogs	Infarction was induced by occlusion of the left descending coronary artery for 6 h. Icatibant was administered as an intracoronary infusion (0.5 ng/kg/min), starting 30 min before and continuing until 30 min after the end of the occlusion. Mortality: 7 of 12 icatibant-treated dogs (58%) died vs. 4 of 14 (28%) in the control group. All control animals died within 20 min of occlusion but 4 of the icatibant-treated animals died later. Thus, the immediate mortality was similar; the delayed mortality in the icatibant group appeared to be due to ventricular failure. There was no mortality in a group of 'non-ischaemic' animals treated with icatibant in the same manner. Infarct size: There was no difference in infarct size and 'area at risk', as evaluated post mortem with a double staining technique. Possible mechanism(s): The authors of the report speculate that the excess mortality in the icatibant group might be due to antagonism of protective effects by bradykinin, which seems plausible.
Respiratory effects		
JE049-0208 GLP	Respiratory function Rats	Whole body plethysmography was used to measure respiratory parameters. Icatibant (1, 3, 10 mg/kg, i.v.) was tested, using theophylline as a positive control. ≤ 3 mg/kg icatibant had no effect, while 10 mg/kg had a slight effect suggestive of bronchodilation. As expected, theophylline had a marked effect.
Gastro-Intestinal effects		
JE049-0209 GLP	GI transit Rats	After overnight food deprivation, rats were administered charcoal suspension (2 ml, p.o.), measuring the distance travelled during 20 min as percentage of the total length of the small intestine. Icatibant (1, 3, 10 mg/kg, i.v.) administered 10 min before charcoal had no effect.
JE049-0210 GLP	Gastric acid secretion Anaesthetised rats	Icatibant (1, 3, 10 mg/kg, i.v.) was administered, the rats were anaesthetised and the pylorus was tied. Gastric fluid was collected during 4 h. 1 and 3 mg/kg had no effect 10 mg/kg reduced volume, free chlorohydric activity and total acidity. Gastric fluid pH was marginally increased

Study number GLP compliant	Type of study Test system	Noteworthy findings
JE049-0211 Non-GLP	Histamine-stimulated gastric acid secretion Anaesthetised rats	Rats were anaesthetised, pylorus tied, and the stomach was perfused continuously with saline. The perfusate was collected at 15 min intervals, analysing pH and acid content. Histamine (10 mg/kg/h) was infused after an initial 45 min basal period and icatibant (0.3 mg/kg, i.v.) was administered 90 min later. Icatibant had no effect in this model
Renal effects		
JE049-001 Non-GLP	Effect on plasma renin Anaesthetised rats	Icatibant or DAP was given as intra-arterial infusions (0,83 nmol/kg/min; total dose not given explicitly), collecting blood samples for renin activity determination at 0, 30, and 60 min. Neither icatibant nor DAP had any effect in this model.
JE049-0212 Non-GLP	Salidiuretic effect Rats	Rats were fasted overnight and given saline (20 ml/kg, p.o.). Icatibant (0.1, 1 mg/kg, s.c.) was administered and the animals were placed in diuresis cages, collecting urine from 1-5 and 6-24 h. Icatibant had a slight naturetic and chloruretic effect in the 1-5 h period. Potassium excretion was unchanged.
JE049-0213 Non-GLP	Salidiuretic effect and renal clearance Dogs	Diuresis was established by continuous i.v. infusion (1 ml/kg×min) of saline, collecting blood and urine samples every 10 min for 60 min. Icatibant (0.03, 0.3 mg/kg) was administered as an i.v. bolus at the start of the collection period. 0.3 mg/kg icatibant cased a moderate (about 30%) decrease in urine volume and sodium excretion; potassium excretion, glomerular filtration rate (GFR) and renal plasma flow (C_{PAH}) were unaffected. The lower dose had only marginal effects
Metabolic effects		
JE049-001 Non-GLP	Blood glucose Rats	Icatibant doses: 0.1, 0.5, 1 mg/kg, i.v. 0.1 mg/kg: no effect 0.5 mg/kg: 6.6% reduction at 1 h, compared with controls 1. mg/kg: 9.8-15% reduction at 1 h, compared with controls The effect was ambiguous due to variation in initial glucose values; it was deemed biologically irrelevant by the authors of JE049-001

Besides the cardiovascular effects, the safety pharmacology package did not produce any signals causing concerns about the safety of icatibant. On the other hand, the cardiovascular studies raised such concerns. Bradykinin has been implicated in the protection of the myocardium during ischaemia and it seems likely that the serious adverse effects seen, e.g. prolongation of ventricular fibrillations in isolated rat hearts and excess mortality in a dog myocardial infarction study, are manifestations of a blockade of such protective effects by icatibant. The Applicant has suggested in their response to the D120 LOQs a warning in the SPC for the use of icatibant in the presence of acute ischaemic heart disease or unstable angina pectoris, which has been endorsed by CHMP.

Bradykinin has also been implicated in limiting the extent of brain damage in stroke. Theoretically, icatibant may antagonise the protective effect of bradykinin in this condition as well, leading to a worsening of the ischaemic brain damage, which resulted in a question to the Applicant. In their reply, the Applicant discussed this issue in depth, highlighting the complex role of the kallikrein-kinin system in ischaemic brain injury, and proposed a warning in the SPC. This warning has been endorsed by CHMP.

- Pharmacodynamic drug interactions

No non clinical studies on pharmacodynamic drug interactions were conducted. This is acceptable as drug interactions were investigated clinically.

Pharmacokinetics

Pharmacokinetic studies were conducted in mice, rats and dogs using tritiated icatibant. Placental transfer and excretion into milk were determined in pregnant and lactating rats, respectively. In addition in vitro studies were used to partly characterise the metabolic pathways of icatibant. No pharmacokinetic studies were made in the rabbit, which resulted in a question to the Applicant. In their reply new data, showing that the animals were adequately exposed to icatibant were presented. Overall, there were no remarkable gender or species differences.
The pharmacokinetics of icatibant is simple and straightforward. Absorption was rapid after subcutaneous administration in both rats and dogs; no calculation of bioavailability was made but a rough estimate indicates that it was in the 70-80% range for both species. Plasma protein binding was moderate (38-49%) with only small species differences. Organ distribution studies were conducted mainly in the rat (Wistar) with whole body autoradiography, showing that the highest concentrations of radioactivity for the first 4 hours were found at the injection site and in the organs involved in excretion (kidney, liver and urinary bladder); supplementary studies in mice and rats with longer sampling times showed that any long-lived radioactivity principally resided in the liver. Radioactivity was generally absent from the central nervous system, indicating poor penetration across the blood-brain barrier, and from the adipose tissue. Icatibant passes the placenta and it is excreted in rat milk.
Metabolism of icatibant involves a cleavage of the molecule to two smaller peptides: icatibant (1-5) or M1, and icatibant (7-10) or M2. Interestingly, icatibant (1-6), which is formed during storage, was not detected in any species. Presumably, amino acid number 6 (Thi) is either lost in the cleavage step or too fast thereafter for icatibant (1-6) to be seen *in vivo*. Cytochrome P-450 is, apparently, not involved in the metabolism of icatibant and there were no species differences in the studied species, including humans. Excretion was also simple: most of the radioactive material was excreted in the urine and the only species difference detected was the proportion of intact icatibant, being highest in the mouse and lowest in the rat. Like the rat, humans excrete only a small proportion of intact icatibant in the urine.

Toxicology

- Single dose toxicity

High single doses, particularly when given as an i.v. bolus, produced dramatic symptoms with death following rapidly in mice and rats. It seems likely that the cause is exaggerated pharmacological effects, especially bradykinin agonist activity, leading to circulation collapse. Histamine release, a known effect of bradykinin, may have contributed to the symptoms. No deaths, and much milder symptoms, occurred in rats and dogs when icatibant was administered as an intravenous infusion or subcutaneously, despite higher total doses. Once again, the clinical symptoms can largely be explained from the known pharmacological profile of icatibant, particularly the bradykinin agonist activity. Thus, the cardinal symptoms appear to be more or less general erythema and swelling, and local reaction at the injection site(s).

- Repeat dose toxicity (with toxicokinetics)

Two findings dominated in the repeat-dose studies: nephrotoxicity (necrosis/atrophy of proximal tubules) and changes in the sexual organs. In addition, there was a variety of symptoms like swelling and erythema that was likely due to an exaggerated pharmacological activity of icatibant, particularly the bradykinin agonist activity. Local irritation at the injection site(s) was also common, particularly in the rat studies, and this effect may also be a consequence of the bradykinin agonist effects of icatibant at high local concentrations.

The effects of icatibant on the sexual organs appeared to be reversible and were interpreted as delayed sexual maturation by the Applicant. This interpretation seems reasonable and the findings are,

therefore, not considered as a major concern at the moment. However, if the Applicant considers a wider indication, also including patients below the age of 18 years, the situation may change. In this context, it should be noted that no formal toxicity studies have been conducted in juvenile animals, although the animals in some of the regular repeat-dose toxicity programme were young and characterised as sexually immature. If the Applicant plans to initiate a clinical paediatric development programme, the existing non-clinical data must be carefully re-evaluated and probably supplemented with studies that involve a direct comparison of sexually immature and mature animals over a wide span of dose levels, spanning from below clinical exposure to a reasonable multiple. Further mechanistic studies to clarify the role of bradykinin and B_2 receptors in sexual maturation and function of the gonads are also likely to be necessary.

Signs of nephrotoxicity were seen primarily in the rat, particularly with intravenous administration, but were also seen in one dog study at high dose levels. Excretion of icatibant and its metabolites occurs mainly in the urine and it is possible that the damage to renal proximal tubules is a consequence of a (too) high load on the excretory system at high dose levels, which should have little relevance for the clinical use of icatibant.

Rats appear to be more sensitive than dogs, and rats and humans are similar in that a high proportion of the administrated icatibant is eliminated as metabolites, while in the dog a higher proportion in urine is the intact mother substance. CHMP questioned whether the toxic effect could be due to M1, M2 or some other yet unknown metabolite, or whether it could be the result of the metabolism itself if it occurs in the proximal tubules. These concerns resulted in a question to the Applicant; it transpired the findings were confined to studies at Hoechst using an in-house strain of rats and that similar signs of nephrotoxicity have not been found in later studies.

Chronic toxicity studies (6 months) have only been conducted with nasal administration of icatibant. Because this route of administration results in a low systemic exposure, these studies are regarded being of minor value for the present indication. Nevertheless, in one of two chronic rat studies with nasal administration, there was tubular atrophy at 15 weeks in two high dose males and signs of reactive hyperplasia of the renal pelvic epithelia in the high dose group at 6 months. No similar findings were reported in the other rat study but there was a dose-dependent tendency of increasing s-urea. It should be noted that in both these studies, the high dose resulted in systemic exposures below the expected clinical. These findings raised concerns that the threshold for long-term renal damage may be lower than that indicated by the shorter studies. However, in their response to the Day 180 List of Outstanding Issues, the Applicant submitted preliminary data (including histopathology) from the ongoing 26-week repeated dose toxicity study in the rat that substantially mitigate these concerns.

