CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022150Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-150, SDN 21
Submission Date	February 25, 2011
Brand Name	Firazyr®
Generic Name	*Icatibant*
Primary Reviewer	Partha Roy, Ph.D.
Team Leader (Acting)	Suresh Doddapenani, Ph.D.
Pharmacometric (PM) Reviewer	Atul Bhattaram, Ph.D.
PM Team Leader	Yaning Wang, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Pulmonary, Allergy & Rheumatology Products
Sponsor	Shire Human Genetic Therapies
Submission Type	Resubmission - Class 2
Dosage Form	Solution for Injection
Proposed Indication	Treatment of acute attacks of Hereditary Angioedema (HAE) in adults ≥18 years.

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1 EXECUTIVE SUMMARY

1.1 Regulatory Background

A New Drug Application (NDA) for Icatibant (NDA 22-150) was originally submitted to the Food and Drug Administration (FDA) by Jerini AG on October 22, 2007. Following completion of the review, the FDA issued a *Not Approvable* Action (now referred to as "Complete Response") letter on April 23, 2008. The clinical program did not provide substantial evidence that icatibant is sufficiently safe and effective for the proposed indication primarily due to a failed pivotal Phase 3 trial (JE049-2103). In addition, there were two issues which complicated the interpretation of the clinical efficacy data: 1) uncertain efficacy of the active comparator, tranexamic acid for the proposed indication and 2) concerns regarding the validity of the primary endpoint (time to onset of symptom relief using the Visual Analog Scale) used in the pivotal clinical trials. The Agency also added that without substantial evidence of efficacy of the proposed dose, it is not possible to evaluate appropriate safety.

From a clinical pharmacology perspective, the original submission was deemed acceptable; however following two issues were communicated to the sponsor in the NDA action letter:

1. "Data from study JE049-1103 indicate that both age and gender have effects on icatibant pharmacokinetics. Address the scientific basis for these large differences in systemic exposure and possible role of proteolytic enzymes. Also provide justification for proposing the same dose regardless of age and gender."
2. "Dose selection should be further defined in sufficient patients based on the clinical endpoint or other biomarkers that are validated to be related to the clinical endpoint."

The sponsor had several interactions with the Agency following the NDA action, namely Type C-End of Review meeting on December 15, 2008, No-Agreement Letter for a Special Protocol Assessment on April 2, 2009, Clinical Comments in response to Request for Clinical Protocol Review (JE049-3101) on April 13, 2009 and Type A (teleconference) meeting on June 2, 2009. The sponsor stated that in this resubmission, they have incorporated all the key FDA recommendations for the design and conduct of HGT-FIR-054 (the new Phase 3 study), and JE049-3101 (a safety/local tolerability study), and paid close attention to Agency's overall feedback while preparing this resubmission. In this review cycle, the new clinical pharmacology data submitted in this complete response is reviewed.

1.2 Summary of Clinical Pharmacology

Age and Gender Effects on Icatibant Pharmacokinetics (PK)

In the original NDA, the sponsor noted both age and gender effects on PK of icatibant as clearly evidenced by systemic exposure data from study JE049-1103 in young male, elderly male, young female and elderly female subjects. Following single-dose subcutaneous (SC) administration of 30 mg icatibant, elderly males showed 2.3-fold higher AUC0–∞ compared to young males while, elderly females showed 1.6-fold higher AUC0–∞ compared to young females. However, only minor differences (~12-14%) between Cmax of gender–matched elderly and young subjects were observed. In addition to the age effect, gender effect on PK was also observed. Young females demonstrated about 2.3-fold higher AUC0–∞ and Cmax compared to young males. For elderly

females, AUC0–∞ was about 1.8-fold and Cmax 2.2-fold higher than for elderly males. Although the interpretation of study data is limited due to a small number of subjects (n = 6) per treatment group, the above data unequivocally indicated a general trend towards higher systemic exposure in females compared to males and in elderly subjects compared to young subjects. Based on the above, the sponsor was asked to address the scientific basis for these large differences in systemic exposure and to provide justification for proposing the same dose regardless of age and gender.

