Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Icatibant

Proprietary Product Name: Firazyr

Sponsor: Shire Australia Pty Ltd

September 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Product Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	7 June 2010
Active ingredient(s):	Icatibant acetate
Product Name(s):	Firazyr
Sponsor's Name and Address:	Shire Australia Pty Ltd, PO Box 6240, North Ryde NSW 2113
Dose form(s):	Solution
Strength(s):	10 mg/mL icatibant base
Container(s):	3.0 mL pre-filled syringe (10 mg/mL) with a separate sterile needle.
Pack size(s):	Single
Approved Therapeutic use:	Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).
Route(s) of administration:	Subcutaneous (SC) injection
Dosage:	30 mg via SC injection, preferably in the abdominal area. If insufficient relief or recurrence of symptoms, a second injection can be given after 6 hours and a third after a further 6 hours. No more than 3 injections should be given in a 24 hour period.
ARTG number(s):	160313

Product Background

Hereditary angioedema (HAE) is characterized by episodic bouts of well-circumscribed, non-pitting sub-epithelial oedema that primarily involve the extremities, larynx, face, and abdomen. The condition is inherited as an autosomal dominant trait and is characterised by functional levels of serpin C1 inhibitor (C1-INH) activity in the blood that are approximately 30% of normal values. About 15% of patients have normal levels of antigenic C1-INH, but most of it is non-functional. As a result of the failure of C1-INH to block the enzymatic activity of C1, levels of the early-acting complement components C4 and C2 are low.

Attacks of hereditary angioedema generally last for one to four days. Swelling of the extremities is typically painless and resolves without harm. Abdominal attacks from oedema in the submucosa and serosa of the bowel wall are often associated with nausea, vomiting, and pain severe enough to necessitate the use of narcotic medications. Oedema of the upper airway may result in asphyxiation; before modern prophylactic therapy approximately 25% of

patients died of this complication[1]. Prevalence is estimated at between 1 in 10,000 and 1 in 50,000 people. In one study of 226 patients which was cited in the sponsor's clinical expert report, 5% of sufferers had no attacks during the 19 year follow-up, 26% had <1 attack per year, 23% had 1-5 attacks per year, 16% had 6-12 attacks per year, and 30% had >12 attacks per year.

The lack or dysfunction of CI-INH causes increased plasma levels of kallikrein, the main enzyme responsible for generation of bradykinin (BK) from kininogen. A deficiency of C1-INH is accompanied by an increased release of BK, which is probably the key mediator responsible for the increased vascular permeability during angioedema formation. BK is primarily responsible for the clinical symptoms of angioedema by directly causing increased vascular permeability, vasodilatation and contraction of visceral smooth muscle.

Icatibant (a synthetic decapeptide analogue of BK containing five non-proteinogenic amino acids) is a selective and competitive antagonist of the BK type 2 receptor (B2) with very low affinity for the B1 receptor or any other receptor tested. It is intended for acute treatment of HAE. 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 BK. The aim of acute treatment is to halt progression of the oedema as quickly as possible, which can be life-saving, particularly if the swelling is in the larynx. At the time of the submission, tranexamic acid was the only registered treatment for HAE in Australia. In severe cases fresh frozen blood plasma, which contains C1-INH, can also be used. In most European countries, a C1-INH concentrate derived from plasma is available to patients who are participating in special programs. Such a product has recently been approved in Australia[2]. Patients with episodes at least once a month or who are at high risk of developing laryngeal oedema may be treated with male sex hormones which increase production of C1-INH in the liver through an as yet unknown mechanism. Danazol is the most commonly used, though it is not registered for this indication. The use of androgens is particularly problematic in children and they must not be taken during pregnancy.

Regulatory Status

The product was designated as an Orphan Drug in Australia on 12 February 2009 for the treatment of acute attacks of hereditary angioedema.

This product obtained marketing authorisation in the European Union (EU; rapporteur was Sweden and co-rapporteur was the UK) as an orphan drug on 11 July 2008 and a European public assessment report (EPAR) was available to the TGA. The FDA issued a "non-approvable" letter in April 2008 primarily due to the limited clinical efficacy data. It was agreed that an additional clinical study would be required. In February 2009, the sponsor submitted to FDA a clinical protocol similar to FAST-1 (For Angioedema Subcutaneous Treatment 1; a Phase 3 trial) through the special protocol assessment (SPA) procedure.

Product Information

The approved Product Information (PI) document current at the time this AusPAR was prepared is at Attachment 1.

[1] Waytes,AT, Rosen FS and Frank MM (1996). *Treatment of Hereditary Angioedema with a Vapor-Heated Ci Inhibitor Concentrate. NEJM 334:1630-1634*

[2] Berinert AusPAR: http://www.tga.gov.au/pmeds/auspar/auspar-berinert.pdf

II. Quality Findings

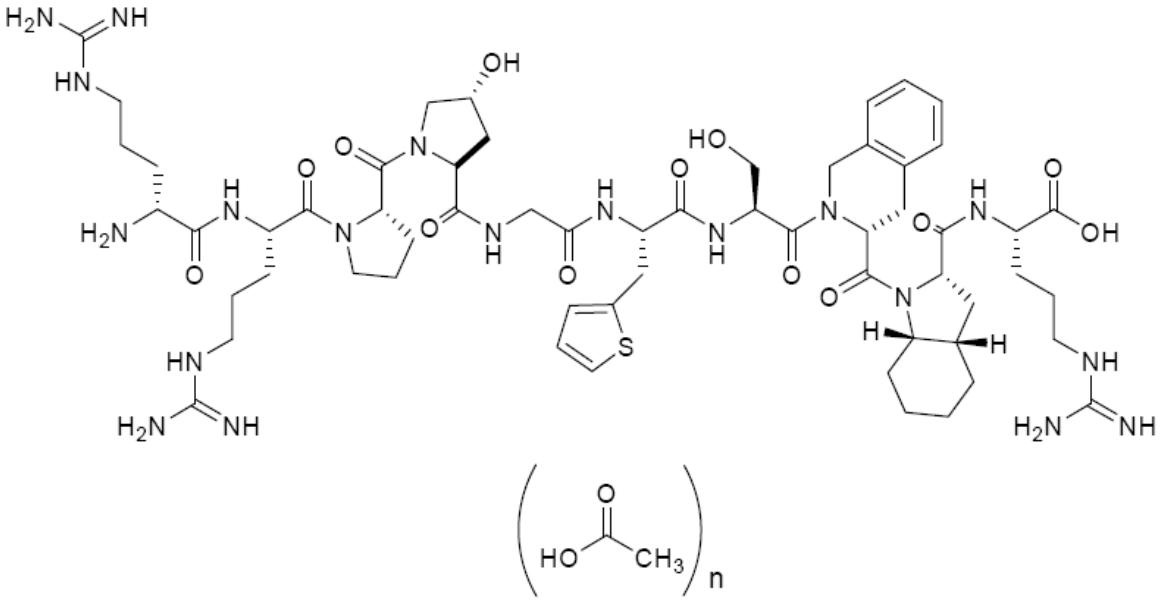
This is an orphan drug application for a New Chemical Entity (NCE), and the quality evaluation has been based on the European Medicines Evaluation Agency (EMEA) evaluation reports.

The formulation proposed for registration was used in most of the clinical studies, including the pivotal phase III studies (2102 & 2103) and the main bioavailability study (1102).

Drug Substance (active ingredient)

The drug substance has the following structure:

Figure 1. Chemical structure of icatibant



It is 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 or H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate salt. It is isolated as a salt with 1-4 equivalents of acetic acid.

Icatibant acetate is manufactured by a conventional, solid phase peptide synthesis technique.

Icatibant acetate is freely soluble in water and in pH 3.5 and pH 7.4 buffers. As it is isolated by lyophilisation, it is an amorphous powder; no crystalline or polymorphic forms are known. The drug substance is hygroscopic.

The specifications applied to the drug substance were considered satisfactory.

Drug Product

The product is a 30 mg/3 mL aqueous solution of icatibant (as acetate), adjusted to pH 5.5 with sodium hydroxide and/or acetic acid, and containing sodium chloride to render it isotonic. It is contained in a pre-filled syringe, which is sealed in a blister pack and enclosed in a cardboard carton together with a syringe needle. The filled syringe is terminally sterilised with steam.

The specifications applied to the drug product were considered satisfactory.

Adequate stability data have been provided to support the proposed shelf life of 2 years below 25°C.

Bioavailability

One bioavailability study was submitted (Study 1102). Ostensibly, it demonstrated that icatibant is completely absorbed after SC injection, with a maximum plasma concentration (C_{max}) about half that observed after a 30 minute intravenous (IV) infusion of the drug. However, the analytical method used in the study (liquid chromatography-mass spectrometry; LC-MS/MS) suffered from serious deficiencies, most notably the use of only one quality control (QC) sample and the application of inadequate acceptance criteria to calibration curves and QC samples.

Another study (Study 2101), a parallel group study in patients with hereditary angioedema, was claimed to support the results of Study 1102. However, the same assay method was used and it suffered from many of the same deficiencies.

The company claimed that the absence of a reliable absolute bioavailability study is not critical given that icatibant is used acutely rather than chronically.

Quality Summary and Conclusions

All chemistry and quality control questions raised during the initial evaluation of this submission have been adequately addressed by the sponsor. However, prior to registration approval, Good Manufacturing Practice (GMP) clearances are required for all four overseas manufacturing sites nominated in the submission. In addition, confirmation is required from the Medicines Toxicology Evaluation Section (TGA) that the limits of two degradants have been adequately qualified.

A clinical decision is required on whether the application can be approved in the absence of a reliable study on the absolute bioavailability of icatibant given SC.

III. Nonclinical Findings

Introduction

The nonclinical data package was considered adequate. The sponsor submitted copies of the EMEA reports, questions, and their answers to the questions. In addition to the submission submitted to the EMEA, reports of long term repeat dose toxicity studies using the SC route in mice, rats and dogs were submitted. The SC repeat dose toxicity studies were Good Laboratory Practice (GLP)-compliant and most contained toxicokinetic data, which assisted in interpreting the results. The nonclinical TGA evaluation has utilised information within the EMEA reports, and detailed assessment has been confined to the pharmacology (including safety pharmacology), the pivotal repeat dose toxicity studies and the reproductive toxicity studies.

Following the discovery of icatibant as a B2 receptor antagonist in the early 1990s, initial clinical applications focussed on asthma, rhinitis and analgesia, supported by toxicology studies of up to 6 months duration in rats and dogs by nasal and aerosol administration (with relatively low systemic exposures) and 1 month intravenous (IV) studies. Embryofetal development studies by the SC route were conducted in rats and rabbits. When HAE became the clinical focus, toxicity studies of up to 3 months duration and rat fertility and peri-postnatal development studies were conducted by the SC route. Reproductive effects were further investigated in a 13-week study in young dogs and a 4-week study in mature dogs. The FDA subsequently requested 6-month rat and 9-month dog SC studies, which have been completed, and rodent carcinogenicity studies have been initiated upon request by the FDA.

Pharmacology

The EMEA rapporteur commented that "a fuller overview of the literature than the rudimentary presentation in the non-clinical overview would have been helpful." This comment is endorsed by the TGA nonclinical evaluator.

BK binds to two receptors (B1 and B2), whereas icatibant only binds to the B2 receptor (≥100 times lower affinity for the B1 receptor). The B2 receptor is in general constitutively expressed and rapidly desensitised, whereas the B1 receptor is induced in response to tissue injury and does not become desensitised. Both receptors are G protein coupled receptors in the rhodopsin family containing 7 transmembrane helices. Activation of the B2 receptor results in signalling through G_q and G_i (membrane-associated proteins). Phospholipases A_2, C and B lead to prostaglandin production and ion channels are also sometimes activated. In addition, B2 transiently promotes tyrosine phosphorylation of tyrosine kinases such as mitogen-activated protein kinase (MAP-kinase) as well as activating the JAK/STAT pathway[3]. The activated B2 directly interacts with nitric oxide synthase (NOS) resulting in nitric oxide (NO) production. Physiologically, BK causes vasodilation, inflammation, stimulation of sensorial and sympathetic nervous connections, smooth muscle contraction of the bronchopulmonary tree, intestine and uterus and increased sperm motility, in addition to the increased vascular permeability that leads to the angioedema observed in patients with C1 inhibitor deficiency.

BK is rapidly metabolised by specific zinc metallopeptidases: neutral endopeptidase (NEP, neprylisin), angiotensin 1 converting enzyme (ACE1), carboxypeptidases N and M (CPN and CPM, also known as kininase I), and aminopeptidase P. NEP is the main kinin degrading enzyme in the kidney, and is important in the epithelium, but unlike ACE 1, does not play a significant role in the plasma. NEP and ACE1 cleave BK at the Pro[7]-Phe[8] bond, NEP at the Gly[4]-Phe[5] bond and ACE at the Phe[5]-Ser[6] bond[4]. ACE1 is a membrane bound protein with a short 28 residue cytoplasmic domain. It can be released from the membrane by a zinc metallopeptidase, with plasma ACE1 originating from epithelial cells. Two ACE isoforms are produced from the same gene, with the somatic isoenzyme containing two active sites, the N-terminal active site preferentially cleaving BK. The germinal isoform only contains one active site, the C-terminal one, and is located in the testes; it appears to be involved in male fertility. Another enzyme, angiotensin-converting enzyme 2 (ACE2), has been shown to be a regulator of cardiac function, although BK is not a substrate. ACE1 inhibitors not only inhibit the conversion of angiotensin I to angiotensin II, but also decrease the inactivation of BK. There is *in vitro* evidence that the B2 receptor interacts with ACE1 and that icatibant can decrease ACE1 activity by binding to the B2 receptor. However, icatibant does not inhibit ACE1 directly and is not a substrate of ACE1.

A minor pathway for the metabolism of BK consists of the removal of the C-terminal arginine by CPN and CPM. CPN and CPM also remove the carboxy-terminal arginine residue from Lys-BK (kallidin, formed from low-molecular weight kininogen by tissue kallikrein) as well as from complement anaphylatoxins C3a, C4a, C5a, and other peptides. The products, des-Arg[9]-BK and Lys-des-Arg[10]-BK[5] are agonists of the B1 receptor which, like BK, are inactivated by the removal of the N-terminal arginine by aminopeptidase P.

[3] Janus kinase/signal transducers and activators of transcription
[4] Pro=proline; Phe=phenylalanine; Gly=glycine, Ser=serine
[5] Lys-des-Arg9-BK=des-Arg10- kallidin; Lys=lysine; Arg=arginine.

Icatibant has been designed so that it is not rapidly metabolised. It is slowly metabolised at the Gly[5]-L-Thi[6] and L-Thi[6]-Ser[7] bonds[6], but the enzyme(s) responsible have not been identified.

B2 receptor (B2R) sequences have been determined in the mouse, rat, guinea pig, rabbit and human, and icatibant binding has been demonstrated in many species including mice, rats, guinea-pigs, dogs, pigs, sheep and humans. B2R is expressed by vascular cells (such as endothelial and smooth muscle cells), nonvascular smooth muscle (for example, uterine) cells, nerve cells (afferent sensory), leukocytes and various tumour cells.

The distribution of the B2 receptor within the mouse, rat and human cardiovascular system has been studied in detail[7]. The B2R was present on the luminal face of endothelial cells in the aorta, other elastic arteries, muscular arteries, capillaries, venules and large veins. However, in small arterioles (of the mesenterium, heart, urinary bladder, brain, salivary gland and kidney) the B2R was present in the perivascular smooth muscle cells of the tunica media. In the heart itself, the B2R was abundant in the myocardium of newborn rats (but not in adult rats) and in the endocardium of atria, atrioventricular valves and ventricles of the adult rat heart.

Icatibant is an antagonist of the B2 receptor, but at high concentrations, icatibant acted as a BK agonist. An *in vitro* study, using cell lines that expressed endogenous rat or dog B2 receptor, demonstrated partial agonist activity of the MAPK pathway (but not calcium mobilisation), but this agonistic activity did not occur for the human B2R. Concentrations sufficiently high to result in agonist activity are likely to have occurred at the injection sites in some of the animal studies, contributing to inflammatory reactions, which were severe in some studies.

Icatibant was tested by the sponsor in a variety of normal and disease models in animals, although few of these had any direct bearing on hereditary angioedema. A number of studies showed that icatibant antagonised BK-induced hypotension in rats. Of more relevance to HAE, icatibant was shown to inhibit BK-induced bronchoconstriction in anaesthetised guinea pigs, and rat carrageenin-induced and burn-induced paw oedema. Icatibant was ineffective in disease models where BK was not an essential component of the pathogenesis. The sponsor did not submit any studies that directly investigated icatibant in C1 inhibitor-deficient animals. However, such studies in mice have been conducted. Vascular permeability is increased in C1 inhibitor-deficient mice, and this vascular permeability was restored to wild-type levels upon IV administration of icatibant. Taken together the results indicate that icatibant is likely to have a beneficial effect on HAE disease.

Secondary pharmacology

The wide tissue distribution of the B2 receptor indicates the widespread role of BK in the body and the potential for a variety of toxicities to occur. Although icatibant did not appear to be distributed to the brain, the presence of B2 receptors in the brain indicates that effects on brain function are a theoretical possibility. The role of BK in the contraction of the uterus is consistent with the effects of icatibant on parturition (see below) and the role of BK in sperm motility and the location of the B2 receptor in the testes is consistent with some of the toxic effects observed on the male reproductive system (see below).

[6] Gly= Glycine, Thi=, Ser=serine, the superscript numbers refer to the amino acid position in the protein.

[7] Figueroa CD, Marchant A, Novoa U, Förstermann U, Jarnagin K, Schölkens B and W Müller-Esterl (2001) *Hypertension* 37: 110-120. "Differential distribution of BK B2 receptors in the rat and human cardiovascular system."

The role of BK in the immune system is beginning to be investigated[8]. The B2 receptor is present on neutrophils, macrophages and dendritic cells. BK analogues induced interleukin-12 (IL-12) synthesis by dendritic cells *in vitro*, and in a mouse model of inflammation, BK shifted the T cell response from a Th2 to a Th1 type response[9]. In addition, in B2 (-/-) knockout mice, IL-12 generation (required for the Th1 type response) was severely compromised when challenged with LPS (lipopolysaccharide). B2 (-/-) knockout mice also suffered increased hepatic bacterial burden and dramatic weight loss during infection with *Listeria monocytogenes*[10]. Kinins were endogenously produced in mice after *Trypanosoma cruzi* SC infection, with IL-12 production following B2-receptor signalling. There was also evidence for a complex interplay between the B2-receptor, ACE and toll-like receptor 2 (TLR2). Thus, the B2 receptor appears to be involved in innate and adaptive immunity against both bacterial and parasitic infection. Hence, the limited literature to date indicates that icatibant is likely to increase susceptibility to bacterial and parasitic infections. This possibility has not been specifically investigated by the sponsor, and the standard nonclinical package does not investigate this possibility.