The concerns about possible long-term effects are pertinent for the current indication, considering that the frequency and severity of HAE episodes are highly variable. Thus, there are HAE patients that may require several treatments per month for several years, and each treatment may require several doses of icatibant. For this group of patients the situation will rapidly approach a chronic, albeit intermittent, therapy and the lack of relevant chronic toxicity studies is unfortunate. It can therefore be argued that such studies may be required before approval. On the other hand, the proposed indication for icatibant is treatment of HAE episodes and each treatment will be short (less than one week). Strictly according to the ICH guidelines, chronic toxicity studies should be unnecessary if each treatment is regarded separately. This was the answer given to the Applicant in a central scientific advice about the non-clinical programme in 2003 (EMEA/H/SA/427/2003/PA/I). Given that 6 month study is available, although resulting in insufficient exposure compared to the intended clinical use, and taking the arguments in the advice into account, the lack of chronic toxicity studies with a relevant route of administration is accepted. Consequently, CHMP requires the Applicant to conduct chronic toxicity studies in rodent and non-rodents as a follow-up measure. This solution is justified on the grounds that only a small part of the HAE patients would require frequent and intense treatment with icatibant. Furthermore, it should be noted that such studies are already ongoing further to requests by the FDA.

- Genotoxicity

The genotoxicity studies submitted cover the required standard battery and produced negative results. Icatibant is not genotoxic.

- Carcinogenicity

No carcinogenicity studies were conducted by the Applicant, also in accordance with scientific advice.

- Reproduction Toxicity

In a study on fertility and early embryo-fetal development in the rat, no effects were seen on male fertility in animals exposed to three times the expected level of icatibant. The females in the same study had an increase in pre-implantation losses at the same exposure level; the next lower dose, corresponding to about the expected clinical exposure, was considered NOAEL.

In segment II studies, icatibant was found to have no embryotoxic or teratogenic potential in the rat at a dose level corresponding to roughly ten times the clinical exposure; no malformations were seen in the rabbit but there was an increased rate of embryo-fetal deaths at a dose level of 10 mg/kg/d. Unfortunately, no toxicokinetic data are available and no pharmacokinetic studies were made in the rabbit, which makes the results of the rabbit study difficult to interpret. Finally, the study on pre- and postnatal development clearly demonstrated that icatibant, at exposures about four times, the expected clinical exposure, caused delayed parturition and poor perinatal survival in the rat. The Applicant proposes to include this information in sections 4.6 and 5.3 in the SPC, which is strongly endorsed by CHMP. Considering the proposed indication, Firazyr should not be contraindicated during pregnancy.

- Toxicokinetic data

Toxicokinetic data were collected in the pivotal studies and plasma levels of M2 as well as icatibant were also measured in i.v. and s.c. studies in rats and dogs. There were no sex differences in either rats or dogs, and no accumulation of either icatibant or M2 following repeated dosing. Plasma concentrations of icatibant and M2 increased with dose, but there was no consistency in dose proportionality, between or within studies.
Exposures at the NOAEL in the animal studies were similar to or higher than those in man at the highest exposure seen following TID dosing.

- Local tolerance

Icatibant was well tolerated in rabbits following subcutaneous, intraarterial, intravenous, paravenous, intraarticular, dermal and ocular administration. However injection site reactions have been seen in dogs and in man. Although icatibant at concentrations up to 1μM did not stimulate histamine release from mast cells, a subsequent study using higher concentrations (50-1000μM) have shown that icatibant produces degranulation of human skin mast cells, with the release of histamine and tryptase, and also leads to the release of inflammatory prostaglandin and leukotriene mediators that are synthesised de novo. Studies with mouse skin showed icatibant dose-dependently (1-10mM) stimulated the release of iCGRP, in a partly calcium and TRPV1-dependent manner but that this was independent of mast cells and the B2 receptor. The findings would suggest that the inflammatory reaction (reddening with occasional burning/pain sensation and/or pruritus and hives) noted in patients may result from a combination of mast cell activation, release of neuropeptides from peripheral nerves and partial agonist activity of icatibant, depending on local concentrations at the injection site.

- Other toxicity studies

- Antigenicity

Studies of the antigenic potential of icatibant showed that it is not a strong antigen but it was possible to evoke a response with Freund's complete adjuvant. This is a fairly common result for small peptides and raises no concerns for the clinical safety.

- Impurities / Metabolites

Two unnatural amino acids that are constituents of icatibant were tested in single-dose toxicity studies. D-1,2,3,4-tetrahydroisoquinoliine-3-carboxylic acid (D-Tic) was found to be toxic but at a very high dose, which is totally unrealistic in clinical use. It would have been informative to test it at lower dose levels to establish the maximum non-lethal dose but this lack is not regarded as important.

One impurity, icatibant (1-6), was qualified by intravenous single-dose toxicity in rats, AMES test, and an *in vitro* chromosome aberration test (human lymphocytes). The results were unremarkable, except for the chromosomal aberration test where an increased number of chromosome aberrations were seen in human lymphocytes at high concentrations of icatibant without S9. However, this increase was moderate and only statistically significant after 44 h. Moreover, these aberrations occurred at concentrations that caused a considerable inhibition in mitotic index. Thus, the results are not considered as a signal of any genotoxic potential for icatibant (1-6).

Ecotoxicity/environmental risk assessment

The Applicant has provided an ERA with a Phase I Assessment, concluding that the nature of icatibant (small peptide) and limited number of patients make significant elimination to the environment very unlikely. The Applicant's arguments are accepted and it is agreed that no further evaluation of the potential environmental risk is necessary.

2.4 Clinical aspects

Introduction

Icatibant was initially under development by Hoechst (now Sanofi-Aventis) in the early 1990s under the designation HOE 140. Early human studies explored the pharmacokinetics, efficacy and safety of intranasal and inhaled formulations of icatibant for the treatment of allergic rhinitis and asthma, and of an i.v. infusion in preparation for later development as a treatment for post operative pain. More recently, Sanofi-Aventis commenced development of an intra-articular dose of icatibant as a treatment for joint pain in osteoarthritis; this program is ongoing.

In 2001 Jerini in-licensed certain development and commercialization rights for icatibant and the drug was designated as JE049. Initial therapeutic indications of interest were the treatment of refractory ascites in liver cirrhosis and the treatment of HAE. In the earlier HAE studies, icatibant was administered i.v.; in later studies, including the pivotal study, s.c. administration was used. The open label extensions to the Phase III studies for HAE are ongoing. There are no other studies ongoing or due to be commenced by Jerini for HAE.

Apart from general regulatory guidance on the conduct of clinical trials with pharmaceutical products, there are no specific guidelines for the development of products to treat HAE.

Centralised scientific advice has been obtained for CMC, preclinical and clinical issues. National scientific advice has not been given.
The applicant also received regulatory advice from the FDA.

The principal recommendations obtained from the Scientific Advice on clinical aspects were in relation to the choice of the primary endpoint and secondary endpoints, issues surrounding blinding of the Phase III studies, inclusion of tranexamic acid as a comparator (EMEA), examination of the potential immunogenicity of icatibant (EMEA), assessment of QTc (FDA), and validation of VAS as a measure of HAE symptoms (FDA).
Jerini did not follow the advice of the EMEA and included patients with laryngeal attacks in the Phase III studies but these were treated with open label icatibant to accommodate the ethical concerns of the EMEA.

No formal Phase II dose ranging study was conducted (as requested by the FDA). Instead based on PK/PD modelling using a bradykinin challenge, pharmacokinetic, safety and efficacy data, a dose rationale was developed.

There is no paediatric development programme.
Icatibant has received designation as an orphan medicinal product for the orphan indication: treatment of angioedema by COMP

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

Two multicentre clinical studies presented in support of icatibant in the indication of Hereditary Angioedema included clinical sites that were outside the European Union. Study number JE049 #2103 was undertaken in the USA and Latin America. Study number JE049 #2102 included centres in Israel in addition to the European Union.

Pharmacokinetics

Plasma concentration of icatibant was in general determined by LC-MS/MS methods. The methods used have been poorly validated, raising some doubts regarding the accuracy of the reported pharmacokinetic data.

- Absorption

After s.c. administration of icatibant, absorption is rapid with maximum concentrations reached after about 30 min. The absolute bioavailability after s.c. administration of 0.4 mg/kg of the 10 mg/ml formulation was 97 ± 15 %.

- Distribution

Icatibant has a low extent of protein binding, 44 ± 3 %. The volume of distribution (Vss) is about 20-25 l.

- Elimination

Icatibant is mainly eliminated by metabolism resulting in formation of the metabolites M1 and M2. The metabolism is probably mediated by NADPH-independent proteolytic enzymes, with no involvement of CYP450 enzymes. Both metabolites are principally excreted unchanged in urine (80 - 90 %) and faeces; therefore there are no theoretical concerns about inclusion of exogenous peptides and amino acids in the amino acid pool. A small part of the dose < 10 % is excreted in urine unchanged. Icatibant clearance is about 15-20 l/h. The terminal half-life is about 1-2 h.

- Dose proportionality and time dependencies

Dose proportionality has been studied in the dose range 0.005 to 3.2 mg/kg. CL and Vss seem to be fairly consistent over the dose range 0.05 to 0.8 mg/kg. Due to the study design with parallel groups it is difficult to draw conclusions regarding linearity at higher doses. In study 1103 three repeated doses were given on Day 1 (which is the maximum recommended dose over 24 h), with additional single doses on Days 8 and 15. Available data do not suggest any time dependency in icatibant pharmacokinetics.
AUC of M1 and M2 are similar and are also in the same range as icatibant. AUC and C_{max} of the metabolites M1 and M2 seem to be dose proportional. The half-lives of M1 and M2 are similar to that of icatibant suggesting that M1 and M2 display formation rate limited elimination.

- Inter- and intra-individual variability

About 20-25% CV% (coefficient of variation) has been reported for C_{max} and AUC after s.c. administration. No information on intra-individual variability has been presented.

- Special populations

The pharmacokinetics of icatibant in patients seems to be similar to that in healthy volunteers. Pharmacokinetic data in special populations are limited.

The available data suggest no significant influence of hepatic impairment or renal impairment on icatibant pharmacokinetics.

In study 1103 evaluating effects of age and gender on icatibant pharmacokinetics there was a 4-fold difference in AUC between young men and elderly women with elderly men and young women having exposure in a similar range and somewhere in between the other two groups. Differences in weight could not explain the age and gender related PK differences. A population PK analysis of all PK data indicated that age, but not weight or gender affected icatibant clearance resulting in 50-60% higher AUC in elderly (75-80 year old) compared to a patient aged 40 years. Due to the low level of detail of the population PK report full analysis has not been possible. However, the totality of data suggests that gender has no marked effect on icatibant PK and that clearance decreases with age.

The influence of race on icatibant PK has not been evaluated and there are no PK data in children.

- Pharmacokinetic interaction studies

In vitro data did not indicate any relevant inhibition of CYP450 isoenzymes. No *in vivo* interaction studies have therefore been conducted

In summary, there is a remaining uncertainty regarding the validity of the analysis methods used in pharmacokinetic studies. However, given the proposed use of the product (intermittent administration in HAE patients, with the possibility of an additional dose in case of poor response), the uncertainty regarding the quality of the pharmacokinetic data can be accepted. The pharmacokinetic data suggest fairly uncomplicated pharmacokinetics with metabolism by proteolytic enzymes and low interaction potential. Elderly patients have been identified as a group with risk for increased exposure; information regarding this is included in sections 4.2 and 5.2 of the SPC. Hence, given the use of the product the pharmacokinetic data, although limited, are considered sufficient.

Pharmacodynamics

- Mechanism of action

C1-INH is responsible for inactivating approximately 40% of plasma kallikrein. The lack or dysfunction of C1-INH causes increased plasma levels of kallikrein. Kallikrein is the main enzyme responsible for generation of bradykinin (BK) formation from high molecular weight kininogen (HMWK). Furthermore, factor XIIa (activated Hageman factor), which converts prekallikrein to active kallikrein, is inactivated by C1-INH.