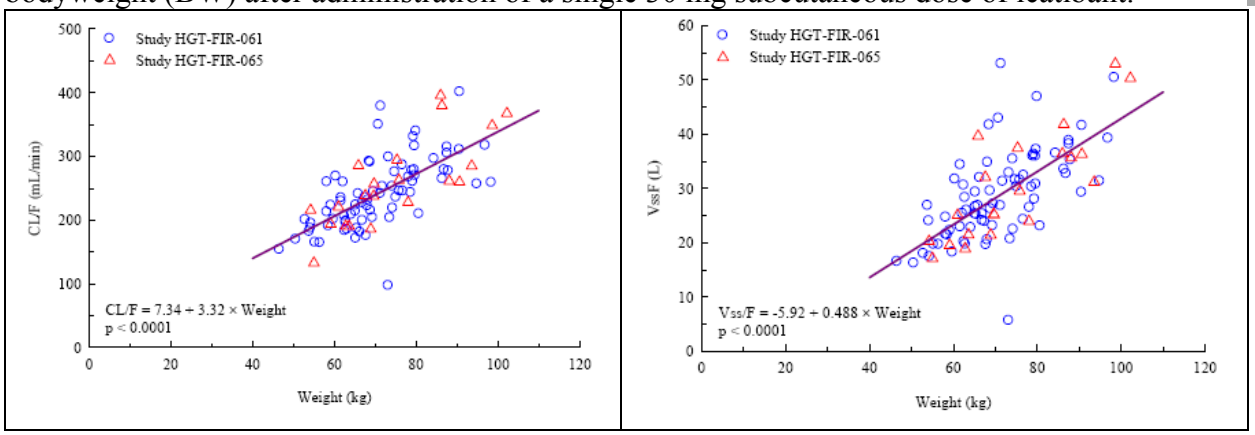
In response to age and gender issues in the non-approval letter, the sponsor provided two sets of analyses in this resubmission:

1) A post-hoc analyses of the effects of demographic variables (age, gender, bodyweight etc) on the PK of icatibant and metabolites M1 and M2 based on the two newly conducted PK trials with rich sampling (HGT-FIR-061 and HGT-FIR-065). The two studies combined had 51 males and 52 females for a total of 103 healthy subjects with an average bodyweights of 79 kg and 65 kg for males and females, respectively.

2) A population PK report (JE049-5120) pooling data from seven different clinical trials evaluating the influence of age and gender on PK of icatibant.

Clearance (CL/F) and apparent volume of distribution (Vss/F) of icatibant are found to be significantly correlated with bodyweight (BW) indicating that both clearance and volume of distribution increase as BW increases as has been shown in Figure 1 based on data from studies HGT-FIR-061 and HGT-FIR-065.

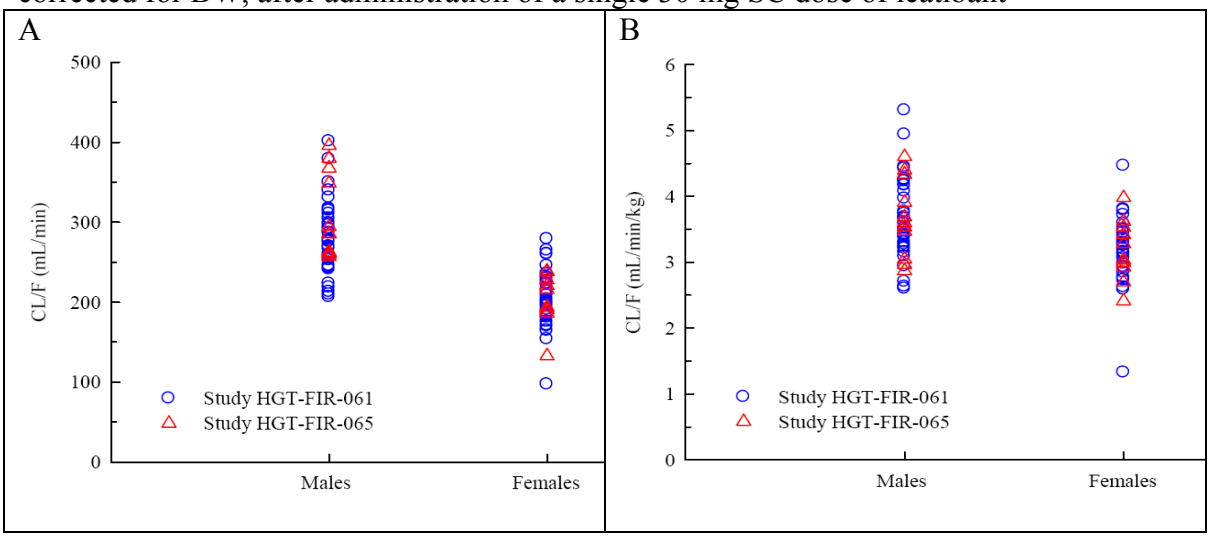
Figure 1. Relationship between icatibant clearance (CL/F), volume of distribution (Vss/F) and bodyweight (BW) after administration of a single 30 mg subcutaneous dose of icatibant.