Safety pharmacology

Cardiovascular effects

There is a considerable body of nonclinical evidence from a number of species that BK has a cardioprotective function and that icatibant interferes with this. The sponsor has provided their own Expert Opinion Report on the cardiovascular safety of icatibant, in which both the nonclinical and clinical data were examined. The sponsor's expert stated:

> "The preclinical studies convincingly demonstrate that BK is an important mediator of many cardioprotective effects and that it contributes to the BP lowering and cardiac effects of ACEI and AT_1 (angiotensin-1) receptor antagonists. The BK B_2 receptor antagonist seems to attenuate most of the BK effects and showed detrimental actions in different experimental models."

BK B2R knockout (B2 (-/-) mice suffer from dilated cardiomyopathy followed by cardiac failure. Mice that lack tissue kallikrein also develop cardiovascular abnormalities in most tissues (septum and posterior wall thinning, a reduced left ventricular mass and a tendency to dilation). In the isolated perfused heart mouse model of ischaemia/reperfusion injury, BK administration upon reperfusion attenuated infarct size, with this protection depending on eNOS (endothelial nitric oxide synthase). In this ischaemic/reperfusion mouse model, an ACE inhibitor reduced the infarct size in wildtype mice, but not in kallikrein deficient mice. Icatibant administration to wildtype mice blocked the effect of the ACE inhibitor.

[8] Schulze-Topphoff U, Prat A, Bader M, Zipp f and O Aktas (2008). Roles of the kallikrein/kinin system in the adaptive immune system. *Int Immunopharmacol* 8: 155-160.

[9] Two types of effector T helper cell responses can be induced, designated Th1 and Th2, each designed to eliminate different types of pathogens. The Th1 response is characterized by the production of interferon-gamma, which activates the bactericidal activities of macrophages, and induces B-cells to make opsonizing (coating) antibodies, and leads to "cell-mediated immunity". The Th2 response is characterized by the release of interleukin-4, which results in the activation of B-cells to make neutralizing (killing) antibodies, leading to "humoral immunity". Generally, Th1 responses are more effective against intracellular pathogens (viruses and bacteria that are inside host cells), while Th2 responses are more effective against extracellular bacteria, parasites and toxins. Like cytotoxic T-cells, most of the helper cells will die upon resolution of infection, with a few remaining as memory cells.

[10] Kaman WE, Wolterink AF, Bader M, Boele LC and D van der Kleij (2009). The BK B2 receptor in the early immune response against Listeria infection. *Med Microbiol Immunol* 198: 39-46.

In rats, systemic delivery of the kallikrein gene attenuated hypertension, cardiac hypertrophy and fibrosis in fructose-induced hypertensive rats and pressure- and volume- overload hypertensive rat models such as spontaneously hypertensive (SHR), two-kidney one clip (2K1C), Dahl salt-sensitive (DSS) and deoxycorticosterone acetate (DOCA)-salt rats[11]. Kallikrein gene transfer also attenuated cardiac hypertrophy and fibrosis in normotensive rats after myocardial infarction, and reduced myocardial infarct size and incidence of ventricular fibrillation and apoptosis after acute ischaemia. Icatibant abolished these effects. Icatibant and the NOS inhibitor NAME (N(w)-nitro-L-arginine methyl ester) blocked the effects of the human tissue kallikrein gene delivered by adenovirus to rat hearts prior to ischaemic reperfusion injury, namely improved cardiac function, prevention of inflammation, suppression of oxidative stress, transforming growth factor-b (TGF-b1)/ Smad2[12] and JNK/p38MAPK pathways[13] and transcription factor nuclear factor kappa B (NF-kB) activation[14]. The sponsor conducted a study with post-ischaemic arrhythmias using isolated rat hearts. Icatibant at 0.1 and 1 nM prolonged the duration of the ventricular fibrillations, whereas 10 nM icatibant decreased the duration of the ventricular fibrillations, presumably by acting as an agonist at the B2 receptor.
Hence, experiments in mice and rats consistently indicate that BK has a cardioprotective effect, and that icatibant attenuates this effect. A cardioprotective effect also seems to exist in rabbits; in isolated rabbit hearts another B2 receptor antagonist (deltibant) increased coronary vascular resistance and decreased the amplitude of left ventricular pressure after myocardial ischaemia.

Although icatibant decreases the cardioprotective effect of BK, this effect was not related to cardiac conduction changes. Thus, icatibant did not elicit any cardiac conduction change *in vitro* (via hERG ion channels) or *in vivo* in normal dogs or in exercising dogs. However, the cardioprotective effects of BK do occur in dogs. In a study conducted by the sponsor, the left descending coronary artery of dogs was occluded for 6 h; the icatibant-treated group had late mortalities (between 3.5 and 5.5 h) that were probably from left ventricular failure, in addition to early mortalities (within 20 min) due to ventricular fibrillation (which were also observed in the control group). In dogs with pacing-induced congestive heart failure, BK levels increased four-fold[15]. After icatibant infusion coronary blood flow was significantly reduced and coronary vascular resistance increased.

Thus, a cardioprotective effect of BK has been demonstrated in the mouse, rat, rabbit and dog, with an attenuation of this effect by icatibant observed in mice, rats and dogs, and by another B2R antagonist in rabbits. In patients, injection of icatibant into the left coronary artery increased the coronary vascular resistance.

The sponsor's Cardiovascular Expert Report cited a couple of examples of results that appeared to contradict the hypothesis that icatibant attenuates the cardioprotective effects of BK. A study in India using cats showed that icatibant improved haemodynamic recovery and attenuated myocardial reperfusion induced lipid peroxidation. However, cats are not a well

[11] Chao J and L Chao (2004) *Exp Physiol* 90: 291-298. Kallikrein-kinin in stroke, cardiovascular and renal disease.
[12] The SMAD proteins are homologs of both the drosophila protein, mothers against decapentaplegic (MAD) and the *Caenorhabditis elegans* protein SMA. The name is a combination of the two.
[13] Extracellular signal–regulated kinases, c-*Jun* NH_2-terminal kinases, and P38 enzymes
[14] Yin H, Chao L and J Chao (2008) *Life Sci* 82: 156-165. Nitric oxide mediates cardiac protection of tissue kallikrein by reducing inflammation and ventricular remodelling after myocardial ischemia/reperfusion.
[15] Cheng C, Onishi K, Ohte N, Suzuki M and WC Little (1998) *J Am Coll Cardiol* 31: 1679-1686. Functional effects of endogenous BK in congestive heart failure.

studied animal model, and similar results have not been reported by other laboratories. In addition, in a rat model of ischaemia followed by reperfusion of the superior mesenteric artery, icatibant attenuated several inflammation-induced events. The sponsor's cardiovascular expert argued that as inflammation plays a key role in atherosclerosis, icatibant might have a protective effect in ischaemic heart disease. However, although atherosclerosis plays a role in ischaemic heart disease, the direct effect of BK on the heart, and the attenuation of this effect by icatibant, seems of direct relevance to ischaemic heart disease. In conclusion, although the sponsor's cardiovascular expert argues that there are results contradictory to the overall picture of icatibant attenuating the cardioprotective effects of BK, these contradictory results are minimal.

The concentration threshold at which icatibant agonistic effect overlaps with antagonistic activity differs between species. The sponsor's cardiovascular expert considers that this makes the translation of the results obtained in animals to humans difficult, but the nonclinical evaluator disagrees with this conclusion. An extremely consistent picture emerges from the animal studies: icatibant at concentrations that are effective at antagonising the B2 receptor attenuate the cardioprotective effect of BK. Therefore, therapeutic levels of icatibant in humans are expected to attenuate the cardioprotective effect of BK.

Stroke

Kallikrein and the B2 receptor have been demonstrated to have a protective effect against ischaemic stroke in the rat, and postischaemic brain injury is exacerbated in B2 (-/-) knockout mice. Icatbant has been shown *in vitro* to attenuate the effects of kallikrein on cultured glial cells[16]. However, the extent that icatibant SC is distributed to the brain is small, and therefore the relevance of these observations to SC icatibant administration is unclear.

Renal Disease

Urinary kallikrein originates from the kidney, and patients with renal disease have reduced levels of urinary kallikrein, with the level of reduction correlating with the severity of the renal disease. IV infusion of kallikrein to DSS rats fed a high-salt diet reduced renal damage without affecting blood pressure, with this effect being abolished by icatibant. Kallikrein also resulted in renal protection in normotensive rats with gentomycin-induced nephrotoxicity, although the effect of icatibant was not studied. Therefore, it is possible that icatibant would be detrimental to patients with renal disease in the same way as it is expected to be detrimental to patients with cardiovascular disease.

Pharmacokinetics

Absorption of icatibant was rapid after SC 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. There were no marked differences in pharmacokinetic parameters in animals, but in humans there were notable differences between males and females, young and old. Plasma protein binding was moderate (38-49%) with only small species differences. Organ distribution studies were conducted in the rat with whole body autoradiography showing that the highest concentrations of radioactivity were found at the injection site and in the organs involved in excretion (kidney, liver, urinary bladder and the contents of the gastro-intestinal tract). Radioactivity was also present in lymph nodes (intestinal, bronchial, axillary and inguinal), epiphyseal cartilage, red pulp of the spleen, bone marrow, skin, vascular walls, connective tissue structures, the pancreas, epididymides, vesicular glands and adrenal glands. In the brain, radioactivity was limited to the ventral part

[16] Xia C, Yin H, Borlongan CV, Chao L and J Chao (2004). Kallikrein gene transfer protrects against ischaemic stroke by promoting glial cell migration and inhibiting apoptosis. *Hypertension* 43: 452-459

of the pituitary and the great cerebral vein. Radioactivity was generally absent from adipose tissue.

Unlike BK, icatibant is stable in the presence of ACE and neutral endopeptidase. Metabolism of icatibant in all species investigated (including humans) involved cleavage of the decapeptide icatibant to two smaller peptides: icatibant (1-5) or M1, and icatibant (7-10) or M2 by an unidentified peptidase. Interestingly, icatibant (1-6), which is formed during storage, was not detected in any species. Hence, amino acid number 6 (Thi) must be released either in the cleavage step or immediately thereafter. Liver cytochrome P-450 enzymes do not appear to be involved in the metabolism of icatibant. M1 and M2 have very low affinity for the B2 receptor, so the toxicities observed are considered to be due to icatibant itself, and not the metabolites.

Icatibant was mostly excreted in the urine, with the only species difference between the mouse, rat and dog being the proportion of intact icatibant excreted. This was highest in the mouse and lowest in the rat. Like the rat, humans excrete only a small proportion of intact icatibant in the urine.

Relative Exposure

Animal: human exposure ratios have been calculated using clinical data from JE049-1103. In this study young (19-36 year old) and old (66-88 year old) men and women were studied. The pharmacokinetic values differed depending on age and sex. Therefore, the appropriate age and sex have been used depending on the toxicity being discussed. For example, for reproductive toxicities the values in young people were used, with the male results for male reproductive toxicity and female values for female reproductive toxicity. The clinical AUC values used for someone who received 90 mg total in three doses on one day were taken to be three times the AUC value obtained after the first dose on Day 1 (1.20, 2.92, 2.71 and 4.76 μg.h/mL in young men, old men, young women and old women respectively).

With the exception of three dog studies, dosing was daily in animals, whereas dosing in humans is expected to be intermittent. Exposure margins have been calculated by comparing the maximum human exposure in a day to the daily exposure in animals (Table 1). Hence, the calculated exposure ratios do not take into account the difference between an intermittent clinical dosing regimen and the daily dosing of animals. These exposure margins are therefore worst case estimates, and would be greater if weekly exposure was considered.

Table 1. Animal: human exposure ratios of icatibant.

Species	Study type	Dose (mg/kg/day)	Dose (mg/kg/day twice weekly)	$AUC_{0\text{-}24\ h}$ (mg.h/mL)	Exposure ratio♣	Age & sex of human♦	Study no. (JE049-)
Mouse	13 week SC repeat dose toxicity	10, 25, 50, 100	-	12, 43, 72, 121	0.9, 3, 5, 8	Old female	0159
Rat	13 week SC repeat dose toxicity	10, 20, 30	-	25, 44, 67	1.8, 3, 5	Old female	0160
	26 week SC repeat dose toxicity	3, 10, 30	-	6.2, 22, 58	0.4, 1.5, 4	Old female	0163
	Fertility & 13 week toxicity SC	1, 3, 10	-	1.5, 5.3, 17	0.4, 1.5, 5 0.2, 0.7, 2.1	Young male Young female	0108
	Embryofetal development SC	0.21, 2.1, 21	-	0.34, 3.4, 44	0.04, 0.4, 5	Young female	0139
	Pre/post natal development SC	1, 3, 10	-	1.6, 5.7, 21	0.2, 0.7, 2.6	Young female	0141
Rabbit	Embryofetal development	0.08, 0.83, 8.3	-	0.36, 3.6, 43	0.04, 0.4, 5	Young female	0140
Dog	4 week repeat dose toxicity SC	-	3, 9.9	18/11 (M/F), 44	1.4, 5	Young female	0116
	13 week repeat dose toxicity SC	10, 30, 60, 100	-	35, 87, 230, 383	2.5, 6, 16, 27	Old female	0117
	13 week repeat dose toxicity SC	3, 10	9.9	14, 57 49♥	1.0, 4 3	Old female	0118
	39 week repeat dose toxicity SC	1, 10	3	2.8, 43 9.6	0.2, 3 0.7	Old female	0164

♣: animal: human exposure ratio for a 90 mg/day dose in humans; ♦: Because different human AUC values were obtained for the young and old, males and females, different adults were used in different contexts. Young males and young females were used for male and female fertility respectively, whereas old females were used for general toxicity effects as they had the highest AUC values. ♥: AUC value on Day 1: The AUC value was too low to calculate in Week 13.

Toxicology

Chronic toxicity studies in mice, rats and dogs using the SC route have been submitted to the TGA. Most of these studies were not submitted to the EMEA, and the lack of such studies was of concern to the EMEA because the frequency and severity of HAE episodes are highly variable. Attacks generally last for 2-5 days, and occur from 1-100 times per year. 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 could rapidly approach a chronic, albeit intermittent, therapy.

High single doses in mice and rats when given as an IV bolus produced dramatic symptoms with death following rapidly. It is likely that these were exaggerated pharmacological effects, with BK agonist activity leading to circulation collapse. Histamine release, a known effect of BK, may have contributed to the symptoms. No deaths and much milder clinical signs occurred in rats and dogs when icatibant was administered as an IV infusion or SC, despite

higher total doses. BK agonist activity is the likely explanation for the observed erythema and swelling and local reactions at the injection sites.

Apart from injection site reactions, many of the major toxicities observed in the SC repeat dose toxicity studies involved the male and female reproductive organs. These have been discussed in separate sections below. Other toxicities observed included hypertrophy of the adrenal glands and atrophy of the thymus. Renal toxicity was a concern to the EMEA nonclinical evaluators, but was not related to icatibant treatment in the long-term SC studies submitted.

Atrophy of the thymus and/or thymus lymphoid depletion were observed at high doses in mice and dogs (≥50 mg/kg/day in male mice and 30 mg/kg/day in male dogs) and at lower doses in rats (3 mg/kg/day, AUC = 6.22 mg.h/mL). White blood cells were also decreased in some of the rat studies, and at 100 mg/kg/day in mice. An increase in urine volume and decrease in urine specific gravity was observed in rats and dogs, and hypertrophy of the adrenal glands occurred at 3 mg/kg/day in rats, 50 mg/kg/day in mice and 60 mg/kg/day in dogs. Increased body weight gain (BWG) was observed at ≥25 mg/kg/day in mice and at 10 mg/kg/day in dogs, but BWG was decreased in male rats at ≥3 mg/kg/day. At 10 mg/kg/day the heart rate in dogs was significantly lower than controls.

A no observed effect level (NOEL) for these effects (excluding reproductive toxicity and hormone levels) was 10 mg/kg/day in mice and 3 mg/kg/day in dogs, correspond to exposure ratios for elderly women of 0.9 and 1.0 respectively. No NOEL was established in rats because adrenal gland hypertrophy and thymic lymphocyte depletion in both sexes, and reduced BWG in males occurred at 3 mg/kg/day, which is the lowest dose tested in studies of sufficient duration (exposure ratio for elderly women of 0.4).

Although the distribution of the B2 receptor and the functions of BK are incompletely understood, the majority of the observed toxicities are likely to be pharmacological. With such low exposure ratios, it is clear that these toxicities need to be taken into account in the risk: benefit analysis. However, these exposure margins have been calculated by comparing the maximum human exposure in a day to the daily exposure in animals. As nonclinical studies mostly consisted of daily dosing, whereas human dosing is intermittent, these calculations result in lower estimates of the exposure ratios than if weekly exposure was considered. Intermittent dosing was used in some of the dog studies, and a NOEL for all effects, including reproductive effects, was established as 1 mg/kg three times a day (tds) twice weekly (exposure ratio 1.2 for young women, 2.7 for young men).

Male reproductive organ toxicities observed in repeat dose toxicity studies

Standard repeat dose toxicity studies use sexually immature animals at the beginning of the study. This was the case for the long-term repeat dose toxicity studies submitted to the EMEA. In these studies the male and female reproductive organs failed to develop in icatibant-treated rats and dogs. The sponsor suggested that this was a result of delayed puberty. Thus, in the recently conducted repeat-dose toxicity studies with mice, rats and dogs, the sponsor used older animals, testing the female dogs to ensure that they were sexually mature before study commencement. Hence, these recent studies were able to address whether the effects on the reproductive system observed in younger animals were a result of delayed puberty, or whether icatibant has a detrimental effect on the reproductive organs of animals.

There were marked effects on the male reproductive organs in sexually mature Wistar rats at ≥3 mg/kg/day (the lowest dose tested; the area under the concentration-time curve (AUC) = 6 mg.h/mL). The weight of the prostate and testes/epididymides decreased at ≥3 mg/kg/day and

there was epithelial degeneration of the testes, dystrophic tubular mineralisation in the testes and decreased secretion in the prostate and seminal vesicles. Bilateral hypospermia in the epididymides was observed at 10 mg/kg/day (AUC = 25 mg.h/mL) in the 13 week study, but at only 30 mg/kg/day (AUC = 57 mg.h/mL) in the 26 week study. At 30 mg/kg/day there was intratubule degeneration of spermatazoa/spermatids in the epididymides and spermatid retention in the testes. After a 4 week recovery period in the 26 week rat study, the prostate gland and seminal vesicles had recovered, but germinal epithelial degeneration and dystrophic tubular mineralisation of the testes was still present.

In dogs, the prostate weight was decreased at 3.3 mg/kg tds twice weekly after 13 weeks in immature dogs, and after 1 mg/kg/day or 1 mg/kg tds twice weekly for 39 weeks in mature dogs. The testes, epididymides and prostate had low weights after 10 mg/kg/day for 39 weeks in mature dogs and were still immature at≥3 mg/kg/day after 13 weeks in immature dogs. There were very low numbers of sperm, all of which were immotile in the 10 mg/kg/day dogs (AUC = 42 mg.h/mL), and low numbers of sperm with low motility and velocity in the 1 mg/kg/day dogs. However, the sperm properties in the 1 mg/kg tds twice weekly dogs were unaffected by treatment. Although the prostate weight was slightly lower in 1 mg/kg tds twice weekly group, it is unclear whether this observation was related to treatment, and the NOEL for effects on the male reproductive system in dogs is considered to be 1 mg/kg tds twice weekly ($AUC_{0\text{-}24\ h}$ = 9.6 mg.h/mL). No NOEL was established for daily dosing; the lowest observed effect level (LOEL) was 1 mg/kg/day (AUC = 2.8 mg.h/mL).