BK is primarily responsible for the clinical symptoms of angioedema by directly causing increased vascular permeability, vasodilatation and contraction of visceral smooth muscle. Thus, following a triggering event, the lack of C1-INH leads to the unabated bradykinin production and subsequent increased vascular permeability. The movement of fluid into the interstitial spaces leads to non-pruritic oedema. As HMWK is exhausted and bradykinin degraded, the episode begins to subside and finally the fluid is resorbed by the lymphatic system. Thus, the clinical profile is one of rapid evolution of oedema and pain, reaching a crescendo after a few hours and then slowly subsiding over time with different time courses for the different symptoms of an attack.

Icatibant is a potent and highly selective antagonist of the bradykinin type 2(B2) receptor and, for these reasons, has become a standard research tool for investigation of interactions at the receptor with more than 1000 references in the scientific literature. The primary target for treating an acute attack of HAE is to modulate the kallikrein-kinin system and prevent the formation or the pharmacological action of bradykinin. Thus, icatibant represents a logical therapeutic approach.

- Primary and Secondary pharmacology

Exploration of PK-PD relationships was conducted using the inhibitory profile of icatibant following a bradykinin (BK) challenge in healthy volunteers. The antagonistic effect of icatibant was assessed by measuring the degree of inhibition of exogenous BK-induced decrease in blood pressure (systolic, diastolic, and mean blood pressure), tachycardia (finger plethysmography), and cutaneous vasodilatation (laser Doppler flow meter). Similar EC_{50} was obtained for the PD parameters, with the majority of values being between 8.54 and 9.77 µg/L. Thus, a mean EC_{50} value of 9.5 µg/L (7.3 nM) was used in PK-PD simulation of the response to different i.v. doses. Based on this simulation the i.v. doses 0.4 mg/kg and 0.8 mg/kg were selected for phase II.

The same data have also been evaluated using a population PK/PD model resulting in slightly higher EC_{50} values ranging from 9.2 to 10.8 nM over the different PD endpoints. The PD parameters determined in this analysis and estimated PK parameters after s.c. administration in study 1102 were used to estimate the duration of icatibant effects for s.c. doses of 15, 30 and 60 mg. The applicant concluded that the 30 mg dose would be optimal, and used this dose in the phase III studies 2102 and 2103. The PK/PD modelling showed that the duration of the effect of icatibant is relatively insensitive to the administered dose. In order to maintain effective plasma concentrations over a longer period of time, the simulated data suggest that it would be clinically more useful to repeat administration of the proposed dose of 30 mg when clinically needed instead of using a higher single dose of e.g. 60 mg for all patients. The conducted analyses have been very briefly described and the reports were insufficiently detailed to allow a thorough assessment. However, further analysis of these data in healthy volunteers with PD endpoints for which the relation to clinical outcome is unclear is expected to be of limited value.

The rationale for development of icatibant as a medicinal product for treatment of attacks of HAE and its mechanism of action is reasonably well described.
From available data, no indication of partial agonist activity was found for doses of icatibant up to 1.6 mg/kg/1 hr, but at 3.2 mg/kg signs of a generalised bradykinin agonist reaction occurred. In the clinical trial program for HAE doses up to 0.4 mg/kg iv were given as single dose and subcutaneous doses of 30 mg- 45 mg up to three times/day with 6 hours in between the doses. From these data, the proposed dose of 30 mg s.c. given up to 3 times daily seems acceptable with respect to t½ of icatibant and the margin up to the dose levels where agonist reactions may occur.

No impact on renal function and renal hemodynamics was noted, including GFR, and renal blood flow. No signs of nephrotoxicity were found in the clinical studies. With the recommended dose levels, the risk for nephrotoxicity seems low (despite the observations from non-clinical studies).

Clinical efficacy

Three studies have been performed with the aim to support efficacy of icatibant in acute attacks of hereditary angioedema (HAE).

- JE049-2101: An exploratory open-label Phase II study, involving 15 patients treated for 20 attacks with single iv. infusions at doses up to 0.8 mg/kg over 30 minutes, or a single s.c. injection of 30 or 45 mg icatibant.
- JE049-2102: Double-blind, controlled Phase III, single dose of icatibant 30 mg s.c. injection compared to tranexamic acid in 77 patients. Open-label extension was following, with the option of giving 3 x 30 mg s.c. injections per attack according to response.
- JE049-2103: Double-blind, controlled Phase III, single dose of icatibant 30 mg s.c. injection compared to placebo in 64 patients. Open-label extension was following, with the option of giving 3 x 30 mg s.c. injections per attack according to response.

The open-label part of the studies is ongoing and a data cut-off point of March 31st 2007 (May 30th 2007 for adverse event data) has been used to present unaudited results of the open-label extension (JE049-2102-B and JE049-2103-B) in the initially submitted documentation. Further patient data until September 2007 have been submitted in the response document

- Dose response studies

JE049-2101

In this open, 3 centres, dose-finding study including 5 treatment groups, (3 intravenous, 2 subcutaneous) 15 patients with known HAE received one dose of icatibant.
The primary outcome was symptom relief according to visual analogue scale (VAS) reported by subject for the more severe symptom, taking only "abdominal pain" and "cutaneous swelling" into consideration. Symptom relief was defined as "absolute reduction from the pre-treatment VAS" of ≥20 mm if baseline VAS was ≥30 mm and ≤50 mm, or of ≥30 mm if baseline VAS was >50 mm.

Table 2 - Time from Onset of Symptoms to Start of Treatment, and Time to Onset of Symptom Relief According to VAS

Treatment Group, dose, route	Treatment number	HAE type	HAE manifestation	Time from onset of symptoms to start of treatment[3] [h:min]	Δ VAS (cm) after 4 hours[2]	Onset of symptom relief after start of treatment (reported by subject) [h:min][1]	Onset of symptom relief after start of treatment (based on VAS) [h:min][5]	Time to almost complete Symptom Relief (VAS) [h:min][3]	Time to complete Symptom Relief (VAS) [h:min][4]
Group I 0.4 mg/kg i.v. over 2 h	101	I	Arms	8:00	9.07	1:00	2:00	2:00	2:00
	102	I	Left cheek, arms, legs	8:45	8.25	2:00	2:00	22:00	50:00
	103	I	Abdomen	9:45	0.72	5:00	Not assessable	10:00	50:00
	104	I	Lids / periorbital	7:25	2.37	1:00	6:00	22:00	74:00
	Median (range)			8:22 (7:25 – 9:45)	5.31 (0.72 – 9.07)	1:30 (1:00 – 5:00)	2:00 (2:00 – 6:00)	16:00 (2:00 – 22:00)	50:00 (2:00 – 74:00)
Group II 0.4 mg/kg i.v. over 30 min	201	I	Abdomen	8:40	1.58	2:55	Not assessable	8:30	72:30
	202	I	Legs, abdomen	9:35	1.88	1:20	Not assessable	4:30	20:30
	203	II	Complete face, perioral, arms	5:15	4.02	0:45	4:30	20:30	48:30
	204	I	Legs	9:30	1.96	1:30	2:30	8:30	8:30
	Median (range)			9:05 (5:15 – 9:35)	1.92 (1.58 – 4.02)	1:25 (0:45 – 2:55)	3:30 (2:30 – 4:30)	8:30 (4:30 – 20:30)	34:30 (8:30 – 72:30)
Group III 0.8 mg/kg i.v. over 30 min	301	I	Abdomen	UNK	1.72	0:45	8:30	8:30	20:30
	302	I	Arms, abdomen	7:10	6.88	1:30	2:30	8:30	20:30
	303	I	Left foot	10:20	5.86	1:30	2:30	20:30	96:30
	304	I	Legs, abdomen	9:50	5.36	0:35	4:30	8:30	8:30
	Median (range)			9:50 (7:10 – 10:20)	5.61 (1.72 – 6.88)	1:08 (0:35 – 1:30)	3:30 (2:30 – 8:30)	8:30 (8:30 – 20:30)	20:30 (8:30 – 96:30)
Group IV 30 mg s.c.	401	I	Legs, abdomen	8:30	4.11	1:40	2:00	4:00	48:00
	402	I	Arms, legs, gluteal	7:35	2.19	1:00	4:00	20:00	20:00
	411	UNK	Lids / periorbital, perioral, arms, legs, abdomen	7:05	7.29	0:10	0:30	4:00	8:00
	412	UNK	Arms	5:00	0.63	0:05	20:00	20:00	72:00
	Median (range)			7:20 (5:00 – 8:30)	3.15 (0.63 – 7.29)	0:35 (0:05 – 1:40)	3:00 (0:30 – 20:00)	12:00 (4:00 – 20:00)	34:00 (8:00 – 72:00)
Group V 45 mg s.c.	501	II	Perioral, neck, arms	7:30	6.18	0:10	2:00	20:00	48:00
	502	I	Lids / periorbital, perioral	7:05	1.36	0:40	20:00	20:00	48:00
	503	I	Arms, legs, abdomen	5:10	6.77	0:45	2:00	4:00	72:00
	531	I	Legs, abdomen	3:49	2.43	0:14	8:00	8:00	84:00
	Median (range)			6:07 (3:49 – 7:30)	4.31 (1.36 – 6.77)	0:27 (0:10 – 0:45)	5:00 (2:00 – 20:00)	14:00 (4:00 – 20:00)	60:00 (48:00 – 84:00)

1 as reported by subject; median values were manually calculated; if different times were reported for different symptoms, onset of relief of the most severe symptom was documented; Source: Section 15.1, Tables 12.1.2.1, 13.1.2.1, 18.1.1, 18.1.2, 18.2 , 18.3, and 18.4, Appendix 16.2, Listings 11 and 12.
2 Source: Section 15.1, Table 15.3.1, Δ calculated manually;
3 Source: Section 15.1, Table 18.1.5.1, 18.1.5.2, Appendix 16.2, Listings 25–27
4 Source: Section 15.1, Table 18.1.6.1, 18.1.6.2, Appendix 16.2, Listings 25–27
5. Source: Section 15.1, Table 18.1.4.1, 18.1.4.3
UNK = unknown

In this open single dose study, it should be noted that symptoms occur from a variety of locations, corresponding to the characteristics of the disease. The main target in this study is the Median value for the outcome parameter, for each administration form/dose, which has been used to support the choice of dose. The number of patients in this dose-finding study is low; moreover, the different appearances of HAE in combination with the great variability and wide range in the responses make evaluation of dose-finding difficult. However, bearing in mind these limitations, subcutaneous

administration is convenient and is to be preferred for the patient. The chosen 30 mg subcutaneous dose seems at least similar to the higher s.c. dose and this choice appears therefore reasonable.

- Main studies

Study JE049-2102

METHODS

Study JE049-2102 was a Phase III, randomised, double blind, double dummy, multicentre, controlled, parallel-group study of a 30 mg s.c. formulation of icatibant compared to tranexamic acid for treatment of patients with moderate to very severe symptoms of cutaneous and/or abdominal symptoms of HAE.

The three phases of the study were:
Phase 1
A randomised, double blind, controlled, parallel group phase for patients with cutaneous and/or abdominal angioedema
OR
An open label treatment with subcutaneous icatibant for patients with laryngeal angioedema as their first attack
Phase 2
Open label extension phase for all patients who experienced a hereditary angioedema attack after the controlled phase (either double blind treatment or open label treatment of laryngeal attack as their first attack).
Phase 3
Modified open label extension phase after the end of the double blind phase for all patients, including the patients who were screened, but did not experience an attack severe enough to require treatment while the double blind phase was still ongoing.