Since females generally have lower BWs compared to males, therefore females, on average, are expected to exhibit lower clearance values (Figure 2A) resulting in higher systemic exposure compared to males. Correction for body weight results in more comparable ranges of CL/F values for males and females (Figure 2B). Taking into account the overall magnitude and variability in parameter estimates, the sponsor stated that these are not expected to be of any clinical significance. Since a flat dose of 30 mg has been proposed for icatibant, subjects with markedly different BWs will exhibit large inter-individual differences in systemic drug exposure

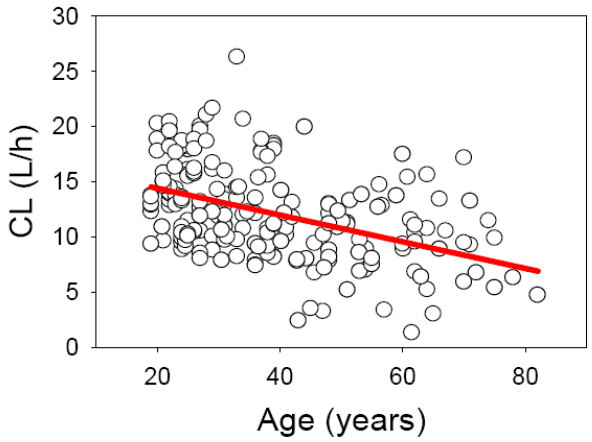
irrespective of gender. So, this is not a true gender effect rather a BW effect on the PK of icatibant. In light of females having lower BW and hence higher systemic exposure from the same absolute dose compared to males, any dose adjustment based on gender would be dependent on any differences seen in the the efficacy and/or safety aspects between males and females in the clnical database (see Clinical review by Dr. Brian Porter for details on this).

Figure 2. Relationship between icatibant CL/F and gender, A) uncorrected for BW and B) corrected for BW, after administration of a single 30 mg SC dose of icatibant



The age range for the two new studies was only limited to 18-50 years, hence, effect of age on icatibant PK can not be fully elucidated over a wider age range that also includes elderly subjects. To evaluate age effect on icatibant PK, it is more appropriate to rely on population PK analysis as data was pooled from seven different trials representing a total of 98 male and 42 female subjects with a broad age range of 19 to 82 years. Icatibant clearance exhibits a decreasing trend with increasing age (Figure 3). Older subjects tend to exhibit lower clearance compared to younger subjects and thereby higher systemic exposure. For details on population PK data analysis, refer to the Pharmacometric Review by Dr. Atul Bhattaram (Appendix 4.2).

Figure 3. Relationship between icatibant clearance and Age



Dose Selection
No formal dose-ranging study based on clinical efficacy measure was performed, and given the orphan status of the proposed indication, this was not unusual.

Dose selection was based on a number of clinical pharmacology studies and PK/PD modeling using bradykinin challenge in healthy subjects. For details, refer to Clinical Pharmacology review by Drs. Partha Roy and Nitin Mehrotra dated 03/21/2008. The phase 3 dose was selected based on expected systemic bradykinin concentration anticipated during an HAE attack and levels of icatibant needed to completely antagonize the bradykinin effects. Although the biomarker-based PK/PD approach may seem reasonable from a mechanistic level and such modeling data suggest that a higher dose is unlikely to increase pharmacodynamic effect substantially, it is unclear how representative the modeling is in HAE patients. The clinical pharmacology review in the first cycle concluded that these concerns may have contributed to the failed placebo-controlled Phase 3 clinical trial JE049-2103 (FAST-1) submitted with the original NDA. The sponsor now has conducted a new Phase 3 study, HGT-FIR-054 (FAST-3), with placebo-controlled trial design similar to FAST-1, with the new primary efficacy endpoint of time to onset of symptom relief based on a composite VAS rating (denoted as VAS-3) and presumably has been able to demonstrate statistically significant decrease in time to onset of primary symptom relief in the icatibant group compared to placebo. Therefore, the sponsor reasonably argues that the 30 mg SC dose has been rigorously evaluated in three independent phase III clinical trials including the recently completed placebo-controlled trial, HGT-FIR-054 with which the sponsor believes that they have been able to establish replicate efficacy results in support of the proposed claim. Taken together, these clinical data appear to demonstrate that icatibant at the 30 mg SC dose is a clinically safe and effective treatment for acute angioedema attacks and this reviewer agrees that further dose exploration is not necessary, pending review of efficacy and safety data of icatibant.