The sponsor has proposed that the effect on the sexual organs is secondary to gonadotrophin levels. The sponsor measured follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels in rats and dogs. There were probably treatment-related decreases in FSH levels in male rats and dogs, but there was no clear effect of icatibant on LH in male rats or dogs. However, there was a dramatic decrease in testosterone levels in both rats and dogs at ≥3 mg/kg/day. A NOEL was established in dogs as 1 mg/kg/day (AUC 2.8 mg.h/mL). The effects of twice weekly dosing in dogs of 1 mg/kg tds and 3 mg/kg tds were each investigated in two studies. Marked decreases in testosterone levels were observed in both studies at 3 mg/kg tds twice weekly, but only in one study (the 4-week study but not the 39-week study) at 1 mg/kg tds twice weekly. A possible explanation for the difference in effect between the two 1 mg/kg tds studies is that in the 4-week study, in which an effect was observed, the icatibant AUC was higher (18 compared with 9.6 mg.h/mL). The drop in testosterone levels may have been a result of decreased gonadotrophin and gonadotrophin releasing hormone, but the evidence for this is weak. The low testosterone levels could equally be due to the direct interaction of icatibant with the B2 receptor in the testes.

The sponsor has addressed the clinical relevance of the effects on the male reproductive system observed in nonclinical studies. In clinical trial JE049 #1103, FSH and LH were measured, but no relevant changes were observed. However, the effect of icatibant on these hormones was also difficult to discern in the nonclinical studies. In contrast, the effect of icatibant on testosterone levels was marked in the nonclinical studies, including in an intermittent regimen (3.3 mg/kg tds twice weekly in dogs). Testosterone levels do not appear to have been measured in the clinical studies. It is therefore considered possible that testosterone levels are lowered temporarily in men receiving icatibant.

Female reproductive organ toxicities observed in repeat dose toxicity studies

The epithelium of the cervix and vagina degenerated and was mucinous in mice, with a NOEL of 10 mg/kg/day (AUC = 12 mg.h/mL). Mucification of the vagina also occurred in rats at ≥3 mg/kg/day. The mammary gland in rats became mascularised at≥3 mg/kg/day,

whereas in dogs the mammary glands atrophied at 10 mg/kg/day. All female reproductive organs in the rat recovered after a 4 week treatment-free period.

There was muscle loss of the uterine wall in mice, with a NOEL of 25 mg/kg/day (AUC = 43 mg.h/mL), and the uterus atrophied in rats at ≥10 mg/kg/day (AUC = 21.6 mg.h/mL). The ovaries in rats increased in weight at≥3 mg/kg/day, with this increase being accounted for by an increased number of corpora lutea. In dogs at ≥1 mg/kg/day, but not at 1 mg/kg tds twice weekly, the ovarian and uterus weights were decreased by 39 weeks of treatment in mature dogs. In immature dogs the ovaries did not mature at the lowest doses tested: 3 mg/kg/day and 3.3 mg/kg tds twice weekly. In mature dogs in the 1 mg/kg tds twice weekly group and the controls there was a good correlation between ovarian morphology and uterus and mammary gland morphology, but this correlation did not exist for the 3.3 mg/kg tds twice weekly group.

FSH levels were lowered at≥1 mg/kg tds twice weekly in mature dogs (AUC = 10.9 mg.h/mL), but only at a higher dose (10 mg/kg/day) in a second study.

There were no clear effects in dogs on LH, oestradiol or progesterone. However, in rats luteinising hormone levels were lower at≥3 mg/kg/day (AUC = 6.2 mg.h/mL), but FSH levels did not appear to have been affected. Thus icatibant may have had an indirect hormonal effect as well as a direct effect on the female reproductive organs.

Carcinogenicity and genotoxicity

There do not appear to be any genotoxicity concerns. No carcinogenicity study was submitted. This is acceptable, given the proposed duration of treatment and proposed indication. However, the sponsor stated that the 13 week mouse repeat dose toxicity study was a preliminary study for a carcinogenicity study requested by the FDA. A rat carcinogenicity study has also been initiated. It is recommended that a condition of registration should be that the reports of any carcinogenicity studies should be submitted upon completion to the TGA.

Male reproductive toxicity

In mice, the male reproductive organs did not appear to be markedly affected by icatibant SC. At 100 mg/kg/day icatibant SC (AUC =121 mg.h/mL) there was a slight decrease in prostate weight, but at 80 mg/kg/day SC and 30 mg/kg/day IV there were no effects on male fertility. B2 (-/-) knockout mice have no fertility issues.

In dogs icatibant had a marked effect on testosterone levels and sperm numbers, motility and velocity (see above). These effects would clearly have resulted in infertility, or at lower doses, reduced fertility, although this was not investigated in a formal fertility study.

In rats there are conflicting data. The results of the 13-week combined male fertility and toxicity study using SD rats indicated that icatibant had no effect on the male fertility of rats at 10 mg/kg/day; there was no effect on epididymal sperm number, motility or morphology, and no effect on the weight of male reproductive organs. However, in repeat dose toxicity studies that used Wistar rats, icatibant reduced the weights of male reproductive organs, markedly decreased testosterone levels at≥3 mg/kg/day, and resulted in bilateral hypospermia at 10 mg/kg/day in one study and 30 mg/kg/day in the other study. It is possible that the different strains of rat reacted to icatibant in different ways. It is unusual to have such conflicting results from GLP-compliant studies.

In conclusion, B2 receptors do not appear to be involved in male fertility in mice, but icatibant clearly reduced male fertility in dogs. The effect of icatibant on male fertility in the

rat is unclear. It is possible that there are strain-specific differences in the effect of icatibant on male fertility in the rat.

Female reproductive toxicity

BK B2 receptors have been shown to be present in the ovaries of mice and the uterus of rats, guinea-pigs, pigs, sheep and humans. There is evidence in rats and pigs that BK is involved in the implantation process.

When treated male SD rats were mated with females treated with 10 mg/kg/day icatibant SC there was an increase in preimplantation loss (control 6: 10 mg/kg/day 16%: $p<0.001$) that was not observed when the males were mated with untreated females. In rabbits there was an increase in post-implantation loss at ≥8.3 mg/kg/day icatibant SC (AUC ≈ 43 mg.h/mL). These effects are likely to have been a result of the effect of icatibant on implantation into the uterus.

When radioactive icatibant was administered to pregnant rats, radioactivity crossed the placenta. However, in the rat embryofetal development study there was no effect on embryofetal development or pre-or post-implantation loss at up to 21 mg/kg/day (AUC = 44 mg.h/mL). Apart from the above-mentioned post-implantation losses, there was no effect of icatibant on the embryofetal development of rabbits at doses up to 8.3 mg/kg/day SC.

Icatibant had a clear tocolytic effect in the rat pre- and post-natal development study; there was a tocolytic effect at 10 mg/kg/day SC (AUC = 21 mg.h/mL) and an increase in gestation duration at ≥1 mg/kg/day (AUC = 1.6 mg.h/mL). Consistent with this, in an earlier combined rat embryofetal and post-natal development study, the duration of gestation was increased. Dosing in this study stopped at gestation day (GD) 18, whereas dosing in the pre- and postnatal development study stopped on GD 19 or later, explaining why parturition was uneventful in the earlier study.

Apart from the adverse effect of delayed parturition and an adverse effect on early nursing, there were no detrimental effects of icatibant treatment on pup development. BK is involved in the closure of the ductus arteriosis at birth, and it is unclear whether interference in this process by icatibant would have been observed in these studies.

Icatibant was excreted in rat milk as well as crossing the placenta. Some differences that are not considered adverse in pup development may have been treatment-related. Pups in 5/9 10 mg/kg/day litters opened their eyes early; 10 mg/kg/day male pups had increased motor activity compared to controls; and the 10 mg/kg/day group performed slightly better in the water maze (testing learning and memory). Although the study authors and sponsor did not regard these observations as significant, statistics were only conducted to assess whether detrimental differences were significant. B2 receptors have been observed in the hippocampus and cortex of rat and guinea-pig brains, regions involved in learning and memory, and in regions of the sheep brain involved in motor activity. Which cell types in the brain contain the B2 receptor, and the exact role(s) that BK plays in the brain are unknown. However, icatibant has been shown to affect performance in the water maze in another experiment; a greatly improved performance in the water maze was observed in mice treated with both the beta amyloid peptide (Ab_{1-40}) and icatibant (both given intracerebroventriclularly, ICV) compared to the Ab_{1-40} peptide alone[17]. Thus it is possible

[17] Prediger RD, Medeiros R, Pandolfo P, Duarte FS, Passos GF, Pesquero JB, Campos MM, Calixto JB and RH Takahashi (2008) *Neuroscience* 151:631-643. "Genetic deletion or antagonism of kinin B(1) and B(2) receptors improves cognitive deficits in a mouse model of Alzheimer's disease."

that the observed differences between the high dose icatibant group and the control group in pup development were treatment-related. Although the observed effects were not adverse, it is still a concern that icatibant might be interfering with the brain function of rat pups.

In conclusion, icatibant increased pre-implantation loss in rats and post-implantation loss in rabbits, and had a tocolytic effect in rats. Icatibant may have affected pup development in the postnatal rat study, but this was not adverse. The possibility that icatibant interfered with the closure of the ductus arteriosis was not specifically investigated.

Antigenicity

By conjugating icatibant to thyroglobulin and using an adjuvant, antibodies were generated in the rabbit, whereas a sustained immune response was not generated in rats, dogs or monkeys. In this context, the toxicokinetics in dogs receiving intermittent dosing regimens is of interest. After receiving 3.3 mg/kg tds twice weekly for 13 weeks, icatibant levels in dogs were considerably lower after 13 weeks, with the AUC unable to be calculated and the maximum plasma concentration (C_{max}) 0.4-fold that on Day 1. Perhaps this decrease in icatibant levels was a result of antibody generation in response to the higher dose intermittent regimen.

Local tolerance

Icatibant was well tolerated in the rabbit when administered by the intra-arterial, paravenous, IV or SC routes, or when placed onto intact or abraded skin or in the eye. However, in rats, dogs and man injection site reactions occurred. At high concentrations of icatibant (50-100 mM) there was an induction of the release of histamine, tryptase, leukotriene C4 and prostaglandin D2 from isolated human mast cells. Icatibant can also stimulate the release of calcitonin gene related peptide (CGRP) from mouse skin, as could a scrambled icatibant (a nonapeptide composed of identical amino acids to icatibant, but in a different order).

Use in children

Icatibant is contraindicated in children, which is considered appropriate. Studies in sexually immature animals have shown that icatibant delays puberty, and in adult male animals markedly decreases testosterone levels. The implications of these studies would need to be carefully considered before icatibant could be indicated for children.

Nonclinical Summary and Conclusions

- Icatibant was effective in most disease models where BK was an essential component of the pathogenesis. In studies published in the literature, C1 inhibitor deficient mice had increased vascular permeability, and this was returned to wildtype levels when treated with icatibant IV. Thus, the nonclinical pharmacodynamic data are consistent with the proposed clinical use.

- Physiologically, BK causes vasodilation, inflammation, stimulation of sensory and sympathetic nervous connections, smooth muscle contraction of the bronchopulmonary tree, intestine and uterus, and increased sperm motility, as well as the increased vascular permeability that leads to the angioedema observed in patients with C1 inhibitor deficiency. The B2 receptor is expressed by vascular cells (such as endothelial and smooth muscle cells), nonvascular smooth muscle (for example uterine) cells, nerve cells (afferent sensory), leukocytes and various tumour cells. Icatibant binds to the B2 receptor in all species tested, including mice, rats, guinea-pigs, dogs, pigs, sheep and humans.

- There is nonclinical evidence that BK signalling via the B2 receptor is involved in IL-12 production and the innate and adaptive immune responses to both bacteria and parasites. Icatibant is likely to increase susceptibility to bacterial and parasitic infections, but this has not been investigated by the sponsor.

- A cardioprotective effect of BK has been demonstrated in the mouse, rat, rabbit and dog, with an attenuation of this effect by icatibant observed in mice, rats and dogs, and by another B2 receptor antagonist in rabbits. The nonclinical studies indicate that icatibant, at concentrations that are effective at antagonising the B2 receptor, attenuate the cardioprotective effect of BK. Therefore, therapeutic levels of icatibant in humans are expected to attenuate the cardioprotective effect of BK.

- Kallikrein has some renal protective properties in animal models of renal disease, and icatibant attenuated these protective properties.

- The efficacy of ACE inhibitors and AT1-receptor antagonists is partially due to increased levels of BK. Icatibant is therefore likely to reduce the efficacy of ACE inhibitors and AT1 receptor antagonists.

- Absorption after SC administration was rapid and icatibant was mainly distributed to the kidney, bladder and liver. Little or no icatibant was distributed to adipose tissue or the central nervous system. Icatibant was slowly metabolised to two peptides (icatibant(1-5) and icatibant(7-10)) in all species examined, including humans, with the metabolites and intact icatibant excreted in the urine. Icatibant is not metabolised by P450 enzymes.

- Repeat dose toxicity studies showed that the target organs of icatibant are the reproductive organs, adrenal glands and thymus. Icatibant did not elicit renal toxicity in the majority of nonclinical studies conducted.

- Icatibant resulted in atrophy of the thymus and hypertrophy of the adrenal glands at high doses in mice and dogs and lower doses in rats in repeat dose toxicity studies. No NOEL for these toxicities was established in rats (LOEL had an exposure ratio of 0.4). In mice and dogs, NOELs for these toxicities had exposure ratios of 0.9 and 1.0.
- Exposure margins have been calculated by comparing the maximum human exposure in a day to the animal exposure in a day. However, in most of the animal studies dosing was daily, whereas in the clinical situation dosing is unlikely to be on more than two days per week. Hence, comparison of weekly exposure would result in larger exposure ratios for the rodent studies and the dog studies in which daily dosing occurred.
- Repeat dose toxicity studies in sexually mature rats and dogs, as well as studies in sexually immature rats and dogs, showed that icatibant resulted in decreased testosterone levels (at exposure ratios of 3 and 5 respectively), small male reproductive organs (prostate, testes and epididymides) and low sperm counts. A NOEL of 1 mg/kg/day in rats and 1 mg/kg tds twice weekly in dogs was established for effects on the male reproductive system. Icatibant may have a similar effect on testosterone in men.
- Repeat dose toxicity studies in sexually mature mice, rats and dogs showed that icatibant reversibly affected the female reproductive organs, with changes to the epithelial mucus, changes to the size of the uterus and ovaries, masculinisation of the mammary glands and changes to plasma levels of FSH (dogs) or LH (rats). In icatibant-treated sexually immature animals the female reproductive organs did not mature.

- Studies in sexually immature animals have shown that icatibant delays puberty in both sexes. The implications of these studies would need to be carefully assessed before icatibant is considered for use in children.

- Icatibant increased pre-implantation loss in rats and post-implantation loss in rabbits, but was not teratogenic in rats or rabbits. Icatibant had a tocolytic effect in rats. The effects on implantation and parturition are consistent with antagonism of BK, and the location of B2 receptors in the uterus of many species.

- There were no adverse effects of icatibant on pup development. However, there were some observations in the high dose pups (early eye opening, increased motor activity, and better performance in the water maze) that may have been a result of icatibant treatment.

- Icatibant was found not to be genotoxic in adequate studies. The carcinogenicity studies currently being conducted should be submitted to the TGA once completed.

- It is brought to the attention of the clinical delegate that nonclinical data indicate that icatibant is likely to attenuate protection by BK in cardiovascular ischaemic events, and may also attenuate renal protection in patients with renal disease.
- Limited nonclinical data indicate that icatibant may have the potential to increase susceptibility to bacterial and parasitic infections.
- In many cases the potential risks posed by adverse effects identified in the nonclinical studies will depend on the frequency and duration of clinical use.
- Given the severity of the proposed indication, there are no nonclinical objections to the registration of icatibant for the treatment of adults with hereditary angioedema.

IV. Clinical Findings

Introduction

The submission to the TGA to register Firazyr (icatibant acetate) solution for injection was prepared based on the European submission. There are a number of updates to the European submission, either due to questions/requests for additional data raised during the European centralised assessment procedure or at the sponsor's discretion following approval. The following six documents are in addition to the European submission:

1. JE049-5121: Additional Efficacy Analyses for Studies JE049 #2102 and JE049 #2103
2. JE049-5113-B: Addendum to the Integrated Safety Summary
3. JE049-5115: Evaluation of Market Research Reports in Hereditary Angioedema to Support Patient-Reported Outcome (PRO) Submission Package
4. JE049-5125: Assessment of Signs and Symptoms of Hereditary Angioedema: Patient-Reported Outcome (PRO) Briefing Document
5. JE049-4104-B: Hereditary Angioedema Patient Interviews to Support PRO Submission Package
6. JE049-5126: Roadmap to Assessment of Signs and Symptoms of Hereditary Angioedema: Patient-Reported Outcome (PRO)

Four of the six reports, JE049-5115, 5125, 5126, and 4104-B, contain information from non interventional investigations relating to further validation of the Visual Analogue Scale (VAS). These reports became available after the EU approval.

Pharmacokinetics

CHMP evaluation

Icatibant pharmacokinetic (PK) studies submitted to the European Union (EU) have been evaluated by the Committee for Medicinal Products for Human Use (CHMP). The IV and SC formulation of icatibant was extensively studied in healthy volunteers and in patients. The PK profile of icatibant in patients with HAE is similar to that in healthy volunteers, and is summarised below.

Absorption

After SC administration of icatibant, absorption is rapid with maximum concentrations reached after about 30 min. The absolute bioavailability after SC 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. Both metabolites are principally excreted unchanged in urine. A small part of the dose < 10 % is excreted in urine unchanged. Icatibant clearance is about 15-20 L / hour. The terminal half-life ($t_{1/2}$) is about 1-2 hours.

PK in special populations

The PK data in special populations are limited. The available data suggest no significant influence of hepatic impairment or renal impairment on the PK of icatibant.

Study 1103 evaluated the effects of age and gender on icatibant PK, and it showed that 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.

Dose proportionality and time dependencies

Dose proportionality has been studied in the dose range 0.005 to 3.2 mg/kg. Clearance (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 PK.

AUC of metabolites M1 and M2 are similar and are also in the same range as icatibant. AUC and C_{max} of M1 and M2 seem to be dose proportional. The $t_{1/2}$s of M1 and M2 are similar to that of icatibant suggesting that M1 and M2 display formation rate limited elimination.

Drug Interactions

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

Pharmacodynamics

CHMP evaluation

Mechanism of action

Icatibant is a potent and highly selective antagonist of the B2R 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 pharmacodynamic (PD) action of BK. Thus, icatibant represents a reasonable therapeutic approach.