Study Participants

It was planned to enrol 74 patients with cutaneous and/or abdominal angioedema (37 patients in both the icatibant and tranexamic acid groups) to provide 66 evaluable patients (33 patients in both the icatibant and tranexamic acid groups).

Treatments

In the double blind phase of the study, patients who were randomised to receive study medication had one 30 mg (3 mL) subcutaneous (sc) icatibant injection in the abdominal region plus oral placebo or 3 mL sc. placebo injection in the abdominal region plus oral tranexamic acid, (500 mg tablets, over-encapsulated with gelatine). Oral medications were given as 3 x 2 capsules for 2 days, 6 to 8 hours apart.
During the open label extension phase, patients experiencing any angioedema attack severe enough to warrant treatment were treated with one 30 mg (3 mL) sc. injection of icatibant in the abdominal region.
Additional injections of icatibant during an attack were allowed during the open label extension.
The maximum dose for icatibant was set at eight injections of 30 mg over 4 weeks or 90 mg/day.
Treatment was to be administered no later than 6 hours after the angioedema attack became moderate (according to the Investigator).

Prior and concomitant therapy

All prescription and OTC medicinal products taken by the patient at entry of the study or were given in addition to the study treatment during the study, were regarded as concomitant treatments and were documented in the patient's CRF. All medication taken 30 days prior to study drug was documented. .
Routine use of antipyretics (aspirin, acetaminophen, non-steroidal anti-inflammatory drugs [NSAIDs]) antihistamines, and corticosteroids was to be avoided, but were permitted in cases of demonstrated medical need.
During the double-blind phase, narcotics and other pain medication were not to be used during onset of the acute attack and study treatment and avoided, for the first 8 to 9 hours following study treatment. If required, rescue medication was to be administered and recorded.
The use of androgens for prophylactic treatment of HAE was permitted (if the dose was stable or decreased). However, increasing the dose resulted in exclusion from the efficacy analysis of the double blind study.
Patients were to record details of all concomitant medications administered outside the study centre in the diary cards provided.
If a patient had received treatment with replacement therapy, including C1-INH products within 3 days from onset of any new angioedema attack, the patient was not to receive treatment with study medication for this new attack.
Patients were not to be withdrawn from the study or from any study population as a result of receiving any concomitant medications.

Rescue therapy

In the double blind phase rescue therapy for the relief of any symptom was to be withheld during the period from the onset of attack for at least the first 8 to 9 hours of treatment. If rescue medication was provided, the investigator documented drug name, dose and time administered. Administration of rescue therapy could include C1-INH and symptomatic therapy (e.g. for nausea or vomiting).

Objectives

Primary Objective:

The primary objective was to assess the efficacy of icatibant, compared with tranexamic acid, on the onset of relief of symptoms resulting from moderate to very severe acute cutaneous and/or abdominal oedema attacks in patients with HAE.

Secondary Objectives:

- Rate of response
- Time to almost complete relief
- Global outcome
- Severity of each symptom
- Safety
- Tolerability

The efficacy and safety of repeated treatments with s.c. icatibant were also assessed during the open label extension phase.
The efficacy and safety of open-label treatment with s.c. icatibant in patients experiencing laryngeal oedema attacks were also assessed during the study period. For clarification, the definition of laryngeal oedema included any angioedema that occurred in the laryngeal or pharyngeal area.
In addition, the relative pharmacoeconomic impact of icatibant and the economic burden associated with onset of an oedema attack under icatibant treatment were to be assessed and compared with tranexamic acid after the double blind treatment of the first attack and compared with historical data after 6 months open label treatment. The pharmacoeconomic results were not part of the CHMP review.

Inclusion criteria

Eligible patients must have met all of the following inclusion criteria before treatment initiation:

- Age ≥ 18 years
- Documented diagnosis of HAE Type I or II. The diagnosis could be confirmed either by functional and immunogenic C1-INH deficiency results from the central laboratory or by medical history. Inclusion was permitted initially based on medical history alone if a clear diagnosis had been made on all of the following criteria:
    - Family history
    - Characteristic attack manifestations, recurrent attacks
    - Historical functional C1-INH level < 50%
    - Exclusion of other forms of angioedema

Subsequent confirmation of the diagnosis was to be made by functional C1-INH, measured in the central laboratory. If there were any discrepancies between central and local laboratory results, the patient could only be included in the efficacy analysis if diagnosis of HAE had been clearly confirmed and a rationale for the functional level of C1-INH > 50% could be given

- Current angioedema attack was in the cutaneous, abdominal, and/or laryngeal areas
- Current attack was moderate to very severe
- Able to complete Baseline assessments and commence treatment no later than 6 hours after the current attack became moderate
- Women of childbearing potential were to have a negative urine pregnancy test before treatment and for the duration of the study was to use consistently and correctly a highly effective method of birth control (failure rate less than 1% per year) such as implants, injectables, combined oral contraceptives, reliable intrauterine devices (IUDs), sexual abstinence or a vasectomised partner
- Signed written Informed Consent given
- Patients with abdominal and/or cutaneous symptoms only:
- Visual Analogue Scale (VAS) for primary symptoms (abdominal pain or cutaneous pain or cutaneous swelling) at time of randomisation ≥ 30 mm.

Exclusion criteria

- Eligible patients must have had none of the following exclusion criteria at treatment initiation:
- Diagnosis of angioedema other than HAE, for example, acquired angioedema (AAE)
- Participation in a clinical trial of another investigational medicinal product (IMP) within the past month
- Treatment with any pain medication since onset of the current angioedema attack
- Treatment with replacement therapy, including C1-INH products, less than 3 days before onset of the current angioedema attack
- Treatment with tranexamic acid replacement therapy within a week before onset of the current angioedema attack
- Treatment with ACE inhibitors
- Contraindications for tranexamic acid i.e. known hypersensitivity to tranexamic acid, severe renal failure, active thromboembolic disease, massive bleeding in upper urinary tract, impaired colour vision
- Evidence of coronary artery disease based on medical history or screening in particular unstable angina pectoris or severe coronary heart disease
- Congestive heart failure (class 3 and 4)
- Serum creatinine level of ≥ 250 µmol/L (≥ 2.82 mg/dl)
- Serious concomitant illness considered to be a contraindication for participation in the trial
- Pregnancy (as assessed prior to treatment) and/or breast-feeding
- Mental condition rendering the patient unable to understand nature, scope, and consequences of the study
- Unlikely to comply with the Protocol.

Outcomes/endpoints

Visual Analogue Scale: (No Symptom (0 mm) - Worst Possible symptom (100 mm)), measuring intensity of each symptom of the attack at Baseline for cutaneous swelling, cutaneous pain, abdominal

pain and nausea, and also symptom relief at the predetermined time points throughout the treatment period.

Symptom score (patient and investigator): Symptoms assessed by the patient and the investigator or designee using **5-Point Symptom Score Scale [**0 = None, absence of symptoms; 1 = Mild (no or mild interference with daily activities); 2 = Moderate (moderate interference with daily activities and no other countermeasures required); 3 = Severe (severe interference with daily activities and with or without other countermeasures); 4 = Very severe (very severe interference with daily activities and other countermeasures required)].
Cutaneous swelling, cutaneous pain, abdominal pain, nausea, erythema, irritation (patient assessment only), abdominal tenderness (investigator (or designee) assessment only), vomiting and diarrhoea were assessed. For laryngeal HAE attacks, the patient and investigator (or designee) made an assessment of dysphagia and voice change. In addition, the investigator assessed breathing difficulties, stridor, and asphyxia.

Global assessment
The investigator (or designee) made a Global Assessment (i.e., considering all abdominal symptoms combined, all cutaneous symptoms combined and/or all laryngeal symptoms combined) using the 5-point scale.
Clinical global impression and improvement
At Baseline, the investigator completed a Clinical Global Impression (Severity of Illness): **Seven-Point Clinical Global Impression Symptom Scale**

Global improvement was assessed by the investigator on Day 1 (4 hours post-treatment), Day 2 (24 hours post-treatment) and Day 14 ± 2 of the double-blind phase using a "**Seven-Point Clinical Global Improvement Symptom Scale**.

Primary endpoint
The primary endpoint: **time to onset of symptom relief of the first attack** using VAS.
Symptom relief was defined as a reduction from the pre-treatment VAS between 21 mm (Baseline VAS of 30 mm) and 30 mm (Baseline VAS of 100 mm). Only symptoms with VAS ≥ 30 mm at Baseline were included in this analysis.
The primary efficacy endpoint was assessed for a single primary symptom: cutaneous swelling, cutaneous pain, or abdominal pain. The decision to count each subject only once for the endpoint analysis mandated to define a single primary symptom for each patient, despite the fact that patients often presented with mixed symptoms (e.g. cutaneous and abdominal).
For the patients presenting with cutaneous symptoms, the primary symptom was defined either as cutaneous swelling or cutaneous pain, taking the most severe (VAS). For the patients presenting with abdominal symptoms (e.g. abdominal pain, vomiting, nausea, or diarrhea), the primary symptom was defined as abdominal pain. Patients presenting with both cutaneous and abdominal symptoms were allocated to the abdominal group if abdominal symptoms were classified as moderate to very severe by the investigator (based on Global Assessment, which considers all abdominal symptoms combined). Patients were classified as cutaneous if the abdominal symptom(s) were mild, and at least one cutaneous symptom was moderate to very severe.
Patients presenting with laryngeal symptoms were always assigned to the laryngeal group irrespective of the severity of other symptoms.

Time to onset of symptom relief was defined as the time between time of injection to time of first documented onset of symptom relief. This time point was determined retrospectively after symptom relief had been documented at three consecutive measurements. The earliest of the three measurements was taken as the point of cessation.
Patients with no documented onset of symptom relief were censored at the time of their last symptom assessment. Patients were censored when the events (symptom relief) did not occur within the observation period.

Secondary endpoint

Response rate at 4 hours after start of treatment: proportion of patients with onset of symptom relief for the primary symptom within 4 hours after treatment.

Time to relief of each symptom present in pre-dose VAS other than the primary symptom: time of injection to time of first documented onset of symptom relief (Response) defined as a reduction from the pre-treatment VAS as described for the primary endpoint.

Time to almost complete symptom relief: time from injection to the first measurement of a value between 0 and 10 mm on the VAS for at least three consecutive measurements for all symptoms (present at pre-dose or not).

Symptom score (patient and investigator): assessment of each symptom and were assessed by the Symptoms assessed by the patient and the investigator or designee using the **5-Point Symptom Score Scale**

For laryngeal HAE attacks, the patient and investigator assessed dysphagia and voice change. In addition, the investigator assessed breathing difficulties, stridor, and asphyxia.

Global assessment

Global assessments considered all abdominal, cutaneous, and/or laryngeal symptoms combined performed by the investigator using the 5-point scale and 7-point scales.

Clinical global impression/improvement: by the investigator using the 5-point scale and 7-point scales.

Regression of symptoms (start of improvement) according to patient: time of injection until time of start of improvement.

Observable regression of visual symptoms according to investigator: time of injection to the time visual (visible) symptoms started to improve.

Overall patient improvement according to investigator: time of injection to time when overall patient improvement was first noted.

Patient satisfaction questionnaire: assessed during the open label extension phase (Week 24).

Sample size and Randomisation

Screening took place prior to enrolment in the study. The investigator instructed the patient about the specifics of the onset of an angioedema attack.