TQT (HGT-FIR-061) Review:

A Thorough QT (TQT) study (Study HGT-FIR-061) was conducted to determine whether SC administration of icatibant at the clinical dose (30 mg) and the supra-therapeutic dose (90 mg) has the potential to cause QT interval prolongation in healthy adults. This was a randomized, 4-period, placebo- and active-controlled (400 mg moxifloxacin) single-center Phase I study with crossover design in 72 healthy subjects. No significant QTc prolongation effect of icatibant (30 and 90 mg) was detected in this TQT study. The largest upper bounds of the two-sided 90% confidence interval for the mean differences between icatibant (30 and 90 mg) and placebo of QTcI were below 10 ms, the threshold for regulatory concern. The dose of 90 mg is adequate to represent the highest possible exposure expected to be encountered in the clinic. Refer to the QT-IRT review of study HGT-FIR-061 by Dr. Moh Jee Ng, dated 05/26/2011 for additional details as well as the proposed label language describing QT/QTc findings.

2 QUESTION BASED REVIEW

2.1 General Attributes

Refer to Clinical Pharmacology review by Drs. Partha Roy and Nitin Mehrotra dated 03/21/2008 for general attributes and proposed mechanism of action, indication, dosage and route of administration.

2.2 General Clinical Pharmacology

2.2.1 What is known about the single and multiple dose pharmacokinetics of icatibant solution for injection?

Refer to Clinical Pharmacology review of original submission by Drs. Partha Roy and Nitin Mehrotra dated 03/21/2008 from the first cycle of review for pharmacokinetic characterization of icatibant. The sponsor conducted two additional trials (HGT-FIR-061 and HGT-FIR-065) in healthy subjects after the initial NDA submission.

The PK data obtained from these trials are consistent with PK results previously obtained. HGT-FIR-061 is the TQT study and is described in detail in the QT-IRT review by Dr. Moh Jee Ng, dated 05/26/2011. Briefly, icatibant exhibited nearly dose-proportional PK across SC doses of 30 to 90 mg. The mean $t_{1/2}$ was slightly longer for the 90 mg dose compared to 30 mg dose (2 hr vs. 1.5 hr). Mean clearance (CL/F, uncorrected for bioavailability) ranged from 230 to 241 mL/min across dose groups and mean volume of distribution at steady state (Vss/F, uncorrected for bioavailability) was approximately 30 L.

Study HGT-FIR-065 was designed to characterize and substantiate previously observed PK characteristics of icatibant after SC administration of three individual 30 mg doses each given six hours apart. Systemic exposure, as measured by Cmax and AUC0-6hr, was similar for all three doses, indicating no accumulation, consistent with the 6-hour dosing interval, which is essentially 6-fold longer than the mean $t_{1/2}$ value of ~1 hr for icatibant.

2.2.2 What was the rationale for route of administration and dose regimen selection of icatibant for evaluation of clinical efficacy and safety?

No formal dose-ranging study based on clinical efficacy measure was performed. Icatibant dose selection was based on a biomarker (bradykinin challenge) rather than a clinical endpoint and/or clinical surrogate.

Icatibant is a competitive antagonist of the bradykinin type 2 (B2) receptor. It is hypothesized that inhibition of endogenous bradykinin (BK) is required to control key symptoms elicited by overproduction of BK during an acute angioedema attack. Therefore, an exogenous IV BK

challenge was used as a pharmacological tool in healthy subjects to investigate the dose range and regimen for later trials. It was hypothesized that near complete BK antagonism would be required to establish the optimal dose, dose regimen, and time window for a clinically relevant inhibition. The phase 3 dose was selected based on expected systemic bradykinin concentration anticipated during an HAE attack and levels of icatibant needed to completely antagonize the bradykinin effects.