PK-PD relationship

Exploration of PK-PD relationships was conducted using the inhibitory profile of icatibant following a 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, tachycardia, and cutaneous vasodilatation. Similar 50% effective doses (ED_{50}) were obtained for the PD parameters, with the majority of values being between 8.54 and 9.77 µg/L. Thus, a mean ED_{50} value of 9.5 µg/L (7.3 nM) was used in PK-PD simulation of the response to different IV doses. Based on this simulation, the IV doses 0.4 mg/kg and 0.8 mg/kg were selected for Phase II study. The same data have also been evaluated using a population PK/PD model resulting in slightly higher ED_{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 SC administration in Study 1102 were used to estimate the duration of icatibant effects for SC doses of 15, 30 and 60 mg. It was concluded that the 30 mg dose would be optimal, and this dose was used 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 for example, 60 mg for all patients.

In the clinical trial program for HAE doses up to 0.4 mg/kg IV were given as single dose and SC doses of 30 mg- 45 mg up to three times/day with 6 hours in between the doses. The proposed dose of 30 mg SC given up to 3 times daily seems acceptable.

Potential pharmacodynamic drug interaction

Inhibition of degradation of BK by ACE inhibitors, leading to an increased BK 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. Subjects taking ACE inhibitors were excluded from clinical trials with icatibant.

Clinical Evaluator's comments on PK and PD

The evaluator agrees with the CHMP's conclusion with regard to the PK and PD analyses: icatibant PK are uncomplicated with metabolism by proteolytic enzymes. The limited PK data is considered sufficient given the use of this product. The rationale for development of icatibant as a drug for treatment of acute attacks of HAE and its mechanism of action has been reasonably described.

Efficacy

CHMP evaluation report stated:

On 11 July 2008, Firazyr (icatibant) received marketing authorisation from the European Commission based on a positive CHMP opinion for the indication of symptomatic treatment of acute attacks of HAE in adults. The complete CHMP assessment documents were provided and have been summarised below.

The evaluation of efficacy was based on one Phase II study and two Phase III studies:

• JE049-2101: This was 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 SC injection of 30 or 45 mg icatibant. In this study, 30 mg SC dose showed at least a similar effect to the higher SC dose, and 30 mg was selected as the recommended dose and was used in the two Phase III studies.

• JE049-2102 (FAST-2): This was a double-blind, controlled Phase III study. A single dose of icatibant 30 mg SC injection was compared to tranexamic acid (TA) in 77 patients. Double-blinded phase was followed by an open-label extension, which had an option of giving 3 x 30 mg SC icatibant injections per attack according to response.

• JE049-2103 (FAST-1): This was a double-blind, controlled Phase III study. A single dose of icatibant 30 mg SC injection was compared to placebo in 64 patients. Double-blinded phase was followed by an open-label extension, which had an option of giving 3 x 30 mg SC icatibant injections per attack according to response.

The open-label part of the studies up to the data cut-off point of 31 March 2007 (30 May 2007 for adverse event data) was 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.

The two Phase III studies were similar in design. A total of 130 patients were randomised to receive either a 30 mg dose of icatibant (n = 63) or comparator (either tranexamic acid, n=38, or placebo n = 29 patients). Subsequent episodes of HAE were treated in an open label extension. Patients with symptoms of laryngeal angioedema received open label treatment with icatibant.

For both Phase III studies, the primary endpoint was time to onset of symptom relief of the first attack using VAS. VAS was used to measure the intensity of each symptom of the attack for cutaneous swelling, cutaneous pain, and abdominal pain. The VAS of 0 mm corresponded to no symptoms while 100 mm in VAS corresponded to the worst possible symptom.

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.

The patient diary includes four 100mm VASs that assess "Skin swelling," "Skin pain," "Abdominal pain" and "Nausea.

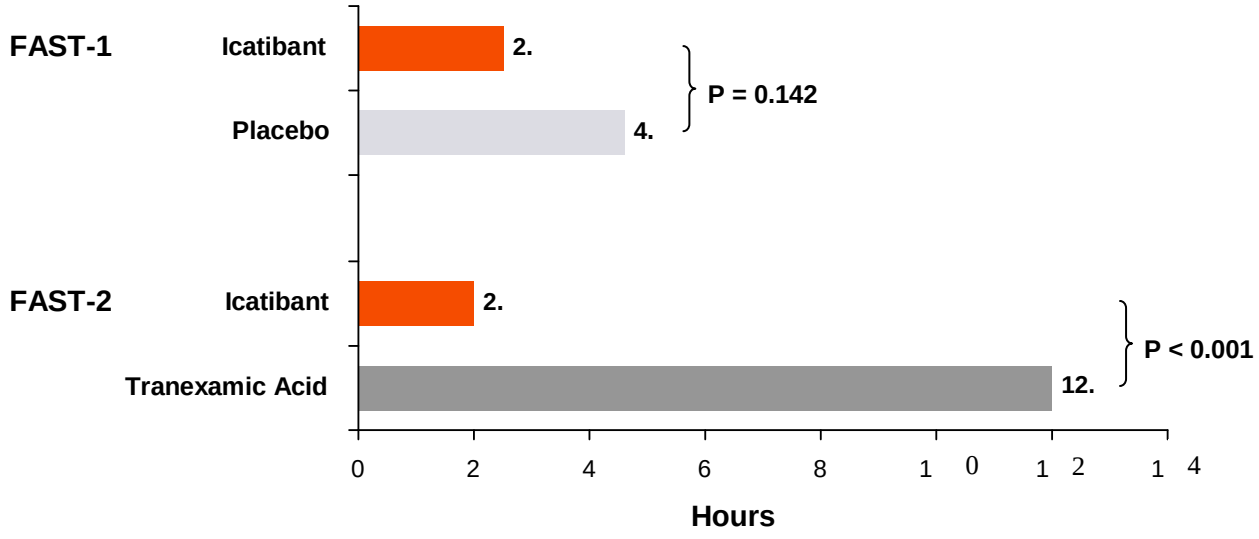
Secondary endpoints used in the studies included:

- Response rate at 4 hours after start of treatment.
- Time to relief of each symptom present in pre-dose VAS other than the primary symptom (defined as abdominal pain in study #2102; see Table 2).
- Time to almost complete symptom relief.
- Symptom score using the 5-Point Symptom Score Scale.
- Global assessment performed by the study investigator.
- Clinical global impression of improvement by the investigator.
- Regression of symptoms (start of improvement) according to patient.
- Observable regression of visual symptoms according to study investigator.
- Overall patient improvement according to study investigator.
- Patient satisfaction questionnaire.

Efficacy results in the controlled Phase

Efficacy results from both main studies are shown in Figure 2 and Table 2 and below.

Figure 2: Median time to onset of symptom relief using VAS (ITT Population)



ITT=Intent to treat population

JE049 #2102 (FAST-2): the time to onset of symptom relief (primary endpoint) was significantly shorter in the icatibant group than in the tranexamic acid group (Table 2). This was also true for the secondary analyses of the subgroups (cutaneous or 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.

JE049 #2103 (FAST-1): the time to onset of relief (primary endpoint) was shorter with icatibant but a statistically difference as compared to the placebo was not achieved for the primary endpoint (Figure 2). However, a rather strong trend consistent with the results of

JE049-2102 was seen and beneficial effects were demonstrated in a number of secondary endpoints (Table 2). There were more patients receiving rescue within 12 hours in the placebo group (11 patients) than in the icatibant group (3 patients).

Table 2: 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

Overall, the difference on all the primary and key secondary efficacy endpoints was statistically significant in the tranexamic acid comparison study (JE049 #2102), however, the placebo comparison study (JE049 #2103) failed to detect any statistically significant

difference for the primary efficacy endpoint. In a number of secondary endpoints, icatibant was shown to be superior to both tranexamic acid and placebo.

Efficacy results in the open-label Phase

Additional efficacy data were provided in the response document with the cut-off date of September 2007. The additional data described 118 patients who were treated with icatibant for a total of 597 HAE attacks treated in the open-label Phase. Of these 118 patients, 93 were initially randomised to the controlled phase (46 to icatibant, 21 to TA, and 26 to placebo); 5 patients with laryngeal symptoms at baseline were treated with icatibant in the controlled phase and then entered the open-label phase, and 20 patients, who had not received any treatment in the controlled phase, were treated solely in the open-label phase. A number of patients were screened initially but were never treated (or example, never presented with eligible attack during the study period). The majority of the 597 treated attacks (537, 89.9%) needed only one icatibant injection (Table 3), and very few required rescue medication. Within these treated attacks, there are no signs of exacerbation of severe symptoms.

Table 3. Number of attacks treated with 1-3 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 (59) of 597 attacks (9.9 %) became worse after the initial treatment with icatibant:

- 30 of them (50.8 %) were treated with icatibant only,
- 7 (11.9 %) were treated with both icatibant and rescue medication,
- 11 (18.6 %) were treated only with rescue medication,
- 11 (18.6 %) attacks that worsened 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, one was treated with icatibant, and one required no additional treatment. Seven of 597 attacks (1.2%) were treated with additional medication due to persistent initial symptoms. Ten of 597 attacks were treated with additional medication due to investigator judgement without reappearance of symptoms or appearance of new symptoms as well as long persisting initial symptoms.

During the open label Phase, a total of 61 HAE attacks with laryngeal involvement were treated with icatibant injection. These patients had experienced, from 2 up to 44 HAE attacks (with different locations of symptoms) during the 6 months before study entry. These pre-study attacks had durations of 1-4 days. The 61 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. The "hours at hospital" was registered in 22/61 attacks,

and the observation time at hospital was no longer than 15 hours, often much shorter. These results provided some reassuring experience, and the quick regression of symptoms in these attacks following icatibant injection indicates sufficient treatment effect with icatibant.

Overall, these additional data from the open label phase provided supporting evidence with regard to the efficacy of icatibant in treating both general attacks and laryngeal attacks of HAE.

Efficacy concerns and further analyses required by CHMP

Concerns with regard to the efficacy were raised by the CHMP, as the placebo comparison study (JE049 #2103) failed to detect any statistically significant difference for the primary efficacy endpoint. In order to fully evaluate the evidence of efficacy, the CHMP requested the following additional analyses for the two studies:

- To reassess the primary analysis, time to onset of symptom relief, by adjusting for the factors used in the minimization approach (centre and type of attack).
- To perform a responder sensitivity analysis, this was to prove that the definition of 'responder' does not influence the outcome 'time to relief' in the Phase III studies;
- To analyse the change from baseline to 4 and 12 hours in the VAS scale-this was to fully evaluate the evidence of efficacy rather than summarize the data in terms of responders or time to onset of symptom relief.

These additional analyses were summarised in JE049-5121.

Additional efficacy analysis required by CHMP

JE049-5121 is a document that summarised the results of the additional efficacy analyses. Although JE049-5121 was not specifically submitted to the EMEA, the additional efficacy analyses contained in JE049-5121 were submitted to the EMEA. For all the responses, the relevant issues were considered resolved by the CHMP.

The three additional efficacy analyses are discussed below:

1. Statistical evaluation of minimization factors used for randomization on the primary endpoint

Both Phase III studies used minimization to allocate patients to treatment. Centre and type of attack were used as factors in this algorithm but were not included in the primary analysis – time to onset of symptom relief - specified in the pre-specified reporting and analysis plan. Re-analyses were carried out to see if inclusion of these factors had an effect on the outcome of the primary analysis in either of the two Phase III studies.

The primary analysis – time to onset of symptom relief – was reassessed by performing three separate analyses for each study taking into account the minimization factors: type of attack and centre. These were as follows:

- A Kaplan Meier survival analysis with a log rank test stratified by type of attack.
- A Kaplan Meier survival analysis with a log rank test stratified by centre.
- A Cox regression model with both type of attack and centre as covariates.

For the purpose of these analyses, centres were grouped by country for FAST-1 (Argentina, Australia, Canada, United States) and by region for FAST-2 (Germany; Austria, Hungary, Lithuania and Poland; France, Ireland, Israel, Italy, Sweden and Switzerland).

The log-rank test stratified by centre showed a highly statistically significant difference ($p \leq 0.001$) in the time to onset of symptom relief in favour of icatibant over tranexamic acid for JE049 #2102. In JE049 #2103, the difference in the time to onset of symptom relief was also observed in favour of icatibant over placebo, however, this difference was not statistically significant ($p = 0.105$).

For JE049 #2102, the log-rank test stratified by type of attack rather than centre showed a highly statistically significant difference ($p \leq 0.001$) in the time to onset of symptom relief.

This difference was not statistically significant ($p = 0.065$) in JE049 #2103. However, the observed treatment effect comparing icatibant to placebo, for the time of onset of symptom relief, favoured icatibant.

The results of the Cox proportional hazards model for the time of onset of symptom relief confirmed the results of the log-rank test for both studies. There was a highly statistically significant difference ($p \leq 0.001$, Hazard Ratio = 4.459) for the treatment effect in JE049 #2102. For JE049 #2103, the results showed the trend for the treatment effect in favour of icatibant versus placebo although the difference did not reach the statistical significance ($p = 0.243$, Hazard Ratio = 1.394).

The analyses concluded that adjusting for the factors used in the minimisation approach does not essentially affect the conclusions in either of the two Phase III studies.

2. Responder sensitivity analysis

In both Phase III studies, a treatment responder was defined as a patient who achieved a reduction in VAS between 20 and 30 mm according to the algorithm described in the Statistical Analysis Plans and the study reports. This definition was based on published data indicating that the minimally clinically significant difference (MCSD) is approximately 15-20 mm for pain.

The VAS for measuring symptoms of a HAE attack was validated in Study JE049 #4102. This study also demonstrated that the MCSD was 9 mm in this patient population. In the phase III studies, a much more stringent definition of the MCSD, that is, a larger difference (20-30 mm) was used together with the requirement that this difference should be maintained for at least 3 subsequent measurements.

Based on a recommendation by the EMEA, sensitivity analyses were performed using fixed cut-off points of 9 mm, 15 mm, 20 mm, 25 mm, 30 mm, 40 mm, and 50 mm. The minimization factors centre and type of attack were included in this analysis. Three separate analyses were performed as for the primary endpoint and centres were grouped in the same way. Results of the sensitivity analyses for both Phase III studies are provided in Table 4 below using these fixed cut-off points.

Table 4. Median Time to Onset of Symptom Relief for the Cut-off Points of 9 mm, 15 mm, 20 mm, 25 mm, 30 mm, 40 mm and 50 mm

Cut-off Point (mm)	JE049 #2103			JE049 #2102		
	Median time to onset of symptom relief (hrs)		p-value	Median time to onset of symptom relief (hrs)		p-value
	Icatibant	Placebo		Icatibant	Tranexamic acid	
9	1.5	2.0	0.158	1.0	5.5	<0.001
15	1.6	2.0	0.475	1.5	8.0	<0.001
20	2.0	3.3	0.196	2.0	10.0	<0.001
25	2.5	5.0	0.092	2.0	12.0	<0.001
30	2.5	5.5	0.137	2.0	13.0	<0.001
40	5.1	8.2	0.192	5.0	23.2	0.001
50	8.0	23.0	0.219	6.0	47.2	0.011

The analyses concluded that for all cut-off points between 9 mm and 50 mm for the primary endpoint of time to onset of symptom relief, highly statistically significant and clinically relevant differences were observed between icatibant and tranexamic acid in JE049 #2102. As expected from the pre-specified analyses, no statistically significant differences for the primary endpoint time to onset of symptom relief were seen using the same cut-off points in JE049 #2103, although the differences were clinically relevant and in favour of icatibant from a cut-off of 25 mm and above.

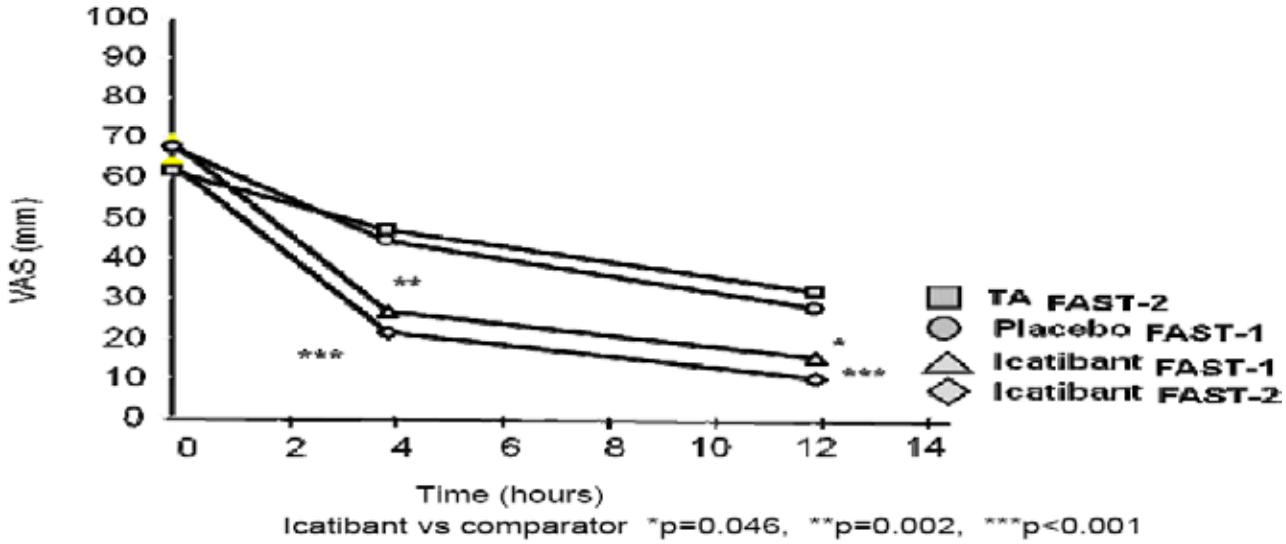
3. Change from baseline and AUC analyses

The primary endpoint and the first secondary endpoint of response rate at 4 hours used a definition of 'responder' and did not directly assess the change in symptom severity. Additional analyses were carried out for the measurement of change from baseline in VAS scores and their respective AUCs. Changes from baseline in VAS scores are direct measures of the VAS which are likely to represent a more accurate clinical picture of the HAE attack.

- Change from baseline in VAS scores

An analysis of change in VAS from baseline to 4 and 12 hours post-dose for both studies (using an analysis of variance model) is presented in Figure 3 below.

Figure 3. VAS scores, significant at 4 and 12 hours: FAST-1 and FAST-2, double blind phase, ITT population.



The results showed that for both studies, there were a substantial and consistent reduction in the VAS score at both post-dose time points in the icatibant groups compared to the comparator groups, and the treatment differences in VAS changes from baseline to 4 hours and 12 hours were statistically significant ($p = 0.002$ and $p = 0.046$ for 4 hours and 12 hours in JE049 #2103 and $p < 0.001$ for 4 hours and 12 hours in JE049 #2102).This analysis is considered the most clinically relevant way of analysing the data from the randomized part of the phase III studies because it uses the raw VAS scores without the artificial construct of the primary endpoint specified by the study protocols. More importantly, this analysis resulted in the difference between icatibant and placebo being statistically significant in JE049 #2103.