A total of 74 patients with moderate to very severe cutaneous and/or abdominal angioedema were randomised in a 1:1 ratio to receive treatment with icatibant (s.c.) plus placebo (oral) or placebo (s.c.) plus Tranexamic acid (oral).

The randomisation was performed using a validated centralised procedure (International Drug Development Institute [IDDI]) that automated the random assignment of treatment groups to randomisation numbers, using the unique kit numbers for allocation.

Patients with both cutaneous and abdominal symptoms were allocated to the abdominal group if at least one abdominal symptom (abdominal pain, vomiting, diarrhoea, nausea) was moderate to very severe irrespective of the severity of cutaneous symptoms. The patient was stratified as cutaneous if the abdominal symptom(s) were mild, and at least one cutaneous symptom was moderate to very severe.

Only when the double blind phase of the study was completed, the data file verified, and any protocol violations determined, were the randomisation codes broken and made available for the final data analysis.

Patients with symptoms of laryngeal angioedema (whether in combination with cutaneous and/or abdominal symptoms or not) were not randomised to the double blind treatment but treated open label.

The randomisation procedure was based on the stochastic minimization procedure.

Blinding (masking)

During the double blind, phase of the study, icatibant and injectable placebo as well as tranexamic acid and oral placebo were labelled such that each remained unidentifiable by the investigator and the patient.

However, a high number of patients experience local injection skin reactions complicating blinding.

Statistical methods

Standard statistical methods were used for the Phase III studies according to the individual study plans. All randomised patients who received a dose of study medication in the controlled phase of the studies were included in the ITT population. Patients who were not protocol violators and who received the dose within 6 h of their attack becoming moderate were included in the Per-Protocol population with the exception of patients with a baseline VAS score for the primary symptom of <30 mm.

Patients in the Phase III studies were allocated to either the 'cutaneous' or 'abdominal' groups' after completion of the controlled phase but prior to lock of the study database. Patients presenting with both cutaneous and abdominal symptoms were allocated to the 'abdominal' group if abdominal symptoms were classified as moderate to very severe by the physician on the Global Assessment rather than by symptom severity as originally intended. Although useful for the purpose of statistical analysis, this categorisation does not reflect the true clinical picture as many patients have a mix of symptoms with different time courses. Therefore, it is important to assess all the endpoints and their clinical relevance in determining the efficacy of icatibant.

The following post-hoc analyses were conducted:

- Analysis taking into account all the symptoms (primary or secondary) with only symptoms with a VAS ≥30 mm at baseline being included.
- Analysis using the VAS with the highest score at baseline as primary symptom.
- Analysis increasing the stringency of the primary endpoint measure by altering the threshold for meeting the criteria for a response from "any value to right and below a line Y = 6/6X-16, with X ≥30 mm" (with X being the baseline VAS score and Y the post-treatment VAS score), to "any value to the right and below a line Y = 4/7X-50/7, with X ≥30 mm". This change corresponds to a reduction of 50 mm from a baseline VAS of 100 mm and of 20 mm from a baseline VAS of 30 mm. A report of all post-hoc analyses is given in addendum reports (JE049-2102-A and JE049-2103-A)

Missing data was handled by censoring those patients at their last observed time point for any symptom. This is a conservative approach since it makes the worst possible assumption about the treatment outcome, e.g. if time to regression of a symptom was not reported then it was assumed not to have occurred.

Additional statistical analyses were requested by the FDA at the pre-NDA meeting and these are reported in JE049-2102-A and JE049-2103-A.

RESULTS

Recruitment and conduct of the study

A total of 74 patients (36 in the icatibant group and 38 in the tranexamic acid group) were randomised into the study and 3 patients with laryngeal symptoms at baseline were treated with icatibant open label.

At data cut-off, 25 July 2006, there were 31 active centres; (Austria, France, Germany, Hungary, Switzerland, Ireland, Israel, Italy, Lithuania, Poland, UK and Sweden).

Baseline data

Baseline demographics are described in table 3.

Table 3

	Icatibant	Tranexamic acid	Total
Number of patients in ITT population	36	38	74
Gender			
Male	12 (33.3%)	15 (39.5%)	27 (36.5%)
Female	24 (66.7%)	23 (60.5%)	47 (63.5%)
Ratio Male/Female	0.50	0.65	0.57
Proportion of patients (%)			
≤ 65 years	94.4	97.4	95.9
> 65 years	5.6	2.6	4.1

Table 4 - History of Hereditary Angioedema: Number of attacks during the last 6 months – ITT population

	Treatment group	N	Mean	SD	Median	Min	Max
Number of patients in ITT population							
	All	74					
	Icatibant	36					
	Tranexamic acid	38					
Number of attacks during the last 6 months							
Cutaneous	Icatibant	35	7.4	6.33	6.0	1.0	24.0
	Tranexamic acid	32	7.9	6.51	5.0	1.0	25.0
Abdominal	Icatibant	26	4.2	3.78	2.5	1.0	15.0
	Tranexamic acid	22	8.7	17.43	3.0	1.0	72.0
Cutaneous and abdominal	Icatibant	12	6.5	6.97	3.5	1.0	24.0
	Tranexamic acid	15	2.9	2.88	2.0	1.0	12.0
Laryngeal	Icatibant	10	2.4	1.90	2.0	1.0	7.0
	Tranexamic acid	6	2.2	2.04	1.0	1.0	6.0

Min = minimum, Max = maximum, ITT = Intent to Treat
Note: The date of reference is the date of Visit 1

Participant flow

As seen below 77 patients with HAE were included in the study.

Table 5 – Patient Populations

	Icatibant		Tranexamic acid		Total	
	N	%	N	%	N	%
Screening phase						
Total number of patients screened					247	
Controlled phase (First attack)						
Total number of patients enrolled*	39	100.0	38	100.0	77	100.0
Number of patients randomised	36	92.3	38	100.0	74	96.1
Number of patients from ITT/Safety population	36	92.3	38	100.0	74	96.1
Number of patients from ITT/Safety population with cutaneous attack	24	61.5	23	60.5	47	61.0
Number of patients from ITT/Safety population with abdominal attack	12	30.8	15	39.5	27	35.1
Number of patients from Per-Protocol population	32	82.1	35	92.1	67	87.0
Number of patients from Per-Protocol population with cutaneous attack	21	53.8	22	57.9	43	55.8
Number of patients from Per-Protocol population with abdominal attack	11	28.2	13	34.2	24	31.2
Number of patients treated without randomisation (due to laryngeal symptoms)	3	7.7	0		3	3.9
Open label extension phase (Second and subsequent attacks)						
Total number of patients treated in the open label extension phase**	35	45.5				
Number of randomised patients treated in the open label extension phase	34	44.2				
Number of patients from ITT/Safety population	34	44.2				
Number of patients from Per-Protocol population	32	41.6				
Number of patients with laryngeal symptoms at Baseline treated in the open label extension phase	1	1.3				

* Patients enrolled include all treated patients, i.e. randomised patients and patients who received first treatment Open-Label due to laryngeal symptoms

** Patients treated in the open label extension phase include all patients who received treatments for second or subsequent attacks

Outcomes and estimation

The **time to onset of symptom relief** (primary endpoint) was significantly shorter in the icatibant group (see Table 7 below summarising the efficacy results for both pivotal trials). This was also true for the secondary analyses of the subgroups (cutaneous, abdominal symptoms). Time to response was shorter in abdominal attacks than in cutaneous attacks.
Efficacy obtained in the 11 events with laryngeal symptoms, treated open label with icatibant, appeared similar to efficacy in cutaneous and abdominal attacks. The number of patients receiving rescue was higher in the tranexamic acid group compared with icatibant.

Rescue medication
No patient in the icatibant group received rescue medication within 12 hours of administration of study drug, compared to 5 patients in the tranexamic acid group, and within 48 hours 5 patients and 11 patients respectively.

Laryngeal symptoms
In summary, a total of 7 patients with 11 laryngeal attacks were treated open label with icatibant in the controlled phase and in the open label extension phase of the study. The efficacy results in the controlled phase for patients with laryngeal symptoms were consistent with those reported for cutaneous and abdominal attacks: median time to regression of symptoms (start of improvement) according to patient was 1.0 hour; median time to overall patient improvement according to investigator was 0.7 hours.

<u>Open label phase of Study 2102</u>
During the open label extension phase (cut-off date 31 March 2007), 47 patients were treated with icatibant up to 80 times (one patient) for a total number of 233 attacks. Of these 47 patients, 42 had been randomised (22 to icatibant and 20 to tranexamic acid) during the controlled phase, 2 patients with laryngeal symptoms at baseline treated with icatibant open label during the controlled phase entered the open label extension phase and 3 patients, who had not received any treatment during the controlled phase, were treated. A total of 17 male and 30 female patients (age between 22 and 66 years) were treated in the open label extension phase of the study.
Of 233 attacks, there were 115 cutaneous, 101 abdominal and 17 laryngeal attacks. Two hundred twelve attacks (91.0 %) were treated only with 1 icatibant injection, 20 attacks (8.6%) with 2 injections and 1 attack (0.4%) with 3 injections. Only 3 patients required a second injection as early as

6-7 hours after the initial treatment (for 7 attacks). All other patients received repeated icatibant injections more than 7 hours after the first injection. Overall, 14 patients were discontinued from the study. Nine patients were discontinued during the controlled phase (4 patients in the icatibant treatment group, 4 in the tranexamic acid group and 1 patient with laryngeal symptoms at baseline) and 5 patients were discontinued during the open label extension phase. No patient was discontinued due to AEs or any significant medical condition.

Study JE049-2103

Study 2103 comparing icatibant to placebo had a similar design as study JE049-2102 with identical definitions of endpoints.

METHODS

This was a multicentre (26 active centres: 17 active centres in the US, 5 centres in Canada, 3 centres in Australia, 1 centre in Argentina), Phase III study consisting of:
1) A randomised double blind, placebo controlled, parallel group phase for patients with cutaneous and/or abdominal angioedema An open label treatment with subcutaneous icatibant for patients with laryngeal angioedema as their first attack.
2) An open label extension phase for all patients who experienced a HAE attack after the first attack (double blind treatment or open label treatment of laryngeal attack).
3) A modified open label extension phase, for all patients, including the patients who were screened, but were not treated with study drug while the double blind phase was still ongoing. The results of this phase of the study will be presented separately.

Study Participants

It was planned to enrol 56 patients with cutaneous and/or abdominal oedema to provide 50 evaluable patients (25 patients in both the icatibant and placebo groups).

Treatments
Icatibant subcutaneously was the active therapy included in this study and was compared with placebo.
For concomitant use of other medications see study 2102.

Rescue therapy
In the double blind phase, rescue therapy for the relief of any symptom was to be withheld during the period from the onset of attack for at least the first 8 to 9 hours of treatment to limit study variability. However, if pain medication was required, morphine sulphate could have been administered at a dose of 0.05 mg/kg or an alternative low-dose narcotic. An anti-emetic could be used to treat nausea.

Objectives
Study 2103 is identical in design, objectives and outcome/endpoints as study 2102.

RESULTS

Recruitment and conduct of the study

A total of 178 patients were screened for this study. Of these, 64 patients were enrolled, 56 patients were randomised into the study (27 patients in the icatibant group and 29 patients in the placebo group) and 8 patients with laryngeal symptoms at baseline were treated with icatibant open label.