Although the biomarker-based PK/PD approach may seem reasonable from a mechanistic level and such modeling data suggest that a higher dose is unlikely to increase pharmacodynamic effect substantially, it is unclear how representative the modeling is in HAE patients due to: 1) uncertainty about the relationship between the biomarker and the clinical endpoint; and 2) larger variability in the clinical endpoint than the biomarker, which may have led to an underpowered study (FAST-1). Subsequently, the sponsor conducted a new Phase 3 study, HGT-FIR-054 (FAST-3), which enrolled a greater number of patients (n = 88) compared to FAST-1 (n = 55). FAST-3 is also a placebo-controlled trial similar to FAST-1, with the new primary efficacy endpoint of time to onset of symptom relief based on a composite VAS rating (denoted as VAS-3) and apparently has been able to demonstrate statistically significant decrease in time to onset of primary symptom relief in the icatibant group compared to placebo. The sponsor argues that the 30 mg SC dose has been rigorously evaluated in three independent phase 3 clinical trials including the recently completed placebo-controlled trial, FAST-3 with which the sponsor believes that they have been able to establish replicate efficacy results in support of the proposed dose and the proposed claim. Taken together, this reviewer agrees with the sponsor's rationale for dose selection and hence further dose exploration is not necessary, pending review of the clinical efficacy and safety data for icatibant. Moreover, due to injection site reactions with higher dose/concentration of icatibant solution, raising the dose beyond 30 mg with the proposed formulation and route of administration may not be practically feasible. For details of population PK/PD and simulation studies in support of dose selection, refer to the Clinical Pharmacology / Pharmacometric first-cycle review by Drs. Partha Roy and Nitin Mehrotra dated 3/21/2008.

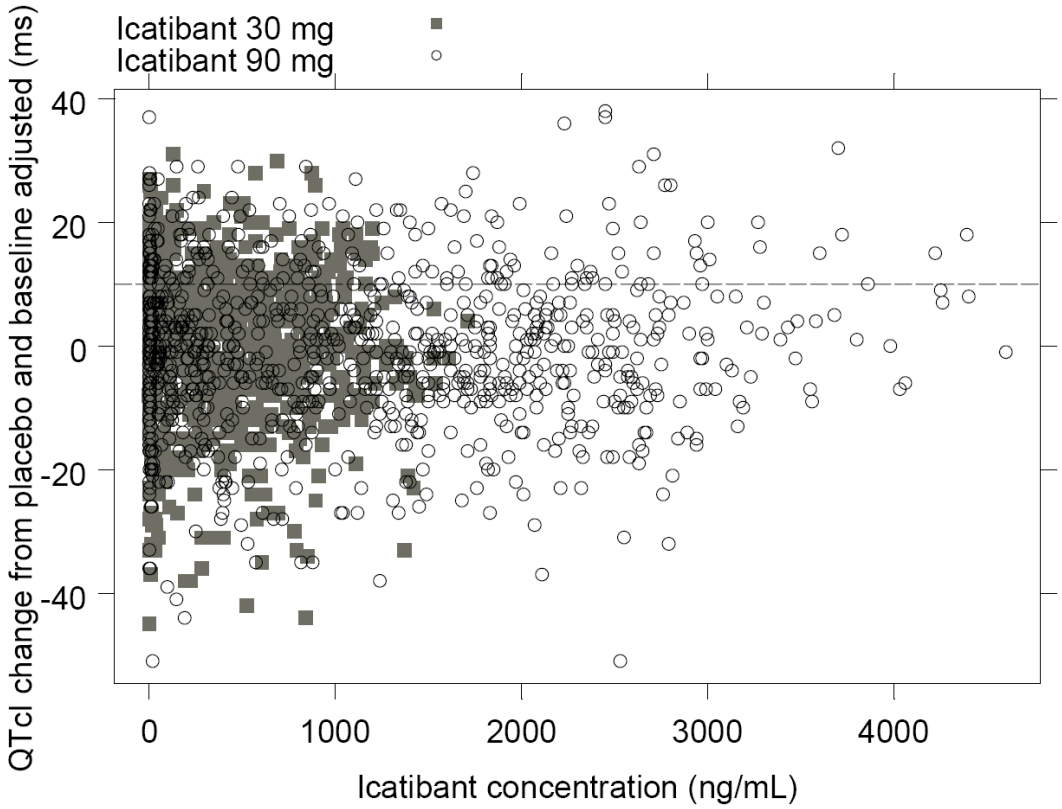
2.2.3 Does Icatibant prolong the QTc interval?