- VAS AUC from 0 to 12 hours

The same mixed model was used to compare the VAS AUC from 0 to 12 hours. Areas under the curve were calculated using the trapezoidal method. Figure 4 and Figure 5 present the mean VAS AUC from 0 to 12 hours for JE049 #2103 and JE049 #2102, respectively.

Figure 4. Mean VAS AUC from 0 to 12 hours, Study JE049 #2103 (FAST-1), ITT population.

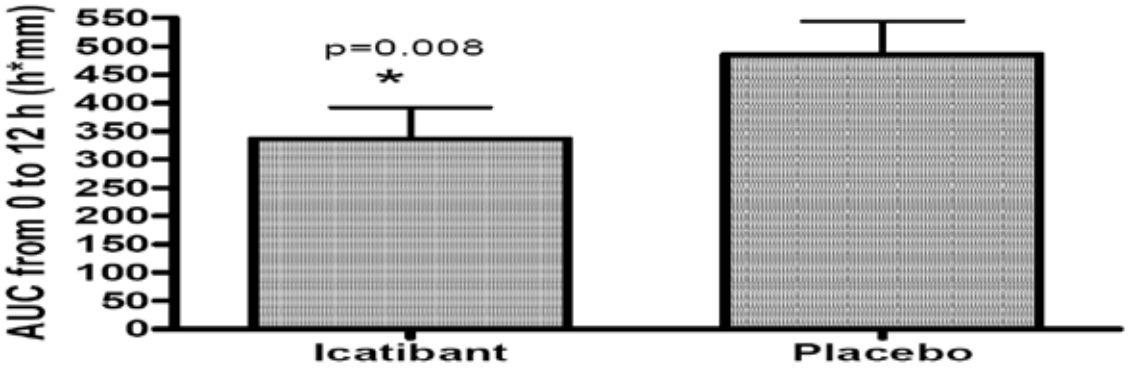
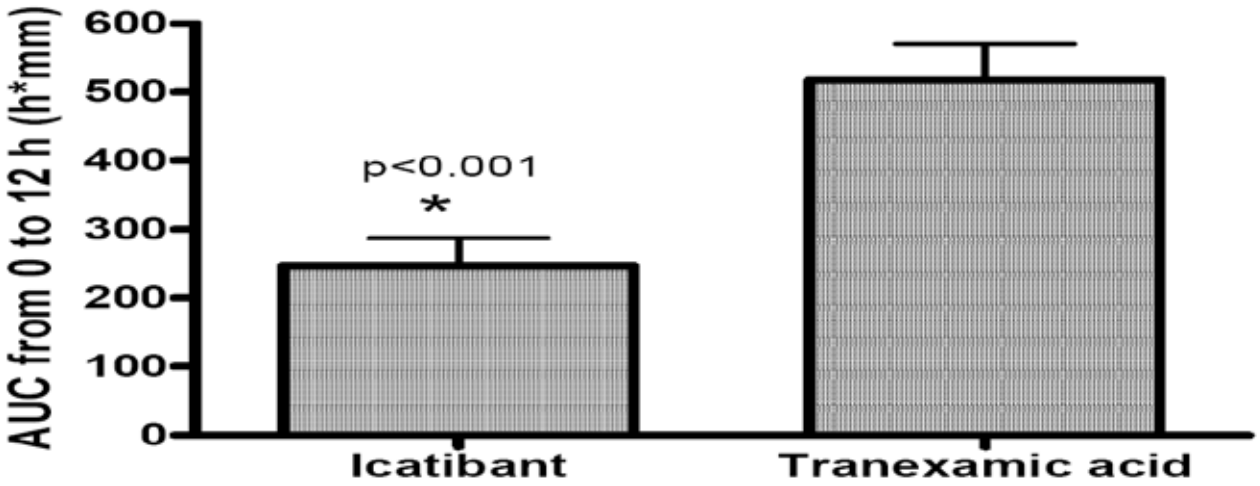


Figure 5. Mean VAS AUC from 0 to 12 hours, Study JE049 #2102 (FAST-2), ITT population.



The analyses shows that for both studies, the difference of VAS AUC (0 to 12 hours) between icatibant and the comparator were significant: p = 0.008 in JE049 #2103 (FAST 1) and p < 0.001 in JE049 #2102 (FAST 2).

TGA Clinical Evaluator's comments on efficacy

In the FAST-2 study (JE049#2102), icatibant demonstrated a beneficial effect in time to onset of symptom relief, the primary endpoint, when compared to tranexamic acid. In the FAST-1 study (JE049#2103) comparing icatibant with placebo, a similar rather strong trend was observed, but no statistically significant difference was demonstrated.

When the change from baseline to 4 and 12 hours in VAS scores was compared (see additional efficacy analysis), a superior effect of icatibant over placebo at both time-points (4 and 12 hours) was demonstrated (Figure 3). Further sensitivity analyses have also been provided fitting centre as a fixed rather than a random effect. These analyses produced very similar results and confirmed the superiority of icatibant over placebo for the VAS endpoint (change from baseline to 4 and 12 hours in VAS scores).

The efficacy data in a total of 118 patients treated for a total of 597 HAE attacks in the open-label Phase of the two studies also provided supporting evidence for the efficacy of icatibant. The beneficial effects of icatibant have been demonstrated both in the treatment of "general" HAE attack without laryngeal symptoms and in HAE attack with laryngeal symptoms. Most of the 597 attacks needed only one icatibant injection, and very few of them required rescue medication. Within these treated attacks, there are no signs of exacerbation of severe symptoms.

The evaluator agrees with the CHMP conclusion: the evidence from the overall clinical package, including additional data from the open-label phase and the additional efficacy analyses, demonstrates that icatibant is efficacious in treating all types of acute HAE attacks.

Safety

CHMP evaluation

Up to a cut-off date of 30 September 2007, 118 patients have been treated in the open label Phase with icatibant for a total number of 597 attacks. A total of 36 patients were treated for 61 laryngeal attacks.

Adverse events

The most common adverse events (AEs) reported were symptoms related to injection site reactions. These reactions were generally mild to moderate and resolved spontaneously within a short time. There were 5 reports of chest pain, but the 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.

A number of patients have received repeated treatment. Of the 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.

Serious adverse events /deaths/other significant events

One patient died 41 days after administration of tranexamic acid, and this patient had coronary artery atherosclerosis and aortic valve sclerosis. Seven serious adverse events (SAEs) were reported by six patients who were treated with the dose of icatibant intended for use. No serious event was reported for tranexamic acid or placebo. The reported SAE include recurrent attacks. There was one report of "hypertensive crisis", but the case does not seem to be related in time to icatibant. One report of laryngeal oedema describes a rapid deterioration of symptoms, which was probably not related to icatibant given just 5 minutes before a need for intubation.

Discontinuation due to adverse events

There were no reports of discontinuations due to AEs.

Laboratory findings

Electrocardiograms (ECGs), including QT evaluations, have been thoroughly performed. No safety signals of concern have been found.

Safety in special populations

No difference 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.

BK has been implicated in the protection of the myocardium during ischemia and it seems likely that the serious adverse effects seen in nonclinical infarction studies are manifestations of a blockade of such protective effects by icatibant. The sponsor suggests a warning in the Summary of Product Characteristics (SPC) for the use of icatibant in the presence of acute ischaemic heart disease or unstable angina pectoris, which is endorsed. BK has also been implicated in limiting the extent of brain damage in stroke. Theoretically, icatibant may antagonise the protective effect of BK in this condition as well, leading to a worsening of the ischaemic brain damage.

Safety related to drug-drug interactions and other interactions

Inhibition of degradation of BK by ACE inhibitors, leading to an increased BK 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).

Safety update (JE049-5113B)

The data lock date for the original Integrated Safety Summary (JE049-5113) was 31/9/2007. JE049-5113B updates the safety information up to the end of both Phase III studies (last patient out: 31 March 2008; Data base lock: 2 October 2008 for JE049 #2102 and 2 September 2008 for JE049 #2103). JE049-5113B presents the data obtained from the controlled phase of the Phase III studies separately from the corresponding data collected in the open-label phase. In addition, safety data from the Phase II study JE049 #2101 are presented, analysed and discussed separately.

Safety updates from the two Phase III studies

Exposure to the study medicines

Controlled Phase: A total of 130 patients with an acute attack of HAE were included in the randomized treatment groups in the controlled phase of the two Phase III studies – 63 received a single SC dose of icatibant 30 mg, and 29 and 38 patients received placebo and TA, respectively. All icatibant patients received a single dose of the drug as per the protocol. One patient in the placebo group received open-label icatibant after being granted a waiver on compassionate grounds. Additionally, 11 patients were treated with a single SC dose of icatibant 30 mg open-label due to laryngeal symptoms presenting during the controlled phase.

Open-label Phase: A total of 126 patients participated in the open-label phase; this could include patients initially participating in the controlled phase, those patients initially screened but unable to participate in the controlled phase, and those patients allowed to enter the study for the first time following the controlled Phase. In these patients, a total of 714 attacks of HAE were treated. The majority of attacks (approximately 89%) only requiring a single dose of icatibant.

Overall, a total of 149 patients received 871 SC doses of icatibant 30 mg for 788 attacks of HAE in both controlled and open-label extension phases of the studies.

Demographics and other characteristics of study population

Controlled Phase: the majority of patients were female in all the groups, with a slightly greater number of females in the placebo group (M/F ratio 0.38) than in the icatibant (0.58) or the TA (0.65) groups. The majority of patients in all groups were Caucasian (86.2 – 100%) with 'Other' being the next most common racial category. All the groups were broadly similar for mean age, weight and height. The majority (97.7%) of patients were 65 years of age or less, with only 2 (3.2%) patients being > 65 years in the icatibant group and 1 (2.6%) patient in the TA group. In patients with laryngeal symptoms at baseline, M/F ratio was 0.83 and all patients were Caucasian of age < 65 years.

Open-label Phase: the demographics of the study population were similar to the icatibant population in the controlled phase. Only 3 (2.4%) out of the 126 patients were > 65 years of age.

- **Adverse Events**

Controlled Phase: In the Safety Population (n =130), there were 31 (49.2%) patients who reported at least one AE in the icatibant group compared to 19 (65.5%) and 16 (42.1%) patients in the placebo and TA groups, respectively.

In all three treatment groups, the most common AE by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) was hereditary angioedema – 14 (22.2%), 5

(17.2%), and 6 (15.8%) patients in the icatibant, placebo, and TA groups, respectively. These events were most likely to be reported a few hours to 2 days after treatment and could possibly be related to inadequate initial treatment, relapse of symptoms, or a secondary HAE attack. It should be noted that only one dose of icatibant was allowed in the controlled phase of the trials – in the market up to three doses at 6 hourly intervals is advised.

Using the icatibant group as the reference, the next most common AEs that occurred in more than one patient were: nasopharyngitis (4.8%), injection site pain (3.2%), injection site reaction (3.2%), pyrexia (3.2%), gastroenteritis (3.2%), dizziness (3.2%), headache (3.2%), nasal congestion (3.2%), and rash (3.2%).

In the patients with laryngeal symptoms at baseline, there were 7 (63.6%) patients who reported at least one AE. The most common AE in this group was hereditary angioedema – 5 (45.5%), followed by headache (18.2%).

Open-Label Phase: In the open-label phase of the Phase III studies, there were 95 (75.4%) patients who reported at least one AE following treatment with icatibant.

The most common AE was hereditary angioedema (HAE), reported in 35 (27.8%) of patients. A report of HAE as an AE could mean that icatibant is either not efficacious, is causing exacerbation of symptoms, a late relapse is occurring, or a secondary attack has occurred.

The other common AEs (>2%) were: headache (11.1%), nasopharyngitis (7.9%), urinary tract infection (7.9%), upper respiratory tract infection (7.9%) pharyngitis (4.8%), chest pain (4.0%), injection site pain (4.0%), pyrexia (4.0%), urticaria (4.0%), vomiting (3.2%), abdominal pain (3.2%), hypertension (3.2%), cough (3.2%), blood creatine phosphokinase (CPK) increased (3.2%), acne (3.2%), Increase in CPK (3.2%), conjunctivitis (2.4%), influenza (2.4%), respiratory tract infection (2.4%), diarrhoea (2.4%), nausea (2.4%), anxiety (2.4%) and contusion (2.4%).

The following AEs, although they occurred at a very low frequency, warrant special attention:

• Chest pain (4.0%) – there is a theoretical risk that icatibant could attenuate the cardioprotective benefit of BK in acute myocardial ischemia. There were 5 reports of chest pain, 1 report of chest wall pain and 1 report of atypical chest pain due to HAE. However, there is no evidence that icatibant was a causative factor for these reports of chest pain.

• Increase in CPK (3.2%) – elevations in CPK can occur as a consequence of acute myocardial ischemia. There is no evidence that icatibant was a causative factor with the reported cases. Muscle swelling occasionally occurs as a consequence of an HAE attack and elevated creatinine kinase (CK) levels have been reported as a result of muscle involvement.

- **Deaths**

One patient died in study JE049 #2102. This was a 53 year old male with an adverse cardiac history, who received TA during the controlled phase for an HAE attack. Subsequently, 41 days later, the patient collapsed and died. An autopsy revealed coronary artery atherosclerosis and aortic stenosis. The event was regarded as unrelated to TA.

- **Other serious adverse events**

Controlled Phase: a total of 5 patients reported at least one SAE in the safety population; 4 (6.3%) following icatibant and 1 (2.6%) death following TA. No patients reported an SAE following placebo. The most common SAE reported was hereditary angioedema (3.2%) in the icatibant group. Other SAEs which occurred in single patients are: cholelithiasis, cystitis, gastroenteritis, and hypertensive crisis. In the controlled phase in patients with laryngeal

symptoms at baseline, 2 (18.2%) patients reported at least one SAE. The two reported events were both HAE. None of the SAEs were considered as being related to the study medication.

Open-label Phase, 13 (10.3%) patients reported at least on SAE following icatibant. The most common SAE was again HAE in 5 (4.0%) patients. Other SAEs which occurred in single patients are pancreatitis, chest pain, rotavirus gastroenteritis, salmonella gastroenteritis, bacterial urinary tract infection, road traffic accident with head injury and wound, pancreatic enzymes increased, myalgia, cervix carcinoma stage 0, suicide attempt, renal failure, and tooth extraction. None of the SAEs were regarded as being related to icatibant.

- **Adverse events leading to discontinuation**

Controlled Phase: there were no AEs that led to patient discontinuation.

Open-label Phase: in the 126 patients participating in the open-label phase, one patient had new onset of coronary heart disease which was considered not related to the study drug. She was withdrawn from the study due to coronary heart disease being a study exclusion criterion.

Safety results from the Phase II study

A total of 15 patients were treated for a total of 20 attacks of HAE (5 patients being treated twice for separate attacks) with either a 0.4 or 0.8 mg/kg IV infusion, or a 30 or 45 mg SC dose of icatibant. A total of 11 patients reported 40 AEs in the entire course of the study. One AE was reported by one patient following 0.4 mg/kg IV infusion over 2 hours, no AEs were reported following 0.4 mg/kg IV infusion over 30 minutes, and 3 AEs were reported by 2 patients following 0.8 mg/kg IV infusion over 30 minutes. A total of 17 AEs were reported by 4 patients following a 30 mg SC injection and 19 AEs were reported by 4 patients following a 45 mg SC injection. Most of the AEs observed were local reactions related to the SC injections, with 16 local reactions at the injection site in the 30 mg dose and 17 in the 45 mg dose group. Of these local reactions, 3 were considered definitely, 21 were considered probably and 9 were considered possibly related to treatment; 18 were of mild, 13 were of moderate and 2 were of severe intensity. The 2 severe local reactions were “burning sensation” (lasted 10 minutes) and “pain” (lasted 15 minutes) occurring in one patient following a 45 mg SC injection. No local reactions were recorded in any of the IV groups. All local injection site reactions after SC injection resolved spontaneously without sequelae. No deaths occurred during the study.

Two SAEs were reported:

• One patient receiving 0.4 mg/kg IV infusion over 2 hours (= 48 mg) was treated for HAE type I. He left the clinic 20 hours after the end of infusion. Seven days after the study drug infusion, he was admitted to a psychiatric hospital due to an acute manic episode of a pre-existing schizoaffective psychosis. He showed signs of increased aggression, affective lability and restlessness. CK and its isozymes MB (CK-MB) activities were elevated. Since no clinical symptoms or ECG abnormalities were observed and the CK-MB: CK ratio of 1954.2 U/L:66.5 U/L did not correspond to acute ischemic heart disease, a cardiac event was not suspected. The increase of CK and CK-MB could be explained by the acute psychotic episode; association of acute psychotic episodes with increased levels of these two laboratory parameters is a well known clinical finding. In conclusion, the SAE was considered unrelated to the study drug, but was attributable to the pre-existing disease.

• One patient receiving 30 mg SC injection for his HAE attack reported onset of relief 10 minutes after icatibant injection. Twenty hours after treatment, recurrence of mild cutaneous and abdominal symptoms was documented. The patient received 500 IU Berinert. This event was classified as a SAE because of prolonged hospitalization and was rated as probably not

related to study drug. This SAE resolved without sequelae. There were no clinically relevant changes in vital signs or clinical laboratory parameters during the study.

TGA Clinical Evaluator's comments on safety

Although the most commonly reported AE was "hereditary angioedema", based on the time of occurrence, the majority were recurrent attacks and not related to treatment with icatibant. It is possible that late relapse of symptoms may occur following treatment with icatibant. It is therefore important to state in the PI that up to 2 further doses of icatibant may be administered at 6-hourly intervals.

Symptoms related to injection site reactions were one of the commonly reported AEs, and these reactions were generally mild to moderate in severity and resolved spontaneously within a short time. There were no clinically relevant changes in clinical laboratory parameters. There were no trends observed in vital signs. There are no discernible safety signals from adverse event reporting.

As icatibant is a potent and selective antagonist of the B2 receptor, a theoretical risk with the use of icatibant is a deterioration of cardiac function and reduction in coronary blood flow under ischaemic conditions due to a possible protective effect of BK. Patients with cardiac risk factors were excluded in the clinical trials. A warning statement is included in the PI with regard to patients with acute ischaemic heart disease, unstable angina pectoris, and stroke, which is considered sufficient.

The potential lack of treatment efficacy in patients with laryngeal oedema is a major safety concern. Acute attacks with laryngeal oedema require particular attention due to its life-threatening nature. Reassuring data have been received from 61 attacks involving laryngeal symptoms, and the majority of attacks had moderate to very severe symptoms at baseline. Treatment of laryngeal attacks should continuously be monitored in the post-marketing period. Instructions for use in proper medical settings for the laryngeal attacks have been included in the PI.

Overall, the safety profile of icatibant observed in the clinical trials is considered acceptable when it is used at the dose and regimen proposed.

Non interventional investigations to further validate the VAS

In the Phase III studies, the primary endpoint was the time to onset of symptom relief, utilizing patient reports of symptoms using VAS to assess relevant symptoms. Secondary endpoints also included patient reports of symptom severity and clinician global impressions.