Participant flow

Table 6 - Patient populations in JE 049-2103

	Icatibant	Placebo	Total
	N (%)	N (%)	N (%)
Screening phase			
Total number of patients screened			178
Controlled phase (First attack)			
Total number of patients enrolled *	35 (100.0)	29 (100.0)	64 (100.0)
Number of patients randomised	27 (77.1)	29 (100.0)	56 (87.5)
Number of patients from ITT/Safety population	27 (77.1)	29 (100.0)	56 (87.5)
Number of patients from ITT/Safety population with cutaneous attack	14 (40.0)	13 (44.8)	27 (42.2)
Number of patients from ITT/Safety population with abdominal attack	13 (37.1)	16 (55.2)	29 (45.3)
Number of patients from Per-Protocol population	24 (68.6)	27 (93.1)	51 (79.7)
Number of patients from Per-Protocol population with cutaneous attack	13 (37.1)	12 (41.4)	25 (39.1)
Number of patients from Per-Protocol population with abdominal attack	11 (31.4)	15 (51.7)	26 (40.6)
Number of patients treated without randomisation (due to laryngeal symptoms)	8 (22.9)	0	8 (12.5)
Open label extension phase (Second and subsequent attacks)			
Total number of patients treated in the open label extension phase **	42 (65.6)		
Number of randomised patients treated in the open label extension phase	39 (60.9)		
Number of patients from ITT/Safety population	39 (60.9)		
Number of patients from Per-Protocol population	35 (54.7)		
Number of patients with laryngeal symptoms at Baseline treated in the open label extension phase	3 (4.7)		

* Patients enrolled include all treated patients, i.e. randomised patients and patients who received first treatment open label due to laryngeal symptoms.
** Patients treated in the open label extension phase include all patients who received treatments for second or subsequent attacks.
ITT = Intent to Treat

Outcomes and estimation

The time to onset of relief (primary endpoint) was shorter with icatibant but a statistically difference as compared to placebo was not achieved with regard to the primary endpoint (table 1 below). However, a rather strong trend consistent with the results of study JE049-2102 was seen and beneficial effects were demonstrated in a number of secondary endpoints (Table 1). There were furthermore more patients receiving rescue within 12 hours in the placebo group (11 patients) than with icatibant (3 patients).
See also combined efficacy tables for the two studies below.

Rescue medication
A total of 20 patients (35.7%) in the ITT population received rescue medication during the controlled phase of the study. In the icatibant treatment group, 6 patients (22.2%) received rescue medication on the day of study drug administration. Of these, 3 patients (11.1%) received rescue medication within the first 12 hours of administration of icatibant. Some patients required several different medications and some patients received multiple administrations.
In the placebo treatment group 14 patients (48.3%) required rescue medication during the controlled phase of the study. Of those, 11 patients (37.9%) received rescue medication within 12 hours of receipt of placebo. Some patients required several different medications and some patients received multiple administrations. There was 1 patient in the placebo treatment group who experienced a laryngeal HAE attack after entry to the study and was treated open label with icatibant.

Laryngeal symptoms
At baseline, the Global Assessment by investigator showed 1 patient with severe, 2 patients with moderate, and 5 patients with mild laryngeal symptoms. At 4 hours after administration of icatibant, all patients were assessed by the investigator as 'much' or 'very much' improved (Clinical Global Improvement) with only 1 patient assessed as having mild symptoms and 7 patients having no symptoms.
Of the 8 patients with laryngeal symptoms at baseline, 3 patients (37.5%) received rescue medication within 24 hours of receiving treatment with icatibant. Of these, 2 patients received a single

administration of rescue medication, 1 of whom received icatibant as a rescue medication, and 1 further patient received many rescue medications due to recurrent abdominal HAE attacks.

Open label extension phase

Concomitant medication

A total of 35 patients (89.7%) received concomitant medications during the open label phase of the study. "Antigonadotropins and similar agents" (danazol; 13 patients, 33.3%) and anilides (11 patients, 28.2%) were the most common concomitant medications. In patients with laryngeal symptoms at Baseline, anilides (2 patients, 66.7%) were the most common concomitant medications.

Rescue medication

Of the 42 patients who were treated in the open label extension phase of the study, a total of 10 patients (23.8%) received rescue medication. The most common rescue medications in the ITT population were aminoalkyl ethers (diphenhydramine; 3 patients, 7.7%), natural opium alkaloids (3 patients, 7.7%) and piperazine derivatives (3 patients, 7.7%). One patient received rescue medication within 6 hours of receiving icatibant, 2 within 12 hours, 3 within 24 hours, 1 within 35 hours, 1 within 72 hours, 1 within 50 to 66 hours and 1 unknown. Two of the 3 patients (66.7%) with laryngeal symptoms at Baseline received rescue medication during the open label extension phase of the study (one within 18 hours and one within 13 days of receipt of icatibant,).

- Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy results from both main studies are shown in table 7.

Table 7 – Comparison of Key Efficacy Results: JE049 #2102 and JE049 #2103

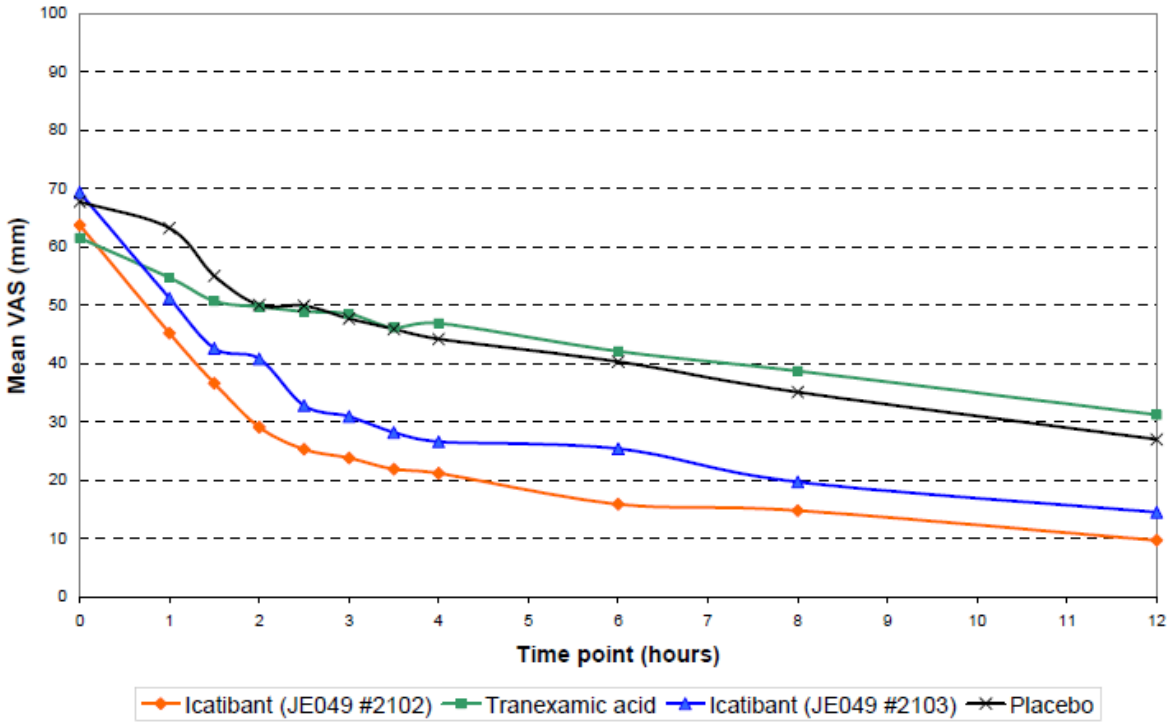
	JE049 #2102			JE049 #2103		
Efficacy endpoint	**Icatibant**	**Tranexamic acid**	**p-value**	**Icatibant**	**Placebo**	**p-value**
Number of subjects in ITT population	36	38		27	29	
Median time to onset of symptom relief (h)[1]						
All attacks	2.0	12.0	<0.001	2.5	4.6	0.142
Cutaneous attacks	2.5	18.2	<0.001	3.4	10.0	0.221
Abdominal attacks	1.6	3.5	0.026	2.0	3.0	0.159
Median time to onset of symptom relief including all symptoms (h)[2]						
Cutaneous swelling	2.6	18.1	<0.001	3.1	10.2	0.039
Cutaneous pain	1.5	12.0	0.003	1.6	9.0	0.007
Abdominal pain	1.6	3.5	0.026	2.0	3.3	0.056
Nausea	1.3	1.5	0.550	1.1	2.3	0.080
Response rate 4 h after start of treatment (%)	80.0	30.6	<0.001	66.7	46.4	0.176
Median time to relief of each symptom present in the pre-dose VAS other than the primary symptom						
Cutaneous swelling	2.0	7.5	0.220	3.5	10.0	0.053
Cutaneous pain	1.5	12.0	0.018	1.6	23.9	0.018
Abdominal pain	-[3]	-[3]	-[3]	2.1	10.0	0.046
Nausea	1.3	1.5	0.550	1.1	2.3	0.080
Median time to almost complete symptom relief (h)	10.0	51.0	<0.001	8.5	23.3	0.069
Median time to regression of symptoms according to the patient (h)	0.8	7.9	<0.001	0.8	16.9	<0.001
Median time to regression of visible symptoms according to the physician (h)	1.7	8.0	<0.001	6.5	14.0	0.240
Median time to overall patient improvement according to the physician (h)	1.5	6.9	<0.001	1.0	5.7	<0.001

[1]Primary endpoint

[2]Post-hoc analysis

[3]This symptom was used as primary symptom

Figure 1: Mean VAS Values Over Time for the Symptom used for the Primary Endpoint: Controlled Phase for ITT Population, JE049 #2102 and JE049 #2103



Additional data provided in Response document (cut-off date, September 2007)

Additional supporting data on efficacy have been submitted, describing 118 patients who have been treated with icatibant for a total number of 597 HAE attacks treated in the open label phase. Of these 118 patients, 93 were initially randomised (46 to icatibant, 21 to tranexamic acid and 26 to placebo) during the controlled phase; 5 patients with laryngeal symptoms at baseline were treated with icatibant during the controlled phase and then entered the open-label extension phase and 20 patients, who had not received any treatment during the controlled phase, were treated solely in the open-label phase. A number of patients were screened initially but were never treated (e.g. never presented with eligible attack during the study period). In the controlled phase, a total of 63 attacks in 63 patients were treated with a single injection of icatibant (as described above, the same patients may appear in both populations).

Most of the 597 treated attacks, needed only one icatibant administration, and very few required rescue medication. Within these treated attacks, there are no signs of exacerbation of severe symptoms.

Table 8 – Number of Attacks Treated with 1 to 3 Icatibant Injections

Type of Attack	Total	1 injection	2 injections	3 injections
Total	597 100%	537 89.9%	56 9.4%	4 0.7%
Cutaneous	258 100%	233 90.3%	23 8.9%	2 0.8%
Abdominal	289 100%	259 89.6%	28 9.7%	2 0.7%
Laryngeal	50 100%	45 90.0%	5 10.0%	0 0%

Fifty-nine of 597 attacks (9.9 %) became worse after the initial treatment with icatibant. Thirty of them (50.8 %) were treated with icatibant injection only, 7 (11.9 %) were treated with both, icatibant and rescue medication, 11 (18.6 %) were treated only with rescue medication, and 11 (18.6 %) attacks that worsened according to the given definition required no additional treatment.
Of these 59 attacks, worsening of symptoms within the first 10 hours occurred in only 3 of the attacks. One of them was treated with rescue medication (the time point of treatment is unknown), one was treated with icatibant, and one attack required no additional treatment.
Seven of 597 attacks (1.2%) were treated with additional medication due to persistent initial symptoms. Five of them were treated with icatibant alone; two attacks were treated with rescue medication alone.
Ten of 597 attacks were treated with additional medication due to investigator judgement without any reporting of reappearance of symptoms or appearance of new symptoms as well as long persisting initial symptoms. Five of them were treated with icatibant alone, and five attacks were treated with rescue medication alone.