A Thorough QT (TQT) study (Study HGT-FIR-061) was conducted to determine whether administration of the proposed single SC dose (30 mg) and the supra-therapeutic SC dose (90 mg) of icatibant had the potential to cause QT interval prolongation in healthy adults. This was a randomized, 4-period, placebo- and active-controlled (400 mg moxifloxacin) single-center Phase 1 study with crossover design in 72 healthy male and female subjects (ages 18-50 years). No significant QTc prolongation effect of icatibant (30 and 90 mg) was detected in this TQT study. The largest upper bounds of the two-sided 90% CI for the mean differences between icatibant (30 and 90 mg) and placebo of QTcI were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The dose of 90 mg is adequate to represent the highest possible exposure expected to be encountered in the clinic.

Exposure-response analysis was also conducted. A plot of ΔΔQTcI vs. icatibant indicated no evidence of exposure-response relationship (Figure 4). The supra-therapeutic dose (90 mg) produces mean Cmax values of 2.8-fold the mean Cmax for the therapeutic dose (30 mg),

indicating PK linearity and far exceeding the worst case clinical scenario of elderly females exhibiting, on average, about 17% increase in Cmax compared to young females (study JE049-1103).

Figure 4. ΔΔQTcI vs. Icatibant Concentrations (Study HGT-FIR-061)



Refer to the QT-IRT review of study HGT-FIR-061 by Dr. Moh Jee Ng dated 05/26/2011for additional details as well as the proposed label language describing QT/QTc results.

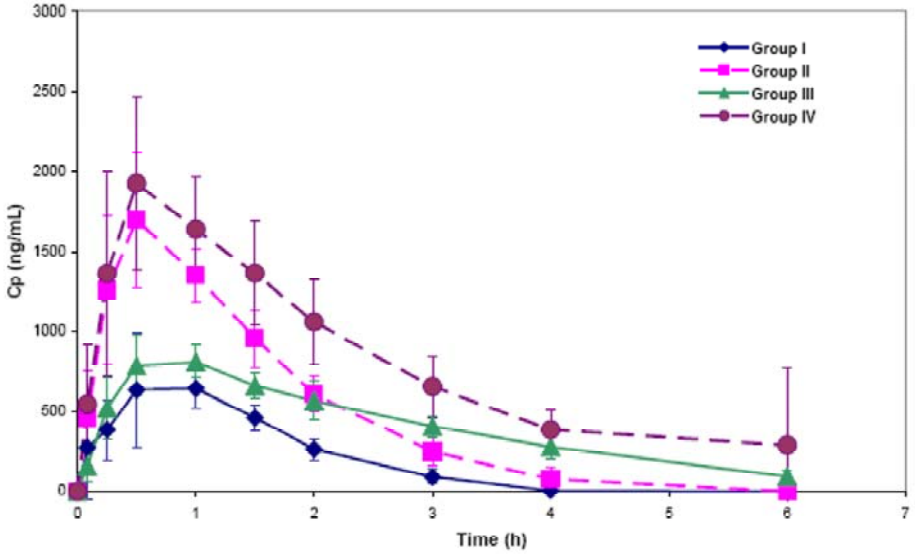
In the first cycle of review, the sponsor submitted QTc analysis from a multiple-dose PK/tolerability study. Upon review, the QT-IRT group concluded that icatibant is associated with QT prolongation. Although this study did not qualify to be a TQT study (no active control), considering the orphan nature of the indication, short half-life of the product and only single or intermittent use of this product in the clinic, the QT-IRT group concluded that the sponsor need not conduct a TQT study as long as QT prolongation issues can be addressed in the labeling. For this resubmission, the sponsor decided instead to conduct a new TQT study to rule out the QT issues so as to obtain a clean label without the QT prolongation issue.

2.3 Intrinsic Factors

2.3.1 Age and Gender effects on Icatibant PK

In the original NDA, the sponsor noted both age and gender effects on PK of icatibant as clearly evidenced by concentration-time profiles from study JE049-1103 in young male, elderly male, young female and elderly female subjects (Figure 5).