At the time these studies were designed, there was no official guidance with regard to Patient-Reported Outcome (PRO) assessment strategies. Since the completion of the study, a specific guidance on the research needed to support PROs used in clinical trials has been issued by the FDA[18]. The key elements of what is currently requested by the FDA for all PROs are as follows:

1. Demonstration of face and content validity.

2. Clinical validity, responsiveness.

3. Definitions for a MCID (minimum clinically important difference).

4. Reliability, or 'test-retest reliability'.

[18] Guidance to Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims' (Draft Guidance, February 2006)

Several non-interventional investigations were specifically conducted for the FDA in accordance with the FDA's guidelines on PROs. It is noted that the EMEA accepted PRO Measures (VAS score) without the above requirements.

Reports for four of the non-interventional studies (JE049-4104-B, 5115, 5125, 5126) became available after the EU approval. These reports were submitted in the Australian submission in addition to the EU submission. The findings from these four reports are briefly discussed below.

JE049-4104B

JE049-4104B was an interview study conducted to assess the face and content validity of the patient reported outcomes (PROs) use in the FAST clinical trials. The primary objectives of JE049-4104B were:

1. To assess the comprehensiveness of the FAST diary symptom assessments by asking patients to spontaneously report their symptoms (content validity).

2. To assess patient understanding of the FAST diary (face validity).

A total of 32 interviews were conducted across 6 sites in USA and 1 site in Argentina.

Overall, it is concluded that face validity of the primary and secondary endpoints is acceptable because the majority of patients were able to understand and interpret the items well. Some of the sections of the diary such as the instructions and the location of the skin oedema section still contain a large amount of medical terminology; however patients were able to complete and understand these parts of the diary and these were not key components of the endpoints. Therefore while it can be said that for the primary and secondary endpoints in the FAST diaries, face and content validity has been achieved, a small number of patients did have difficulty with some items suggesting that for future use some changes could be made to clarify some of the items for the patients.

JE049-5115

JE049-5115 was qualitative and quantitative market research. The objectives of this report were:

- To assess whether the PROs used in the clinical trials (FAST dairy) comprehensively and sufficiently measure the most relevant and important symptoms to patients.
- To assess the similarity of comments made by clinicians to those made by patients.
- To provide supportive evidence for the PRO conceptual framework in the PRO briefing document.

Individual in-depth face-to-face interviews with HAE sufferers (n=38) and HAE specialists (n=25) were carried out to gain qualitative data. Interviews were performed in Germany, France, UK, Italy and Spain. In addition to the patient and specialist interviews, a quantitative research into patient experiences with HAE was conducted by mailing a survey. A total of 1579 questionnaires were sent out to HAE sufferers, the number of responders was 684 (43%).

Overall, this qualitative and quantitative market research provides evidence that the primary endpoint of 'time to onset of symptom relief ' of the primary symptom is appropriate and supported by the patient diary, as the diary enables the patient to report their primary symptom and measure the change in severity of the symptom. This market research supports the use of the FAST diaries and suggests the items within the diary address the symptoms of importance to patients.

JE049-5125

JE049-5125 aimed to provide a supportive documentation on the development and validation of the PRO measures.

To develop the patient-reported diary, the following steps, in chronological order, were used:

1. Clinical experts input.
2. Development and translation of diary, and implementation into the two Phase III trials.
3. Qualitative/quantitative market research to support the validity of the diary (JE049-5115).
4. Independent study to assess MCIDs with the VASs (JE049 #4102).
5. Literature review to assess the use of VAS (JE049-5111).
6. Psychometric validation of diary using pooled trial data (JE49-5110)
7. Patient interviews to assess the face and content validity of the diary (JE049-4104).

Clinical experts input, literature review (JE049-5111), qualitative and quantitative market research (JE049-5115), and post-hoc patient interview study (JE049-4104) all support the face and content validity of the diary used in the FAST trials. Specifically, all three types of attacks and the relevant symptoms for those attacks were assessed. Though the primary endpoints were not developed with patient input, the subsequent patient qualitative research suggests that the relevant symptoms were indeed covered in the diaries.

Assessment of MCID (JE049 #4102): This non-interventional, observational study was designed to establish the minimal clinically important difference (MCID) in VAS scores as the basis for defining "onset of symptom relief" for skin swelling, skin pain, or abdominal pain in HAE subjects experiencing an acute moderate to very severe attack involving skin and/or abdomen. MCID was established by determination of the MCSD for the three VAS categories ('skin swelling', 'skin pain' and 'abdominal pain'). The study evaluated 57 subject-reported changes in symptom severity following an HAE attack using VAS and verbal descriptor scale at 12 fixed intervals for 48 hours after baseline or until the VAS score was 0 (no symptoms) – whichever occurred first. The results demonstrated a 9 mm change in VAS as the MCID for onset of symptom relief using ROC (Receiver Operating Characteristics) curve analysis, with this cut-point providing 88.24% specificity and 82.61% sensitivity at 6 hours post baseline.

Psychometric validation of diary (JE049-5110) was performed to assess the psychometric properties of the VAS and patients symptoms used in the FAST studies using pooled data from both of the FAST studies. Results of the psychometric testing support the following aspects of validation of the VASs and symptom severity scales:

- Construct (convergent) validity: correlation between VAS and patient symptom severity scores range was 0.82-0.89.
- Known groups (discriminant) validity: statistically significant differences between those experiencing a symptom and those not experiencing a symptom, $p < 0.0001$ for all VAS and symptom severity measures.
- Clinical validity: statistically significant differences were noted for VASs between clinician
  ratings of severity in 10 out of 12 comparisons. For patient symptom scores a substantial to almost perfect agreement between two scores for all of the symptoms could be demonstrated when analysing the scores according to physician symptom scores (range 0.66-0.82).

- Responsiveness: for VASs effect sizes increase from small to moderate or large with greater clinical improvement as rated by the clinician. The patient symptom scores also showed that they are responsive to change in the condition of the patient over time.
- Test-retest reliability**:** this was difficult to assess, as the majority of patients had changed in their clinical status within four hours of treatment. However excellent agreement was detected for the test-retest analyses for "Abdominal Pain", "Skin Pain" and "Nausea" VASs when a sufficient number of stable patients were available (Kappa > 0.7)..

The results of JE049-5110 suggested that the four VASs assessing 'Abdominal Pain', 'Skin Pain', 'Skin Swelling' and 'Nausea' respectively and the patient symptom scores are valid and responsive in terms of changes in a patient's condition following treatment; however the test-retest reliability of the scales could not adequately be addressed by the analysis of FAST study data due to the interventional nature of the study leading to small sample sizes in the stable group.

Patient interview study (JE049 #4104), as discussed previously, the outcome of this patient interview study supports the face and content validity of the FAST diaries.

Overall, the VASs have been shown to be valid and responsive and are appropriate to use in trials of HAE. In addition, the responder definition has been shown to be appropriately stringent in its measurement.

JE049-5126

JE049-5126 was intended to provide the roadmap to the different steps undertaken to validate the PRO instrument and FAST dairy used in the two pivotal studies. This roadmap was provided to navigate through the relevant reports and their coverage of the different elements outlined in the draft PRO guidance. The key items of the draft PRO guidance were addressed in the individual reports (see below).

Based on discussions with physicians experienced in this rare disease, it was decided to use a patient-reported diary format to assess HAE symptoms, utilizing VAS to assess HAE symptom severity. In particular, the symptoms of pain related to abdominal and cutaneous attacks and swelling related to cutaneous attacks were thought to be the most clinically relevant symptoms of an HAE attack and therefore were selected as primary endpoints.

Some of the individual studies are briefly mentioned below.

JE049-5125: As discussed previously, JE049-5125 provided comprehensive information on the conceptual framework and linkage of the PRO claims to the concepts (endpoint model), and provided an overview on the discussion with experts to identify relevant items that needed to be covered by the FAST diaries.

JE049-5111 and JE049-5115: literatures review (JE049-5111) and qualitative / quantitative market research (JE049-5115) all support the face and content validity of the FAST diary.

JE049-4104 (patient interview study) supports the overall face and content validity of the FAST diary.

JE049-5110 (psychometric testing) was performed to assess the psychometric properties of the VAS and patients symptoms used in the FAST studies using pooled data from the two FAST studies. The results of JE049-5110 suggested that the four VASs assessing 'Abdominal Pain', 'Skin Pain', 'Skin Swelling' and 'Nausea' respectively and the patient symptom scores are valid and responsive in terms of changes in a patient's condition following treatment; however the test-retest reliability of the scales could not be adequately addressed by the analysis of data in the FAST studies due to the interventional nature of the study leading to small sample sizes in the stable group.

JE049 #4102 (assessment of MCID): The results of JE049 #4102 demonstrated a 9 mm change in VAS as the MCID for onset of symptom relief using ROC curve analysis, with this cut-point providing 88.24% specificity and 82.61% sensitivity at 6 hours post baseline.

TGA Clinical Evaluator's comments on the non-interventional studies

These non-interventional studies support the selection of these key symptoms and the VAS items. The VAS items for the primary endpoint were highlighted by patients as the most important symptoms to them when experiencing an attack, and the majority of other symptoms experienced by patients during an attack were also captured within the FAST diary and assessed as secondary endpoints in the study. The VAS items were well understood by patients, as were the secondary endpoint symptom severity items.

Overall, all major requirements defined in the FDA draft PRO guidance were covered by these studies. The validity and responsiveness of the FAST diary were supported.

Post-marketing Experience

Firazyr is currently marketed in UK, Germany, Austria, Luxembourg, and Sweden. The product is distributed in France via an early access program. Firazyr is distributed under named patient programs (NPPs) in Belgium, Ireland, Spain, Italy and Greece. During the first six months following marketing approval, an estimated total of 215 patients were treated with icatibant: 52 within the NPPs and another 163 patients estimated based on the sales on the market. The latter figure is estimated from product sales, assuming an average of 1.1 doses of icatibant is used per HAE attack. During this period, only one spontaneous, serious adverse drug reaction (SADR) was reported to the company, with no other safety cases being identified from other sources. This serious ADR (Case JER-069) involved a 23 year old male patient who experienced massively elevated liver enzyme values (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and glutamate dehydrogenase (GLDH)) concurrent with the use of unapproved high doses of icatibant. The patient developed septic shock from which he subsequently died. A post mortem examination confirmed multi-organ failure secondary to septic shock. The investigator considered the event to be unrelated to the use of icatibant.

Clinical Summary

The current treatment options for HAE are limited. In patients with frequent attacks of HAE, prophylactic therapy is usually prescribed. The most common class of drugs for prophylactic therapy is the 17-alpha alkylated androgens of which the only approved product in Australia at the time of this submission is danazol. Antifibrinolytics such as tranexamic acid are also used. For acute attacks of HAE, the efficacy of danazol has not been demonstrated. In the case of tranexamic acid, its efficacy is limited by the slow onset of action. Supportive therapy is normally the basis for treatment of acute HAE attacks. Supportive therapy may include fresh frozen plasma which contains C1-INH; however, the attack may be exacerbated due to the presence of vasoactive substances. Berinert, a C1 esterase inhibitor, has recently been registered in Australia for the treatment of acute attacks of HAE.

The efficacy and safety of icantibant in treating acute attacks of HAE were assessed in two pivotal studies: FAST-1 and FAST-2: In the FAST-2 study (JE049#2102), a beneficial effect of icatibant was shown for the primary endpoint, time to onset of symptom relief, in comparison with tranexamic acid. In the FAST-1 study (JE049#2103) comparing icatibant with placebo, a similar trend was observed, but no statistically significant difference. However, when the change from baseline to 4 and 12 hours in VAS scores was compared (see additional efficacy analysis), a superior effect of icatibant over placebo at 4 and 12 hours was demonstrated (Figure 3).

The efficacy data in a total of 118 patients treated for a total of 597 HAE attacks in the open-label Phase also provided supporting evidence for the efficacy of icatibant. A beneficial effect was demonstrated in the treatment of the general and laryngeal attacks of HAE.

The clinical evaluator agreed with the CHMP that the original and additional efficacy analyses of the two Phase III studies and data from the open-label phases provided evidence that icatibant has a beneficial effect in treating all types of acute HAE attacks in adult patients.

With regard to safety, the most commonly reported AE in the two pivotal studies was "hereditary angioedema". However, based on the time of occurrence, the majority were recurrent attacks and not considered relating to icatibant treatment. The other common AEs were injection site reactions and these reactions were generally mild to moderate and resolved spontaneously. No discernible safety signals were detected in the clinical trials. The available safety data suggested that the safety profile of icatibant at the proposed dose regimen is acceptable. The theoretical risk of icatibant in patients with ischemic cardiac diseases and/or stroke has been reflected in the PI.

In view of the potentially fatal nature of the acute attacks of HAE, the limited range of available treatment, and the reasonable evidence of efficacy and safety of icatibant demonstrated in the clinical trials, the evaluator recommends approval of Firazyr (icatibant solution for injection) for symptomatic treatment of acute attacks of Hereditary Angioedema (HAE) in adults with C1 esterase dysfunction. The proposed dose and dose regimen are supported by clinical trial data.

V. Pharmacovigilance Findings

The Risk Management Plan (RMP) has been review by the TGA's Office of Medicines Safety Monitoring (OMSM). The following safety issues were identified by the sponsor in the submitted RMP:

Identified risks	· Injection site reaction
Potential risks	· Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism · Partial bradykinin agonism · Antigenicity · Lack of efficacy
Areas of missing information	· Use in children · Use in pregnancy and lactation

The activities proposed by the Sponsor are routine pharmacovigilance, the Firazyr patient registry and routine risk minimisation activities (including information about each safety issue in the product information).

Five issues were raised by the OMSM evaluator and the sponsor has responded to these issues. These were:

1. Lack of information on effects on cardiac and renal function, antigenicity, use in pregnancy and lactation and use in children and adolescents. The OMSM evaluator considered the sponsor's responses to these concerns were satisfactory. A patient registry has been activity running in the EU and will record long-term observational information to provide better understanding of the long-term safety of icatibant in clinical practice. Entry into the registry is at the discretion of the treating physician.
2. The sponsor was asked to the milestones for reporting results of the patient registry. These results are to be included in each PSUR.
3. Amendments to the PI with respect to: interactions with ACE inhibitors; administration under the supervision of a clinician; use in children and effects on fertility. The sponsor disagreed to use under supervision of a clinician, though the Delegate noted that this is a condition in the EU. The sponsor considered current statements on use in children and adolescents and effects on fertility were adequate.
4. The sponsor was requested to clarify the reason the sponsor stated that 12 hours should elapse after exposure to icatibant prior to breast feeding. The response was accepted by the OMSM evaluator.
5. The OMSM evaluator recommended active follow-up of children, breast feeding women, reports of lack of efficacy, reports of possible hypersensitivity and use in individuals with known renal or hepatic impairment or congestive cardiac failure. The sponsor has stated that it intends to actively follow all adverse reaction reports for subjects on the registry.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no absolute objections to registration raised by the quality evaluator. There were 2 issues of concern:

1. This submission was discussed at the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) meeting of 21 September 2009. The PSC stated that the results of Study 1102, a bioavailability study, should not be reported in the Product Information. The analytical method used in this study (LC/MS/MS) suffered from serious deficiencies, most notably the use of only one QC sample and the application of inadequate acceptance criteria to calibration curves and QC samples. Another study (Study 2101), a parallel group study in patients with HAE, was claimed to support the results of Study 1102. However, the same bioassay method was used and it suffered from many of the same deficiencies. The sponsor claimed that the absence of a reliable absolute bioavailability study is not critical given that icatibant is used acutely rather than chronically. The Delegate considered it reasonable to include the available, though methodologically limited, bioavailability study results in the Product Information.
2. Due to the formation of the degradant icatibant(1-6) during storage and in the absence of appropriate qualification in accordance with the European Pharmacopeia 6.5, *Substances for Pharmaceutical Use*, the sponsor submitted a justification to maintain the shelf-life at 2 years.

The following pre-ACPM response regarding *Shelf-life/Qualification of impurities* was received from the sponsor:

The nonclinical evaluator is concerned about the potential chronic use of Firazyr and as such did not consider the impurity icatibant(1-6) sufficiently qualified without a chronic toxicity study. However, the Sponsor is proposing to apply a monthly limit of 8 injections which will further reduce the patient exposure to this impurity thereby reducing the concerns of the evaluator.

Using the decision tree in ICH Q3B(R2) "Impurities in New Drug Products" (which does not formally apply to synthetic peptides, but is considered to offer guidance), the icatibant (1-6) level is greater than the identification threshold with a known structure, no known human risks, and greater than the qualification threshold. Accordingly, the studies suggested by the guideline were performed for icatibant (1-6) that is, genotoxicity studies and general toxicity studies (one species). The intended dose, regimen and duration of icatibant in humans were also considered.
When administered intravenously to rats as a single 100 mg/kg dose there were no clinical sign, effect on body weight gain, and no detectable abnormalities at necropsy. The mutagenic potential of icatibant (1-6) was evaluated in an Ames test which showed no evidence of mutagenic potential. In a chromosomal aberration test in cultured human lymphocytes, icatibant (1-6) did induce statistically significant increases in chromosome aberrations. Cytotoxicity was monitored in this study as the mitotic index. Prolonged exposure to cytotoxic or cytostatic concentrations may lead to false positive results in this assay. Additionally, the use of mitotic index as a measure of cytotoxicity can underestimate the true degree of toxicity. It is thus likely that the observed increase in chromosome aberrations in human lymphocytes is a consequence of cytotoxicity and not a true genotoxic effect. These *in vitro* studies were complemented with a micronucleus test in the bone marrow of mice. Animals receiving 20 and 60 mg/kg/day intravenously for 2 days did not show any genotoxic potential. The nonclinical evaluator confirmed the "evidence indicates icatibant (1-6) is unlikely to be genotoxic".

It has also been shown that icatibant (1-6) is metabolised into icatibant (1-5), which is identical to metabolite M1 identified and qualified in animal and human studies. The metabolism of icatibant (1-6) is 3-fold slower than icatibant in human hepatocytes. However, data from isolated liver cells probably underestimates the metabolism of icatibant (1-6) as the likely route is via peptidases which are present in several of the clearance organs. Even in the setting of repeat dosing, it is unlikely that accumulation of icatibant (1-6) can occur.

In summary, the overall weight of evidence would suggest that icatibant (1-6) does not pose a genotoxic or toxicological risk to humans. Icatibant is intended for acute treatments of HAE attacks with a limited exposure of 8 doses per month. The resultant low level of icatibant (1-6) represents a minimal risk to patients. To date, over 3,000 HAE attacks have been estimated to have been treated with icatibant since first market launch, with a low frequency of adverse event reporting and no evidence of safety issues. Thus based on the current qualification studies and the clinical context of the use of the drug, the sponsor is of the opinion that icatibant (1-6) has been adequately qualified and a shelf-life of 24 months stored below 25°C is justified for the finished product in pre-filled syringes.