Laryngeal symptoms
Additional reassuring experience from open label treatment of 61 HAE attacks with symptoms indicating laryngeal involvement has been submitted. All individuals (n=36) with laryngeal symptoms (n=61) have been satisfactorily described. Regression of symptoms indicates sufficient treatment effect with icatibant.
The treated patients had experienced, from 2 up to 44 HAE attacks (with different locations of symptoms) during 6 months before study entry. These pre-study attacks had duration of 1-4 days. The 61 open label treated laryngeal attacks, were of moderate to very severe character in 52 of the attacks (27/61 attacks were severe-very severe; nine were mild) when icatibant treatment was initiated. Most attacks therefore seem to be severe enough to reflect the risk population with laryngeal oedema attacks. One icatibant injection was sufficient in the majority of cases and efficacy noted by the patient as "time to regression" was less than 1 hour in 38/61 attacks. Another relevant indication of treatment effect is "hours at hospital" which was registered in 22/61 attacks with observation time at hospital no longer than 15 hours, but often much shorter.

The additional data submitted and the discussion provided, are reassuring in describing efficacy with icatibant in both general attacks of HAE but also in laryngeal attacks.

- Clinical studies in special populations

Gender analyses in Study JE49-2102
No effect of icatibant on gender was seen for the median time to onset of symptom relief, the median time to almost complete relief and evaluation of durability of response. In male patients, the median time to onset of symptom relief was 3.5 hours in the icatibant group and 14.0 hours in the Tranexamic acid group ($p = 0.013$). In female patients, the median time to onset of symptom relief was 1.6 hours in the icatibant group and 10.0 hours in the Tranexamic acid group ($p < 0.001$).
For male patients the median time to almost complete relief for all symptoms was 12.5 hours in the icatibant treatment group, and 51.0 hours in the Tranexamic acid treatment group ($p = 0.014$). For female patients the median time to almost complete relief for all symptoms was 5.1 hours in the icatibant treatment group, and 34.0 hours in the Tranexamic acid treatment group ($p = 0.002$).
In female patients the response rate 4 hours after the start of treatment was 91.7% for icatibant versus 33.3% for the Tranexamic acid ($p \leq 0.001$).

Thus, there appears to be a gender effect on the efficacy endpoints irrespective of the treatment arms. This may be related to how females and males perceive their symptom severity. Since the size of the gender effect is similar for the icatibant and the comparators, it is unlikely that differences in systemic exposure to icatibant can account for the observation. Accordingly there is no need to recommend different doses.

Weight analyses in Study JE49-2102
For the 50 kg to 75 kg population median time to onset of symptom relief was 2.0 hours for the icatibant treatment group and 11.1 hours for the tranexamic acid treatment group (p = 0.002). For the 75 kg to 100 kg population median time to onset of symptom relief was 2.0 hours for the icatibant treatment group and 14 hours for the tranexamic acid treatment group (p = 0.001). The median time to almost complete relief was 4.0 hours for icatibant and 51.0 hours for tranexamic acid for the 50 kg to 75 kg population (p = 0.001) and 10.0 hours for icatibant and 58.8 hours for tranexamic acid for the 75 kg to 100 kg population (p = 0.003). The response rate at 4 hours for the 50 kg to 75 kg population was 80.0% for icatibant and 30.0% for tranexamic acid (p = 0.006) and 81.3% for icatibant and 28.6% for tranexamic acid for the 75 kg to 100 kg population (p = 0.009).

Any trends are most likely explained by the gender effect described above.

- Discussion on clinical efficacy

Icatibant as a treatment for patients with hereditary angioedema attacks, has been clinically evaluated in one open dose-finding study and two comparative, double-blind studies including 130 patients with hereditary angioedema type I or II, whereof 63 patients received icatibant as single dose in the double-blind phase. Open extension phases are ongoing.

The chosen dose based on PK data and an adequately performed dose finding study is judged to be sufficiently justified.

Attacks of hereditary angioedema have a complex pattern with varying symptoms from different organ systems, more or less difficult to analyse in an objective way (e.g swelling of lips is probably easier to estimate compared with e.g. swelling in a leg). Symptoms vary from one attack to another and within-patient. Given these difficulties, the approach taken by the applicant to divide symptoms into two main groups, cutaneous and abdominal seems adequate. There are no established tools for evaluating attacks of HAE or any generally accepted study endpoints. The efforts made to define the primary endpoint, onset of symptom relief, are acknowledged as a reasonable and a rather conservative approach. In addition, to request 3 time points showing response, and thereafter assess the time to response, defined as “time to the first response” is also acknowledged as a clinically relevant and conservative approach.

A beneficial effect was shown for icatibant in the primary endpoint, time to onset of symptom relief, in comparison with tranexamic acid. In the second pivotal study, comparing icatibant with placebo, a similar rather strong trend was observed which however failed to achieve statistical significance. However, the use of a responder analysis as the primary endpoint was likely to decrease the chance of detecting a difference between treatments as this analysis does not use all the available data. When a change from baseline analysis to 4 and 12 hours analysis was conducted clear evidence of superiority over placebo at both time points was seen. Further sensitivity analyses have also been provided fitting centre as a fixed rather than a random effect. These analyses produce very similar results and confirm the superiority of icatibant over placebo for the VAS endpoint. In addition, icatibant was superior to both controls (tranexamic acid and placebo) in a number of secondary endpoints and all endpoints tended to be in favour of icatibant, with less variability and a consistently shorter time to symptom relief. The effect demonstrated in the double-blind studies is judged to be clinically relevant.

In the open label follow up studies that are still ongoing, patients have been treated with repeated doses (up to 3 administrations in 24 hours) and during recurrent attacks. The additional data and the discussion provided are consistent with the pivotal study results and further support the efficacy conclusions. A beneficial effect is judged to have been demonstrated both in the treatment of "general" HAE attacks without laryngeal symptoms and in attacks with laryngeal symptoms. Most of the in total, 597 treated attacks, needed only one icatibant administration, and very few required rescue medication. Within these treated attacks, there are no signs of exacerbation of severe symptoms.

Data from 61 attacks occurring in 36 patients, with laryngeal symptoms have been submitted. Most of the treated attacks seem to represent clinically relevant laryngeal symptoms (27/61 attacks were severe or very severe). Time to regression of symptoms, as well as time to "release from hospital" indicates clinically relevant efficacy of icatibant. In addition, one injection was sufficient in the majority of cases.

As requested by CHMP the applicant proposed additional text in the SPC regarding the instructions of use, with the recommendation to manage patients with laryngeal attacks in hospital setting. However in the future, post-marketing experience and a proposed study may provide more data to ensure safe use with self-administration.

Information from treatment in special populations is limited or lacking. Children/adolescents were not included and only 3 patients above the age of 65 were included in the performed studies. Appropriate information on this lack of knowledge has been included in the SPC

Clinical safety

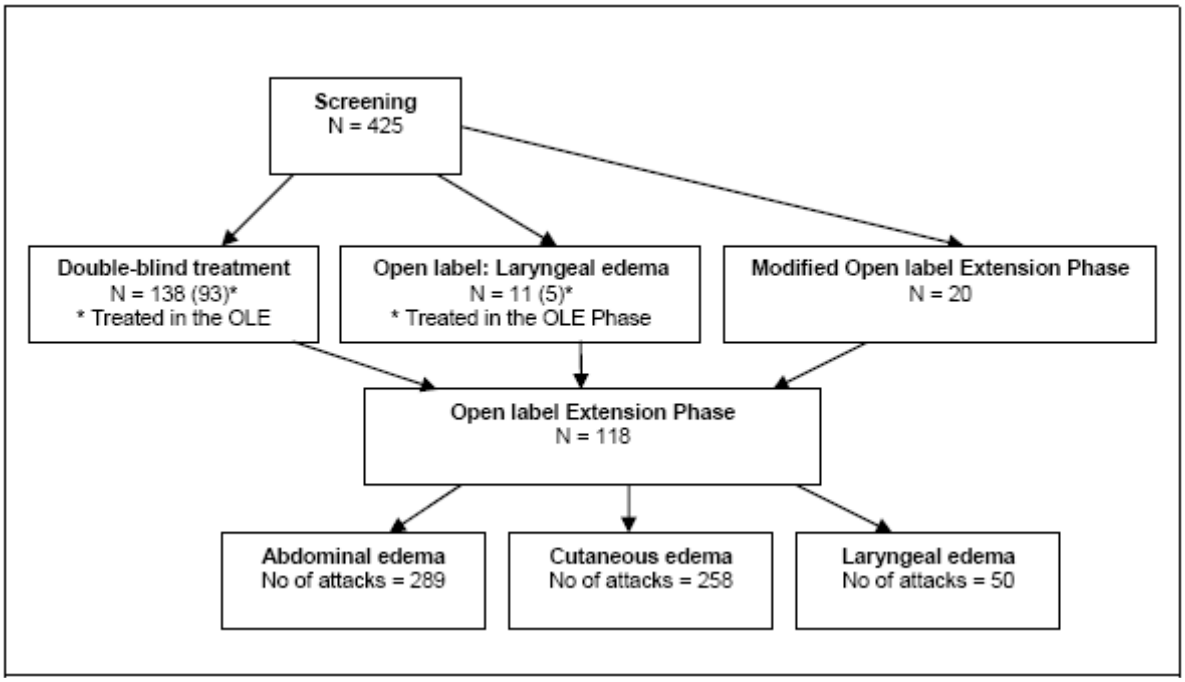
- Patient exposure

Patient exposure in clinical trials, as submitted in the initial dossier is presented in table 9:

Table 9 – Total Number of Healthy Subjects and Patients Receiving At Least One Dose of Icatibant in all Clinical Trials and Via all Routes of Administration

Route of administration	Indication	Duration of treatment	No. of subjects/patients
Intranasal	Allergic rhinitis	Up to 2 weeks	201
Inhalation	Mild to moderate asthma	Up to 4 weeks	205
Intra-articular	Symptomatic knee osteoarthritis	Up to 3 injections at weekly intervals	234
Intravenous infusion	Post-operative pain, liver cirrhosis, HAE	Up to 5-day continuous infusion	180
Subcutaneous	HAE	Up to 5 doses in healthy subjects	60 healthy subjects, 142 patients

New interim clinical study reports have been prepared including data collected from patients participating in the open-label phase of the phase III studies up to a cut-off date of 30th September 2007. Up to the cut-off date, 118 patients have been treated open label with icatibant for a total number of 597 HAE attacks.



Experience from open label treatment of 61 HAE attacks with symptoms indicating laryngeal involvement has in the response document been submitted and described. All individuals (n=36) with laryngeal symptoms (61 attacks) have been satisfactorily described.

- Adverse events

The most common adverse events reported were symptoms related to injection site reactions with icatibant. These reactions are more common with s.c. icatibant than following i.v. administration.
Injection site reactions were seen in the majority of patients following the s.c. dose of icatibant, generally mild to moderate in severity and resolved spontaneously within a short time. Symptoms were itching, burning sensation, erythema, swelling, feeling of warmth, pruritus, as well as pain lasting from 10-20 minutes up to a few hours.
There were 5 reports on chest pain, but the case reports did not indicate any cardiovascular related events. None of the reports indicate a relation to icatibant therapy and some of the patients were rechallenged with no similar symptoms.