Figure 5. Mean (SD) icatibant concentrations (Cp, ng/mL) following single SC 30 mg dose in healthy young males (18-45y, Group I), young females (18-45y, Group II), elderly males (>65y, Group III) and elderly females (>65y, Group IV), n=6/group.



Following single-dose administration of 30 mg icatibant, elderly males showed 2.3-fold higher AUC0–∞ compared to young males while, elderly females showed 1.6-fold higher AUC0–∞ compared to young females. However, only minor differences (~12-14%) between Cmax of gender–matched elderly and young subjects were observed. In addition to the age effect, gender effect on PK was also observed. Gender effect seems to be a little more pronounced in young subjects compared to elderly subjects. Young females demonstrated about 2.3-fold higher AUC0–∞ and Cmax compared to young males. For elderly females, AUC0–∞ was about 1.8-fold and Cmax 2.2-fold higher than for elderly males. Although the interpretation of study data with respect to age and gender effects on icatibant PK is limited due to a small number of subjects (n = 6) per treatment group, the above data unequivocally indicated a general trend towards higher systemic exposure in females compared to males and also in elderly compared to young subjects. Based on the above, the sponsor was asked to address the scientific basis for these large differences in systemic exposure and to provide justification for proposing the same dose regardless of age and gender.

In response to age and gender issues in the non-approval letter, the sponsor provided two sets of analyses in this resubmission:

1) A post-hoc analyses of the effects of demographic variables (age, gender, bodyweight etc) on the PK of icatibant and metabolites M1 and M2 based on the two newly conducted PK trials with rich sampling (HGT-FIR-061 and HGT-FIR-065).

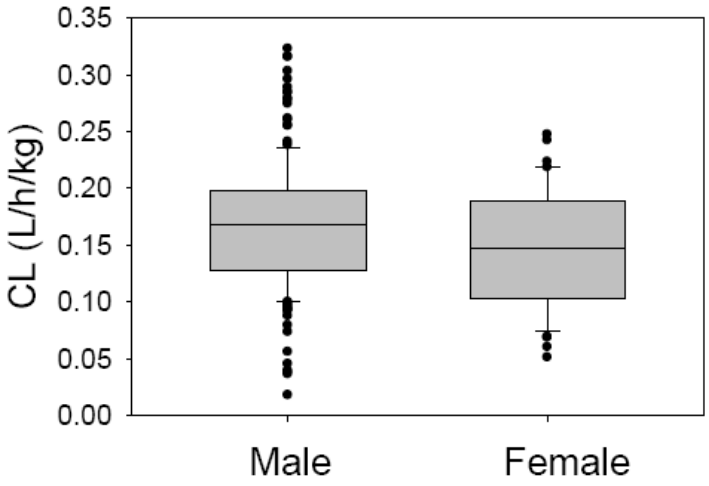
2) A population PK report (JE049-5120) pooling data from seven different clinical trials evaluating the influence of age and gender on PK of icatibant.

The two new studies (HGT-FIR-061 and HGT-FIR-065) combined had 51 males and 52 females for a total of 103 healthy subjects with an average BWs of 79 kg and 65 kg for males and females, respectively. Clearance (CL/F) and apparent volume of distribution (Vss/F) of icatibant were found to be significantly correlated with BW indicating that both clearance and volume of distribution increase as BW increases (Figure 1). On the contrary, the population PK analysis did not identify BW as a significant covariate. Sponsor did not provide explanation for the different conclusions between these two approaches and did not explore factors such as 'outliers' as a potential reason for the conclusion reached in population PK analysis. Since, adequate data is available from the use of rich PK data from studies HGT-FIR-061 and HGT-FIR-065 and no assumptions need to be made in the use of these data, results from these newly conducted studies will be used primarily to draw conclusions regarding gender effect (see Appendix 4.2).

Gender

Since females generally have lower BWs compared to males, therefore females, on average, are expected to exhibit lower clearance values (Figure 2A) resulting in higher systemic exposure compared to males. The mean (SD) BWs were 79 (11) kg for males and 65 (9) kg for females in the two trials, HGT-FIR-061 and HGT-FIR-065. Correction for body weight results in more comparable ranges of CL/F values for males and females (Figure 2B). Population PK analyses also confirmed the findings from the two new studies (Figure 6). Taking into account the overall magnitude and variability in parameter estimates, the sponsor stated and this reviewer agrees that the gender-related differences in systemic exposure are not expected to be of any clinical significance. Since a flat dose of 30 mg has been proposed for all icatibant recipients, patients with markedly different BWs will exhibit large inter-individual differences in systemic drug exposure, irrespective of gender.