Nonclinical

The nonclinical evaluator stated that given the severity of the proposed indication, there were no nonclinical objections to the registration of icatibant for the treatment of adults with hereditary angioedema. The nonclinical evaluator has identified the following concerns:

1. Icatibant, at concentrations that are effective at antagonising the B2 receptor, attenuates the cardioprotective effect of BK. Therefore, therapeutic levels of icatibant in humans are expected to attenuate the cardioprotective effect of BK.
2. Kallikrein has some renal protective properties in animal models of renal disease and icatibant attenuated these protective properties. Icatibant did not however elicit renal toxicity in the majority of nonclinical studies conducted.
3. Icatibant results in atrophy of the thymus and hypertrophy of the adrenal glands at high doses in mice and dogs and lower doses in rats in repeat dose toxicity studies. No NOEL for these toxicities was established in rats. In mice and dogs NOEL for these toxicities had exposure ratios of 0.9 and 1.0. The nonclinical evaluator has noted that these margins were calculated by comparing the maximum human exposure in a day to the animal exposure in a day but that most of the animal studies had daily dosing whereas such dosing was not anticipated in humans.
4. Icatibant resulted in decreased testosterone levels, small male reproductive organs (prostate, testes and epididymides) and low sperm counts. Icatibant also reversibly affected mature female mice, rats and dogs reproductive organs. In sexually immature animals the females reproductive organs did not mature.
5. Icatibant increased pre-implantation loss in rats and post-implantation loss in rabbits but was not teratogenic in rats or rabbits. The effects on implantation and parturition are consistent with antagonism of BK, and the location of B2 receptors in the uterus of many species.
6. Carcinogenicity study reports should be submitted to the TGA upon completion.

Clinical

Pharmacokinetics

Plasma concentration of icatibant was in general determined by LC/MS/MS methods that have been poorly validated, raising some doubts regarding the accuracy of the reported PK data. However, as noted in the European Public Assessment Report (EPAR), after SC injection, icatibant is rapidly absorbed with maximum concentrations reached in about 30 minutes. Absolute bioavailability was estimated to be 97% ± 15%. Vss is about 20 – 25 L. The lower extent of protein binding is 44%. Icatibant is mainly eliminated by metabolism with no involvement of CYP450 enzymes and approximately 10% of the dose is excreted unchanged in urine. Terminal $t_{½}$ is 1-2 hours.

Given the proposed use of the product, that is, intermittent administration in HAE patients with the possibility of an additional dose in case of poor response, the uncertainty regarding the quality of the PK data was accepted.

Efficacy studies

Three efficacy and safety studies in patients with acute attacks of HAE were performed and are described in the sponsor's clinical expert report (CER). Study 2101 was a dose finding study leading to the selection of the proposed dose of 30 mg via SC injection. Studies 2102 and 2103 were double-blind, controlled Phase III single dose studies of icatibant 30 mg SC injection compared to tranexamic acid or placebo respectively. Both of these studies had open-label extensions with the option of 3 x 30 mg injections per attack according to response.

A total of 130 patients received either icatibant (n= 63), or comparator (tranexamic acid, n= 38 or placebo, n= 29). Patients with laryngeal angioedema received open label treatment with icatibant. In both studies the primary efficacy endpoint was time to onset of symptom relief of the first attack, using VAS to measure the intensity of each symptom of the attack for cutaneous swelling, cutaneous pain and abdominal pain. A VAS of 0 corresponded to no symptoms while 100 mm corresponded to the worse possible symptom. Symptom relief was defined as absolute reduction from the pre-treatment VAS of at least 20 mm if the baseline VAS was between 30 – 50 mm and ≥ 30 mm if the baseline VAS was > 50 mm.

Median time to onset of symptom relief for all attacks in the ITT population in study 2102 was 2.0 hours for icatibant versus 12.0 hours for tranexamic acid. The corresponding result in study 2103 was 2.5 hours for icatibant versus 4.6 hours for placebo (p= 0.142). Overall, the differences on primary and key secondary efficacy endpoints including response rate 4 hours after start of treatment, median time to relief of each symptom, and median time to almost complete symptom relief, were statistically significant for the tranexamic acid comparison but not for the comparison with placebo.

The CHMP was concerned about efficacy, given the failure to detect a statistically significant difference in the primary endpoint between icatibant and placebo in study 1203 and requested additional statistical analyses. Of these post- hoc analyses the analysis of change in VAS from baseline to 4 and 12 hours post-dose and VAS AUC analyses that considered all changes, not only those of "responder" subjects, were statistically significant in favour of icatibant and were considered by the CHMP to be the most clinically relevant way of analysing the data from the randomised part of the phase III studies.

Additional efficacy data were provided in the response document to the CHMP where 118 patients were treated with icatibant for a total of 597 HAE attacks in the open-label phase of these studies; 537/ 597 (89.9%) of these patients required only a single icatibant injection and 59 (9.9%) became worse after the initial treatment with icatibant. Only 4 patients (in the ITT data set) received 3 injections and none of these had laryngeal symptoms. Of the 59 attacks the worsening symptoms occurred within the first 10 hours for 3 patients, one of whom received rescue medication, one received another dose of icatibant and the other required no additional treatment. Seven of 597 (1.2%) of attacks were treated with additional medication due to investigator judgement without reappearance of symptoms or appearance of new symptoms.

During the open-label phase 61 HAE attacks had laryngeal involvement with symptoms moderate to very severe in 52/61 when icatibant was given. Time to regression of symptoms was less than 1 hour in 38/61 of these cases.

Safety

A total of 163 patients have received at least 1 dose of icatibant by SC injection or orally in clinical trials. The table below (Table 5), extracted from the sponsor's safety summary shows the exposure to SC icatibant in Phase III studies (controlled and open-label extension phases to 31 March 2008).

Table 5. Exposure to Icatibant: Phase III Trials, All Subjects Treated with Icatibant (Controlled and Open-label Extension Phases)

	Number of subjects exposed	**Number of attacks treated with icatibant**	**Number of doses administered**
Number of treated attacks			
1 attack	56	52	54
2 – 5 attacks	66	194	210
6 – 10 attacks	14	109	123
> 10 attacks	17	433	484
Total	**149**	**788**	**871**
			710
Dose of exposure			146
1 x 30 mg SC.	147	710 (90.1%)	15
2 x 30 mg SC.	30	73 (9.3%)	
3 x 30 mg SC	5	5 (0.6%)	

Five patients have received more than 10 doses of icatibant. It was not clear from the sponsor's safety summary whether 5 or 24 patients had received 3 SC doses of icatibant in a 24 hour period.

In the icatibant groups (using 'all subjects on icatibant' in the table), the most frequently reported treatment emergent adverse events (TEAE) by body system were *general disorders and administration site reaction* (17%) with symptoms of injection site reactions including erythema [9%], burning [7%], swelling [4%], warmth [3%], and pruritus [3%]) being the most commonly reported. The next most common TEAE by body system was *nervous system disorders* (10%) with 'headache' (7%) being the most commonly reported event.

Limited safety data in patients given IV doses were available from 2 studies in patients with hepatic impairment. In one study patients received icatibant (or placebo) at 0.15 mg/kg over 24 h for 3 days. This equates to a dose of somewhat less than 15 mg daily for 3 days. In the second study patients received up to 1.2 mg/ kg/day (approximately the current maximum proposed SC dose). No dose related adverse events were reported. Blood pressure was reported as elevated in 3 patients given placebo and 3 given icatibant.

There were no significant effects on vital signs or cardiac conductivity, including QT interval, seen in clinical trials. Assessment of immunogenicity in patients with HAE was conducted using 1120 samples from 152 HAE patients treated with icatibant or comparator (placebo or tranexamic acid) in the Phase III trials studies that were analysed for anti-icatibant antibodies by validated enzyme-linked immunosorbent assay (ELISA)-based assays. Icatibant was not immunogenic on this assessment however immunogenicity following repeated exposure over a prolonged time period has not been examined.

A reversible, dose dependent effect of icatibant on reproductive organs and sexual maturation has been shown in nonclinical studies. Therefore, in human clinical studies FSH and LH were measured. No relevant changes were observed. In addition standard semen analysis was

performed from 6 patients receiving intranasal icatibant 300 µg tds for 2 weeks and from 4 patients given placebo. Though the bioavailability of icatibant administered intranasally is low and the dose was low compared with the up to 90 mg/ day SC proposed, there were no clinically relevant differences in pre-treatment and post-treatment mean values in either treatment group. No conclusions about the effect on icatibant given at the proposed dose on semen can reasonably be made from the above assessment.

The sponsor has attempted to investigate the cause of the injection site reactions. Studies have been performed to evaluate the effect of icatibant on human cutaneous mast cell populations, cutaneous nociceptors in mice, and to evaluate the potential agonistic effects of icatibant on the B2 receptor *in vitro*. These studies indicate that locally very high SC concentrations of icatibant are likely to occur immediately following the injection, which could potentially induce mast cell degranulation and the release of proinflammatory mediators including histamine and tryptase, which are known to cause short-lived inflammatory responses in the skin. However, the burning sensation and/or pain are not readily explained by mast cell activation. It is postulated that during the pathophysiological condition of an acute HAE attack, icatibant might directly activate *C*-nerve fibres that are pre-sensitised by the raised levels of endogenous BK. This might explain the higher reported incidence of injection site burning and/or pain observed in patients with HAE compared to healthy subjects.

There was no evidence for a more systemic pro-inflammatory effect that can be directly attributed to icatibant. However IV infusion 3.2 mg/kg over 1 hour caused local erythema, itching and, a fall in blood pressure around the time of maximum plasma concentration, which may indicate a partial agonistic effect of the drug at this very high dose level.

Post-market data were available following market authorisation of icatibant in the EU. To February 2009 approximately 500 dose units had been supplied. Based on an average of 3 months in the market, with an average of 1.1 doses being used for each attack and 1 attack being treated per patient per month, it was estimated that up to 150 patients may have been treated in the market. One spontaneous serious adverse drug reaction has been reported which was fatal. A 23 year old male patient who experienced massively elevated liver enzyme values (AST, ALT and GLDH) concurrent with the use of unapproved high doses of icatibant when the patient was entering septic shock from which he subsequently died. Approximately one week before the first use of icatibant, the patient was admitted to hospital with a necrotic tonsillar abscess and throat phlegmon. The patient underwent tonsillectomy. Laboratory tests at the time revealed moderately low platelets, mildly raised activated partial thromboplastin time (aPTT) and highly raised C-reactive protein (CRP) as well as respiratory acidosis. Over the next two days the patient had increased swelling in the throat leading to a fasciotomy and tracheotomy. A preliminary diagnosis of hereditary angioedema was made at the time though this could not be confirmed by diagnostic laboratory tests at this time. He was treated with a C1-esterase inhibitor (Berinert) to no effect and a further fasciotomy and throat operation was performed. At this time laboratory tests showed a moderate elevation of serum urea and mild elevations of AST, GLDH and gamma glutamyl transferase (GGT) along with the coagulation abnormalities, including elevated D-dimer, previously noted. There was no response of the throat swelling to additional doses of Berinert, therefore, approximately a week after the patient was first admitted, icatibant was commenced. The initial dose was 30 mg SC which appeared to have a mild effect on the throat oedema, though this proved to be transient. Nevertheless, two further 30 mg SC doses were given within a 12-16 h period. Due to lack of response, further doses of icatibant together with Berinert were given approximately 16 hours after the first dose of icatibant. The next day further elevations in liver enzymes were observed - AST 86 U/L, ALT 42 U/L, GLDH 13 U/L, GGT 378 U/L,

ALP 199 U/L, lactate dehydrogenase (LDH) 491 U/L together with worsening renal function, coagulopathy, and elevations in markers of inflammation. High doses of icatibant (60 mg SC as a single dose on two occasions plus a further standard dose of 30 mg SC were administered over the next day, again to no effect. The patient's condition deteriorated and tests showed massive elevation in liver enzymes (AST 13'780 U/L, ALT 4'477 U/L, GLDH 9'111 U/L) and subsequent computed tomography (CT) scans performed 5, 12, and 20 days after the first use of icatibant revealed progressive multiorgan failure. Despite these findings, the elevated liver enzymes gradually returned to normal up to just prior to the patient's death approximately 4 weeks after being admitted to hospital and 21 days after the first use of icatibant, the coagulopathy and renal failure persisted through to death. A post mortem examination confirmed multi-organ failure secondary to septic shock, considered to be unrelated to the use of icatibant. The EU sponsor noted the unapproved high dose and frequency of dosing of icatibant during the course of the patient's terminal disease, and the fact that HAE could not be confirmed by diagnostic tests. However, there was evidence of impending septic shock prior to the first use of icatibant and the sponsor agreed that a relationship to icatibant is unlikely.

Risk-Benefit Analysis

Acute episodes of HAE are currently managed with oral tranexamic acid and if severe with fresh, frozen plasma. Tranexamic acid may also be taken prophylactically. For patients with frequent episodes, danazol can be given as prophylaxis, though this use is not approved and is associated with significant side-effects.

The Delegate considered that efficacy of single doses of 30 mg SC icatibant in the treatment of acute episodes of HAE has been adequately demonstrated. It is not clear whether there is an additional effect from further doses for a single episode as so few patients have received the proposed maximum of 3 x 30 mg doses in a 24 hour period. The sponsor has also not nominated a maximum number of days per month that icatibant could be given and this has not been adequately explored in clinical trials.

The data on high dose IV icatibant suggests there may be a weak BK agonist effect at high dose. There are also safety concerns about continued or repeated exposure on sex hormones levels and sexual function, immune function and effects on the thymus. Icatibant should not be used in pregnancy unless clearly necessary given the nonclinical study findings.

Conclusion and recommendation

Given the current lack of information on the effects of prolonged, repeated use, the Delegate proposed to approve use of a single 30 mg dose via SC injection under the supervision of a clinician for each acute attack of HAE. This dose could be repeated up to 3 times in 24 h. This limitation should be reviewed once further information about the safety of prolonged, repeated exposure is available.

The Delegate also proposed to restrict use to patients who have not responded adequately to tranexamic acid. Tranexamic acid has a long history of use and a known safety profile on repeated exposure with patients able to take oral doses each day for prolonged periods.

The sponsor should:

1. Provide information on why the FDA issued a non-approvable letter for icatibant and on the type of additional study that the FDA requested.
2. Agree to the revised expiry of 12 months or provide data to justify an alternative expiry date.

3. The carcinogenicity study that is in progress should be included in the periodic safety update reports (PSURs) to be submitted to the TGA when it is completed.
4. Reviews of the EU patient registry should also be included in the PSURs submitted to the TGA.

The sponsor has provided the following pre-ACPM response:

1. Registration status in USA: Although the efficacy and safety profile of Firazyr was demonstrated to be superior to TA in the active comparator trial (FAST-2), FDA considered use of TA to provide supportive data as TA is currently not approved in the US. Therefore, the FDA requested an additional placebo controlled clinical study be conducted in order to provide confirmatory evidence of efficacy and safety for Firazyr.
2. Expiry date: see discussion under VI. Overall Conclusions and Risk/Benefit Assessment, *Quality*.
3. Carcinogenicity studies: The sponsor confirms that the final studies of the ongoing carcinogenicity studies will be submitted to the TGA on completion.
4. Reviews of Patient Registry: Updates will be included in the regularly submitted PSURs.

The advice of the ACPM is requested on:

- whether icatibant should be restricted to patients who have had an inadequate response to oral tranexamic acid and/ or fresh frozen plasma (for each episode);
- whether patients should be able to self-administer icatibant without supervision of a clinician.
- whether the proposed limitations on dosing are reasonable given the limited data on the effects of higher daily dosing, dose intervals and long term use or whether an alternative regimen would be preferred.

ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission from Shire Australia Pty Ltd to register a new chemical entity icatibant (as acetate) (FIRAZYR) solution for injection pre-filled syringe 30 mg / 3 mL for the indication:

> *FIRAZYR is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency).*

In making this recommendation, the ACPM considered the risks associated with use in the proposed indication, including the possible attenuation of the cardioprotective effect of BK and the potential for possible immune, stroke, endocrine and reproductive system deficits. In view of the acute severity of the condition, the ACPM considered that the evidence of the safety and efficacy of FIRAZYR has been sufficiently demonstrated. Again in considering the available evidence, clinical context and international experience, the ACPM advised that first line therapy was an appropriate indication.

The ACPM noted the lack of sufficient evidence on the frequency of administration in any 24 hour period and maximum dosages per month and therefore supports the Delegate in the proposed maximum of 3 x 30 mg doses per 24 hours. The ACPM advised that it was clinically appropriate in view of the supporting safety data to allow patient self administration.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Firazyr solution for injection containing icatibant 30 mg/ 3 mL (as acetate) in a pre-filled syringe, indicated for:

> "Symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency)."

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Firazyr®

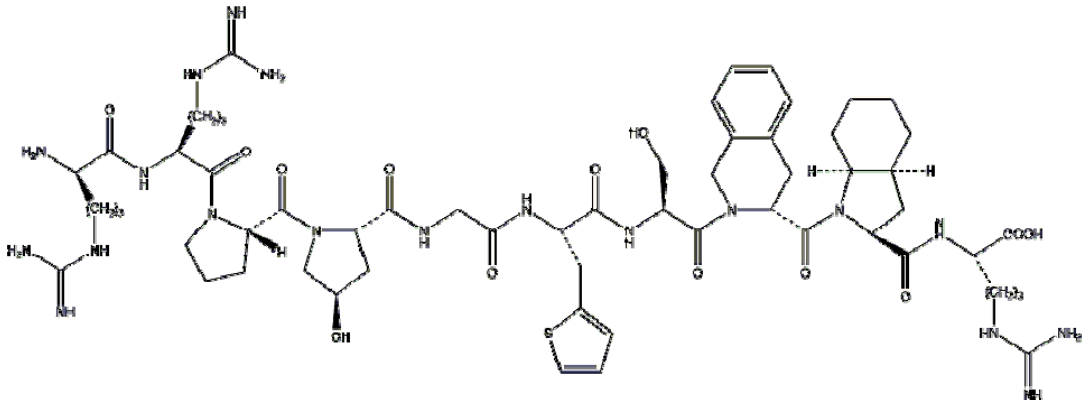
PRODUCT INFORMATION

NAME OF THE MEDICINE
Icatibant acetate

Chemical Name of icatibant**:** 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.

Icatibant is isolated as the acetate salt, containing approximately 1-4 equivalents of acetic acid.

Chemical structure of icatibant:



CAS number of icatibant**:** 130308-48-4
Chemical formula of icatibant: $C_{59}H_{89}N_{19}O_{13}S$
Molecular weight of icatibant: 1304.55
Pharmacotherapeutic group: Other cardiac preparations ATC Code: C01EB19

DESCRIPTION
Icatibant 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 non-proteinogenic amino acids. Bradykinin has been shown to be elevated during hereditary angioedema attacks and is responsible for oedema formation.

Firazyr (icatibant acetate) is supplied as sterile solution for injection in single use pre-filled syringes. The solution is clear and colourless. Each 3 mL pre-filled syringe contains icatibant acetate equivalent to 30 mg icatibant. Each mL of the solution contains 10 mg of icatibant.

Firazyr contains the following excipients: acetic acid glacial, sodium hydroxide, sodium chloride and water for injections. The pH of the injection is approximately 5.5.