Immunological events
A number of patients have received repeated treatment indicating maintained efficacy, whereof one patient has treated 110 attacks. Of the overall total of 36 patients treated for laryngeal attacks (61 attacks), 24 patients received treatment for a single laryngeal attack, 8 patients for 2 laryngeal attacks, 2 patients for 3 laryngeal attacks, and one each for 5 and 10 laryngeal attacks.
No signals of potential immunological events have been found. However, no method of antibody detection is available. The risk for antibody development is considered low, also supported by animal data.

- Serious adverse event/deaths/other significant events

One patient on tranexamic acid died 41 days after administration (coronary artery atherosclerosis and aortic valve sclerosis).

There were 6 patients (7 events) reporting serious events with the dose of icatibant intended for use. No serious event was reported for TA or placebo.
The reported SAE include recurrent attacks. One “hypertensive crisis” (this diagnosis could be questioned) does not seem to be related in time to icatibant. Laryngeal oedema in one patient describes a rapid deterioration of symptoms, probably not related to icatibant given just 5 minutes before a need for intubation

- Laboratory findings

ECGs including QT evaluations have been thoroughly performed by the applicant, also involving expert opinion. No safety signals of concern have been found

- Safety in special populations

No difference in safety reporting was found between male and female.
Icatibant has been studied in severely ill patients with liver cirrhosis and concomitant hepato-renal dysfunction, no safety signals were found.
Bradykinin has been implicated in the protection of the myocardium during ischemia and it seems likely that the serious adverse effects seen in preclinical infarction studies are manifestations of a blockade of such protective effects by icatibant (see preclinical issues). The Applicant suggests a warning in the SPC for the use of icatibant in the presence of acute ischaemic heart disease or unstable angina pectoris, which is endorsed. Bradykinin has also been implicated in limiting the extent of brain damage in stroke. Theoretically, icatibant may antagonise the protective effect of bradykinin in this condition as well, leading to a worsening of the ischaemic brain damage (see preclinical issues). A warning in the SPC has been proposed, which is endorsed.

- Safety related to drug-drug interactions and other interactions

Inhibition of degradation of bradykinin by ACE inhibitors, leading to an increased bradykinin concentration, may contribute to the antihypertensive effect of these drugs. Thus, there is a theoretical risk of a pharmacodynamic interaction whereby icatibant would attenuate the antihypertensive effect of ACE inhibitors. Clinical trials excluded subjects taking ACE inhibitors. However, the possibility that short term administration of icatibant will alter significantly the chronic antihypertensive effect of an ACE inhibitor is remote, especially since patients with HAE should not be using ACE inhibitors (risk for development of HAE attacks).

- Discontinuation due to adverse events

There were no reports of discontinuations due to adverse events.

- Post marketing experience

There is no post-marketing experience.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety issue	Proposed PhV activities	Proposed risk minimisation activities
Injection site reactions	Routine PhV	Routine risk minimisation activities. Erythema, swelling, warm sensation, burning, itching, cutaneous pain is described as very common administration site reactions in the section 4.8 of the SPC (undesirable effects)
Potential worsening of cardiac ischemia due to antagonism of beneficial bradykinin effects	Routine PhV Safety data monitoring via a HAE Register.	Routine risk minimisation activities. The following information is included in the section 4.4 of the SPC (special warnings and precautions for use): Under ischemic conditions, a deterioration of cardiac function and a decrease in coronary blood flow could theoretically arise from antagonism of bradykinin receptor type 2. Caution should therefore be observed in the administration of Firazyr to patients with acute ischemic heart disease or unstable angina pectoris
Potential partial brady-kinin agonism - generalized reactions such as hypotension, swelling of mucous membranes, broncho-constriction, aggravation of pain, erythema or itching injection site reactions	Routine PhV Safety data monitoring via a HAE Register.	Routine risk minimisation activities for injection site reactions only (see above). At the currently proposed dose and administration form, no bradykinin agonistic effects other than injection site reactions are expected.
Antigenicity - potential hypersensitivity - potential lack of efficacy	Routine PhV Safety data monitoring via a HAE Register.	Routine risk minimisation activities. Contraindications in section 4.3 of the SPC list: Hypersensitivity to the active substance or to any of the excipients
Lack of efficacy Potentially life-threatening in case of laryngeal oedema	Routine PhV Safety data monitoring via a HAE Register	Routine risk minimisation activities. The section 4.2 of the SPC (posology and method of administration) specifies: Patients with laryngeal attacks need to be carefully managed in an appropriate medical institution after injection until the physician considers discharge to be safe.

Missing information: Use in children and adolescents	Routine PhV Safety data monitoring via a HAE Register. Paediatric Investigation Plan.	Routine risk minimisation activities. Section 4.1 of the SPC (therapeutic indications) indicates that Firazyr is indicated in adults and section 4.2 specifies that "there is no experience in children"
Use during pregnancy and lactation	Routine PhV Follow-up until outcome of pregnancy is known	Routine risk minimisation activities. The section 4.6 of the SPC (pregnancy and lactation) informs that "animal studies showed effects on uterine implantation and parturition (see section 5.3) but the potential risk for humans is unknown. Firazyr should be used during pregnancy only if the potential benefit justifies the potential risk for the foetus (e.g. for treatment of potentially life threatening laryngeal attacks)." It is also specified in the section 4.6 of the SPC that "it is unknown whether icatibant is excreted in human milk but it is recommended that lactating women, who wish to take icatibant, should not breastfeed for 12 hours after treatment."
Use in self-administration	Routine PhV Study on self-administration	Routine risk minimisation activities. The section 4.2 of the SPC (posology and method of administration) specifies that "Firazyr is not for self-administration".

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The active substance and the medicinal product have been appropriately characterised and generally satisfactory documentation has been provided. The excipients used in the preparation of the medicinal product and manufacturing process selected are typical for injectable preparations. The results indicate that the active substance and the medicinal product can be reproducibly manufactured.

At the time of the CHMP opinion, there were minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

Non-clinical pharmacology and toxicology

The safety pharmacology package did not produce any signals causing concerns about the safety of icatibant other than the cardiovascular effects. Bradykinin has been implicated in the protection of the myocardium during ischaemia and it seems likely that the serious adverse effects seen, e.g. prolongation of ventricular fibrillations in isolated rat hearts and excess mortality in a dog myocardial infarction study, are manifestations of a blockade of such protective effects by icatibant. Theoretically, in stroke icatibant may also antagonise the protective effect of bradykinin (limiting the extent of brain damage). A warning has been introduced in the SPC (see Conclusion on Safety).

The cardinal symptoms in single dose toxicity studies were erythema and swelling and local reaction at the injection site. The dominant findings in repeat –dose toxicity studies were nephrotoxicity (necrosis/Atrophy of proximal tubules) and delayed sexual maturation. The latter are not relevant to the current indication (adults).

The renal findings in the short term studies were mostly explained by the use of a certain in-house strain of rats. However, renal findings observed in chronic toxicity studies (intranasal administration at low systemic exposure) raised some concern about possible long-term renal effects, considering that the frequency and severity of HAE episodes are highly variable. However, as the proposed indication is treatment of HAE episodes, and given that a 6 month study is available (although at lower exposure than the intended use), the lack of the chronic toxicity studies with a relevant route of administration is accepted; the applicant has committed to conduct chronic toxicity studies in rodents and non-rodents as a follow-up measure.

Efficacy

A beneficial effect was shown for icatibant in the primary endpoint, time to onset of symptom relief, in comparison with tranexamic acid.
In the second pivotal study, comparing icatibant with placebo, a similar rather strong trend was observed. When a change from baseline analysis to 4 and 12 hours analysis was conducted clear evidence of superiority over placebo at both time-points was seen. Further sensitivity analyses have also been provided fitting centre as a fixed rather than a random effect. These analyses produce very similar results and confirm the superiority of icatibant over placebo for the VAS endpoint.
In addition, icatibant was superior to both controls (tranexamic acid and placebo) in a number of secondary endpoints and all endpoints tended to be in favour of icatibant, with less variability and a consistently shorter time to symptom relief. The effect demonstrated in the double-blind studies is judged to be clinically relevant.

In the open label follow up studies that are still ongoing, patients have been treated with repeated doses (up to 3 administrations in 24 hours) and during recurrent attacks. The additional data and the discussion provided are consistent with the pivotal study results and further support the efficacy conclusions. A beneficial effect is judged to have been demonstrated both in the treatment of "general" HAE attacks without laryngeal symptoms and in attacks with laryngeal symptoms. Most of the in total 597 treated attacks, needed only one icatibant administration, and very few required rescue medication. Within these treated attacks, there are no signs of exacerbation of severe symptoms.

Data from 61 attacks occurring in 36 patients with laryngeal symptoms have been submitted. Most of the treated attacks seem to represent clinically relevant laryngeal symptoms (27/61 attacks were severe or very severe). Time to regression of symptoms, as well as time to “release from hospital” indicates clinically relevant efficacy of icatibant. In addition, one injection was sufficient in the majority of cases.

As requested by CHMP the applicant proposed additional text in the SPC regarding the instructions of use, with the recommendation to manage patients with laryngeal attacks in hospital setting.

Information from treatment in special populations is limited or lacking. Children/adolescents were not included and only 3 patients above the age of 65 were included in the performed studies. Appropriate information on this lack of knowledge has been included in the SPC

Safety

In the double-blind, controlled studies 63 attacks were treated in 63 patients, with a single dose of icatibant. Up to the cut-off date, 118 patients have been treated open label with icatibant for a total number of 597 HAE attacks. This is considered an appropriate number of attacks in this orphan indication also taking into account that during the clinical studies with icatibant and in the open label treated attacks, no alarming signals have been found.

In the clinical trials a high number of injection site reactions were identified. These reactions are mainly mild-moderate and resolve within a few hours. The mechanism of mast-cell degradation is plausible but also the rather large injection volume of 3 ml might influence the skin reaction.

Theoretically a potential risk is a deterioration of cardiac function and decrease in coronary blood flow, under ischaemic conditions (e.g. during an acute myocardial infarction), due to a possible protective effect of bradykinin. Therefore, in the clinical trials, patients with cardiac risk factors were excluded and in the SPC, a warning is included on patients with acute ischaemic heart disease and unstable angina pectoris and also stroke.

Antigenicity cannot be excluded but no method of detecting antibodies has been possible to develop. No signs of hypersensitivity increasing over time have been found in subjects with repeated administrations. The risk of developing antibodies with this small peptide seems however low, also supported by animal data.

A major concern is the potential risk for lack of efficacy in patients developing laryngeal oedema which must be met with appropriate risk minimisation measures. Cases with laryngeal oedema are of particular concern due to its life-threatening character resulting in serious complications due to delayed transport to hospital or a delay in acute care. Reassuring data have been received from 61 attacks involving laryngeal symptoms, whereof the majority had moderate- very severe symptoms at baseline. It is necessary to learn more from thoroughly assessed open label treated patients and to continuously monitor post-authorisation. Instructions for use in appropriate medical settings have been included in the SPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these

- User consultation

The applicant has submitted results from user testing of the package leaflet, which was performed in English. Overall, the user test is found acceptable.

Risk-benefit assessment

The risk/benefit balance is from a clinical perspective positive. Statistically significant efficacy has been shown compared with both tranexamic acid and placebo for change from baseline in VAS measuring the severity of the attack, and with a consistent pattern of less variability in time to response (primary endpoint) compared to placebo and tranexamic acid. This is also true for secondary endpoints.
No major safety concerns have been found.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Firazyr in the symptomatic treatment of of acute attacks hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency) was favourable and therefore recommended the granting of the marketing authorisation.