PHARMACOLOGY

Pharmacodynamic properties

Hereditary angioedema (HAE), an autosomal dominant disease, is caused by an absence or dysfunction of C1-esterase-inhibitor. HAE attacks are accompanied by an increased release of bradykinin, which is the key mediator in the development of the clinical symptoms.

HAE manifests as intermittent attacks of subcutaneous and/or sub mucosal oedema involving the upper respiratory tract, the skin and the gastrointestinal tract. An attack usually lasts between 2 to 5 days.

Icatibant is a selective competitive antagonist at the B2 receptor. In HAE increased bradykinin concentrations are the key mediator in the development of the clinical symptoms.

In healthy young subjects, icatibant administered in doses of 0.8 mg/kg over 4 hours; 1.5 mg/kg/day or 0.15 mg/kg/day for 3 days, development of bradykinin-induced hypotension, vasodilatation and reflex tachycardia was prevented. Icatibant was shown to be a competitive antagonist when the bradykinin challenge dose was increased 4-fold.

Pharmacokinetic properties

The pharmacokinetics of icatibant has been extensively characterised by studies using both intravenous and subcutaneous administration to healthy volunteers and patients. The pharmacokinetic profile of icatibant in patients with HAE is similar to that in healthy volunteers.

Absorption
Following subcutaneous administration, the absolute bioavailability of icatibant is 97%. The time to maximum concentration is approximately 0.5 hours.

Distribution
Icatibant volume of distribution (Vss) is about 20-25 L. Plasma protein binding is 44%.

Elimination
Icatibant is mainly eliminated by metabolism with less than 10% of the dose eliminated in the urine as unchanged drug. Clearance is about 15-20 L/h and independent of dose. The terminal half-life is about 1-2 hours.

Metabolism
Icatibant is extensively metabolised by proteolytic enzymes to inactive metabolites that are primarily excreted in the urine.

In vitro studies have confirmed that icatibant is not degraded by oxidative metabolic pathways and is not an inhibitor of major cytochrome P450 (CYP) isoenzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) and is not an inducer of CYP 1A2 and 3A4.

Special populations

Data suggest an age-related decline in clearance resulting in about 50-60% higher exposure in the elderly (75-80 years) compared to a patient aged 40 years. Data suggest that gender and weight do not have a significant influence on icatibant pharmacokinetics.

Limited data suggest that icatibant exposure is not influenced by hepatic or renal impairment. The influence of race on icatibant pharmacokinetics has not been evaluated. There are no pharmacokinetic data in children.

CLINICAL TRIALS

Efficacy data were obtained from an initial open-label Phase II study and from two randomised, double-blind controlled multi-centre Phase III studies (one with oral tranexamic acid as the comparator and one placebo controlled). The pivotal Phase III studies were otherwise identical in design. A total of 130 patients were randomised to receive either a 30 mg dose of icatibant (63 patients) or comparator (either tranexamic acid -38 patients or placebo -29 patients). Subsequent episodes of HAE were treated in an open label extension (OLE). Patients with symptoms of laryngeal angioedema received open-label treatment with icatibant.

In the Phase III trials, the primary efficacy endpoint was median time to onset of symptom relief using a visual analogue scale (VAS) defined as absolute reduction from pre-treatment VAS of ≥20mm if the baseline VAS was 30-50mm or ≥30mm if the baseline VAS was >50mm. The FAST-2 study (JE049 #2102) demonstrated that the median time to onset of symptom relief was significantly shorter in the icatibant group than in the tranexamic acid group (2.0 hours compared to 12.0 hours), while in the FAST-1 study (JE049 #2103) comparing icatibant with placebo, the median time to onset of symptom relief was shorter with icatibant than placebo (2.5 hours compared to 4.6 hours) but a statistically significant difference was not achieved.
Additional analyses were carried out with regard to changes from baseline to 4 hours and 12 hours in VAS scores. These direct evaluations of the VAS represent a more accurate clinical picture of the course of the HAE attack. The results show that for both studies, there was a substantial and consistent reduction in the score at 4 hours and 12 hours post-dose in the icatibant groups compared to the comparator groups, and the treatment differences in VAS changes from baseline to 4 hours and 12 hours were statistically significant ($p=0.002$ and $p=0.046$ for 4 hours and 12 hours in study JE049 #2103 and $p<0.001$ for 4 hours and 12 hours in study JE049 #2102).

Table 1 shows the results for the two pivotal trials.

Table 1: Controlled Clinical Study of FIRAZYR vs Tranexamic acid or Placebo:
Efficacy Results

Study JE049 #2102			**Study JE049 #2103**		
	Icatibant	Tranex-amic acid		Icatibant	Placebo
Number of subjects in ITT Population	36	38	Number of subjects in ITT Population	27	29
Baseline VAS(mm)	63.7	61.5	Baseline VAS(mm)	69.3	67.7
Change from baseline to 4 hours	-41.6	-14.6	Change from baseline to 4 hours	-44.6	-23.5

Table 1 cont'd: Controlled Clinical Study of FIRAZYR vs Tranexamic acid or Placebo:
Efficacy Results

Study 2102			Study 2103		
	Icatibant	Tranex-amic acid		Icatibant	Placebo
Difference between treatments (95% CI, p-value)	-27.8 (-39.4, -16.2) p < 0.001		Difference between treatments (95% CI, p-value)	-22.3 (-36.1, -9.3) p = 0.002	
Change from baseline to 12 hours	-54.0	-30.3	Change from baseline to 12 hours	-53.9	-41.0
Difference between treatments (95% CI, p-value)	-24.1 (-33.6, -14.6) p < 0.001		Difference between treatments (95% CI, p-value)	-14.0 (-27.7, -0.3) p = 0.046	
Median time to onset of symptom relief (hr)			Median time to onset of symptom relief (hr)		
All episodes (N = 74)	2.0	12.0	All episodes (N = 56)	2.5	4.6
Response rate (%, CI) at 4 hr after start of treatment			Response rate (%, CI) at 4 hr after start of treatment		
All episodes (N = 74)	80.0 (63.1, 91.6)	30.6 (16.3, 48.1)	All episodes (N = 56)	66.7 (46.0, 83.5)	46.4 (27.5, 66.1)
Median time to onset of symptom relief: all symptoms (hr):			Median time to onset of symptom relief: all symptoms (hr):		
Abdominal pain	1.6	3.5	Abdominal pain	2.0	3.3
Skin swelling	2.6	18.1	Skin swelling	3.1	10.2
Skin pain	1.5	12.0	Skin pain	1.6	9.0
Median time to almost complete symptom relief (hr)			Median time to almost complete symptom relief (hr)		
All episodes (N = 74)	10.0	51.0	All episodes (N = 56)	8.5	23.3
Median time to regression of symptoms, by patient (hr)			Median time to regression of symptoms, by patient (hr)		
All episodes (N = 74)	0.8	7.9	All episodes (N = 56)	0.8	16.9
Median time to overall patient improvement, by physician (hr)			Median time to overall patient improvement, by physician (hr)		
All episodes (N = 74)	1.5	6.9	All episodes (N = 56)	1.0	5.7

One hundred and twenty six patients were treated in the OLE phase for a total of 714 separate attacks. Efficacy results, available for the first 118 patients showed similar efficacy to those seen in the controlled phase of the studies. In the OLE phase, up to three doses of icatibant were permitted. The majority of attacks (89.3% and 90.9%, respectively) in both studies required only a single dose of icatibant. Thirty patients required two doses and five patients required three doses.

A total of 36 patients were treated for a total of 61 attacks of HAE affecting the larynx. The results were again similar to patients with non-laryngeal attacks of HAE with a median time to start of regression of symptoms of 0.6 - 1.0 hours (controlled phase).

INDICATIONS

Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults (with C1-esterase-inhibitor deficiency)

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

PRECAUTIONS

Ischaemic heart disease

Icatibant did not elicit any cardiac conduction change *in vitro* (hERG channel) or *in vivo* in normal dogs or in .dogs undergoing physical exertion. Icatibant has been shown to aggravate induced cardiac ischaemia in several non-clinical models, including a study in dogs involving coronary ligation, probably as a result of left ventricular failure. Bradykinin and the B2 receptors have been shown to have cardioprotective properties in animals, which were attenuated by icatibant.

Under ischaemic conditions, a deterioration of cardiac function and a decrease in coronary blood flow could theoretically arise from antagonism of the B2 receptor.

Caution should therefore be observed in the administration of Firazyr to patients with acute ischaemic heart disease or unstable angina pectoris.

Stroke

There is a theoretical possibility that icatibant may attenuate the positive late phase neuroprotective effects of bradykinin. Accordingly, caution should be observed in the administration of icatibant to patients in the weeks following a stroke.

Effects on fertility

In immature rats and dogs, repeated use of icatibant reversibly delayed sexual maturation. Reversible changes were also observed in sexually mature animals. As Firazyr is indicated for acute use in HAE attacks, the clinical impact of these changes is unknown.

Icatibant had no effect on the fertility of male mice. In a fertility study in SD rats, icatibant at 10 mg/kg/day had no effect on male fertility or on the male reproductive organs. However, in Wistar rats icatibant at 3 mg/kg/day (30-fold the anticipated clinical exposure in young men receiving a maximum of 240 mg per month icatibant, based on AUC) resulted in decreased weights of the prostate, testes and epididymides, and bilateral hvpospermia occurred at 10 mg/kg/day.

Icatibant decreased sperm number, motility and velocity in dogs at 1 mg/kg/day, with no sperm motility at 10 mg/kg/day respectively 3- and 30-fold, the anticipated clinical exposure in young men receiving a maximum of 240 mg per month icatibant, based on AUC). There were marked decreases in testosterone levels in Wistar rats and dogs at 3 mg/kg/day (respectively 30- and 50-fold the anticipated clinical exposure in young men receiving a maximum of 240 mg per month icatibant, based on AUC).

The changes in the weight of the uterus and ovaries were completely reversed over the 4 week recovery period in rats and dogs.

Use in pregnancy
Category C
For icatibant, no clinical data on exposed pregnancies are available.

Bradykinin B2 receptors have been shown to be present in tissues of the female reproductive system in animals and humans, and are likely to be involved in implantation and parturition.

There was an increase in pre-implantation loss in female rats treated with 10 mg/kg/day and post-implantation loss in rabbits treated with 8.3 mg/kg/day icatibant SC (respectively -30- and 50-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC).

There was a decrease in uterus and/or ovarian weight and histopathological changes in the female reproductive tissues in mice, rats and dogs at 25, 10 and 1 mg/kg/day icatibant respectively (50-, 30- and 3-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC). Luteinising hormone levels were lower in rats at 3 mg/kg/day and follicular stimulating hormone levels lower in dogs at 3 mg/kg twice weekly (respectively 30- and 15-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC). The changes in the weight of the uterus and ovaries were completely reversed over the 4 week recovery period in rats and dogs.

Icatibant and/or its metabolites crossed the placenta in rats. Icatibant was not teratogenic when administered by subcutaneous injection during embryonic and fetal development in rats or rabbits (up to 5-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC) Icatibant exhibited a tocolytic effect in the rat resulting in delayed parturition, with increased fetal distress and perinatal death at 10 mg/kg/day (30-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC). The length of gestation was also increased in rats at doses of icatibant 3-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC. There were no observed adverse effects of icatibant administration during pregnancy and lactation on pup development in rats.

Therefore, Firazyr should be used during pregnancy only if the potential benefit justifies the potential risk for the fetus (e.g. for treatment of potentially life threatening laryngeal attacks).

Use in lactation
Icatibant is excreted in the milk of lactating rats at concentrations similar to those in maternal blood. No adverse effects were detected in the post-natal development of rat pups.

Mascularisation or atrophy of the female mammary glands occurred in rats and dogs at 3 and 10 mg/kg/day respectively (9- and 75-fold the anticipated clinical exposure in young women receiving a maximum of 240 mg per month icatibant, based on AUC).

It is unknown whether icatibant is excreted in human breast milk but it is recommended that breastfeeding women who take Firazyr should not breastfeed for

12 hours after treatment. If breastfeeding is to be resumed, then milk should be expressed and discarded for the first 12 hours after treatment.

Paediatric Use
There is no experience of icatibant use in children.

In immature animals repeated dosing of icatibant reversibly delayed sexual maturation in males and females (See section Effects on fertility).

Use in the elderly
Limited information is available on patients older than 65 years of age. Elderly patients have been shown to have increased systemic exposure to icatibant. The relevance of this to the safety of Firazyr is unknown (see section Pharmacokinetic properties).

Carcinogenicity
Long-term studies to determine the carcinogenic potential of icatibant have not been conducted to date.

Genotoxicity
In a standard battery of *in vitro* and *in vivo* tests icatibant was not genotoxic.

Interaction with other medicines
Pharmacokinetic drug interactions involving CYP450 are not expected (see section Pharmacokinetic properties)

Co-administration of Firazyr with angiotensin-converting enzyme (ACE) inhibitors has not been studied. There is a theoretical risk that icatibant may antagonise the effects of ACE inhibitors. Patients with HAE should not be taking these drugs as they can induce and exacerbate HAE attacks.

Effects on ability to drive and use machines
Firazyr has minor or moderate influence on the ability to drive and use machines. Fatigue, lethargy, tiredness, somnolence, and dizziness have been reported uncommonly following the use of Firazyr. These symptoms may occur as a result of an attack of HAE. However, a causal relationship to the use of Firazyr cannot be excluded. Patients should be advised not to drive and use machines if they feel tired or dizzy.

ADVERSE EFFECTS
The safety of icatibant has been established in 1,273 subjects treated with various doses, regimens and routes of administration during Phase I-III studies in various indications.

Sixty three HAE patients received icatibant in two Phase III trials for treatment of an attack in the controlled phase and 126 patients were treated in the open-label phase.

Almost all subjects who were treated with subcutaneous icatibant in clinical trials developed reactions at the site of injection including erythema, swelling, warm sensation, burning, itching and/or cutaneous pain. These reactions were generally mild in severity, transient, and resolved without further intervention.

Table 2 lists treatment related adverse reactions reported with Firazyr during the Phase III trials. Frequency is defined as: very common (≥1/10), common (≥1/100, <1/10) and uncommon (≥1/1,000 to <1/100).

Table 2: Adverse reactions associated with Firazyr

	Adverse reactions		
	Very common	**Common**	**Uncommon**
Gastrointestinal disorders			Nausea, vomiting
General disorders and administration site conditions	Injections site reactions (such as skin irritation, swelling, pain, itchiness, erythema, burning sensation)		Asthenia, fatigue, pyrexia
Infections and infestations			Herpes zoster, pharyngitis
Injury, poisoning and procedural complications			Contusion
Investigations		Blood creatinine phosphokinase increased, prothrombin time prolonged	Weight increased, blood glucose increased, liver function test abnormal
Metabolism and nutrition disorders			Hyperuricaemia, hyperglycaemia
Musculoskeletal and connective tissue disorders			Muscle spasm
Nervous system disorders		Dizziness, headache	
Renal and urinary disorders			Proteinuria
Respiratory, thoracic and mediastinal disorders			Asthma, cough, nasal congestion
Skin and subcutaneous tissue disorders		Rash, pruritus, erythema	Generalised urticaria
Vascular disorders			Hot flush

Table 3 provides the incidence of all adverse events (regardless of relationship to treatment) reported in two or more patients in the controlled phase of the Phase III studies in patients treated with Firazyr, placebo or tranexamic acid.

Table 3: Incidence of adverse events reported in two or more patients in the controlled phase of the Phase III studies

Adverse event	**Firazyr (%)** N=63	**Placebo** (%) N=29	**Tranexamic acid** (%) N=38
Total patients reporting adverse events	31 (49.2)	19 (65.5)	16 (42.1)
Congenital, familial and genetic disorders			
Hereditary angioedema*	14 (22.2)	5 (17.2)	6 (15.8)
Gastrointestinal disorders			
Nausea	0	3 (10.3)	0
General disorders and administration site conditions			
Injection site pain	2 (3.2)	0	0
Inection site reaction	2 (3.2)	0	0
Pyrexia	2 (3.2)	0	0
Infections and infestations			
Gastroenteritis	2 (3.2)	0	0
Nasopharyngitis	3 (4.8)	0	3 (7.9)
Nervous system disorders			
Dizziness	2 (3.2)	1 (3.4)	0
Headache	2 (3.2)	2 (6.9)	2 (5.3)
Respiratory, thoracic and mediastinal Disorders			
Nasal congestion	2 (3.2)	0	0
Skin and subcutaneous tissue disorders			
Pruritus	0	2 (6.9)	0
Rash	2 (3.2)	0	0

* HAE attacks were reported as adverse reactions, however, based on time of occurrence, the majority were recurrent attacks are not related to treatment with Firazyr.

DOSAGE AND ADMINISTRATION

Firazyr is intended for subcutaneous injection. It contains no antimicrobial agent and should be used immediately. Firazyr is for single use in one patient only. Any residue should be discarded.

The solution should be clear and colourless and free from visible particles.

Firazyr is intended for use under the guidance and supervision of a doctor. Patients may self inject Firazyr if their doctor determines, following adequate training of the patient, that it is appropriate. Patients who self inject should be advised to seek urgent medical attention if there is no evidence of resolution of the HAE attack within 2 hours of self-injection, or immediately should the HAE attack progress to involve the face, lips or pharyngolaryngeal area. Patients whose initial HAE attack involves the face, lips or pharyngolaryngeal area should seek urgent medical attention, regardless of their response to Firazyr following self-injection.

The recommended dose of Firazyr is one subcutaneous injection of 30 mg preferably in the abdominal area, for the treatment of a HAE attack. Injection should be given slowly due to the large volume to be administered (3 mL).

Patients with laryngeal attacks need to be carefully managed in an appropriate medical institution after injection until the physician considers discharge to be safe.

In the majority of cases a single injection of Firazyr is sufficient to treat an attack. In case of insufficient relief or recurrence of symptoms, a second injection of Firazyr can

be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of Firazyr can be administered after a further 6 hours. No more than 3 injections of Firazyr should be administered in a 24-hour period.

In clinical trials, not more than 8 injections of Firazyr per month have been administered.

Hepatic impairment
No dosage adjustment is required in patients with hepatic impairment.

Renal impairment
No dosage adjustment is required in patients with renal impairment.

OVERDOSAGE
No clinical information on overdose is available.

A dose of 3.2 mg/kg intravenously (approximately 8 times the therapeutic dose) caused transient erythema, itching or hypotension in healthy subjects. No therapeutic intervention was necessary.

In case of overdose, immediately contact the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS
Firazyr is supplied as 30 mg icatibant (as acetate) in 3 mL in one pre-filled syringe (type I glass) with plunger stopper (bromobutyl coated with fluorocarbon polymer). Solution is clear and colourless and free from visible particles. A hypodermic needle (25 G; 16 mm) is included in the package.

Store Firazyr below 25°C. Do not freeze.

List of excipients:
Sodium chloride
Acetic acid, glacial (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

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POISONS SCHEDULE OF THE MEDICINE
S4

Date of TGA approval: 7 June 2010

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