Figure 6. Relationship between icatibant CL/F and gender, corrected for BW (population PK).



Age

The age range for the two new studies was only limited to 18-50 years. Within this age range of relatively young subjects, there were no apparent trends toward changes in clearance (CL/F) or apparent volume of distribution at steady-state (Vss/F) with or without bodyweight correction. However, due to limited age range enrolled in the new trials, effect of age on icatibant PK can not be completely elucidated over a wider age range including elderly subjects. Therefore, it is best to review the results from the population PK analysis which comprises of seven different trials representing a total of 98 male and 42 female subjects with a broad age range of 19 to 82 years. Population PK data revealed that icatibant clearance exhibits a decreasing trend with increasing age (Figure 3). Older subjects tend to exhibit lower clearance compared to younger subjects and thereby higher systemic exposure. For details on population PK data analysis, refer to the Pharmacometric Review by Dr. Atul Bhattaram (Appendix 4.2).

In conclusion, it is quite clear that body-weight is a significant covariate for icatibant clearance. Clearance increases with increasing body-weight. Since females generally tend to have lower BWs compared to males, females will exhibit higher systemic exposure of icatibant compared to males. Similarly, age was also found to impact icatibant PK with elderly subjects exhibiting higher systemic exposure of icatibant compared to younger subjects. However, given the overall variability in PK parameter estimates and presumably robust clinical data for icatibant, the observed differences are not expected to be of significant clinical relevance to warrant a dose modification by age and gender. For details about benefit-risk assessment by age and gender, refer to the review by Dr Brian Porter (Medical Officer, DPARP).

3 LABELING REVIEW

Below are the sections from the proposed label immediately followed by clinical pharmacology edits/modifications (in red or in strikethrough).

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

PERTINENT REGULATORY BACKGROUND

In the non-approval letter from FDA on 04/23/2008, the sponsor was asked to explore the scientific basis for influence of age and gender on pharmacokinetics of icatibant. In addition, the sponsor was also asked to provide justification for proposing the same dose regardless of age and gender. Sponsor, as a part of response to issues in non-approval letter, submitted two reports which discussed the influence of age and gender on pharmacokinetics of icatibant.

RESULTS OF SPONSOR'S ANALYSIS

Sponsor evaluated the influence of age and gender on pharmacokinetics of icatibant using population pharmacokinetic analysis methodology (Report JE049-5120). Plasma concentration-time data derived from seven different clinical studies and a total of 210 treatments in 98 male and 42 female subjects were used for the analysis. These studies used intravenous infusion and/or subcutaneous routes of administration and included single or multiple dose regimens as shown in Table 1.

Table 1. Summary of studies analyzed to characterize pharmacokinetics of icatibant using population pharmacokinetics approach.

Study JE049 #1001	Renal function, safety and tolerance, pharmacokinetics and pharmacodynamic profiles of icatibant following single and multiple intravenous infusion. Doses between 0.005 and 3.2 mg/kg were administered as 1 or 4 h infusions.
Study JE049 #1101	Randomized double-blind, placebo-controlled study to explore safety, tolerability and pharmacokinetics of icatibant after single intravenous infusions. 0.4 mg/kg using decreasing infusion times (1, 0.5, and 0.25 hours) administered at various infusion rates, in healthy male subjects
Study JE049 #1102	Tolerability and absolute bioavailability of a single subcutaneous dose of icatibant (20 mg/mL or 10 mg/mL formulation) compared to a single intravenous infusion of icatibant in healthy subjects
Study JE049 # 1103	Randomized, double-blind, placebo-controlled study to explore the pharmacokinetics, safety (including QTc analysis) and tolerability of several single subcutaneous doses of icatibant administered to healthy young and elderly, male and female subjects. A total of 32 subjects (8/age and sex group) were treated with 30 mg doses of icatibant subcutaneous at 0, 6, and 12 hours on day 1 and at 0 hour on day 8 and 15 (n=6/group) or with placebo (n=2/group).
Study JE049 #2001	Safety, tolerance, pharmacokinetic and pharmacodynamic profiles of icatibant (0.15 mg/kg/day for 3 days) in hepatic insufficiency following multiple intravenous infusions in 16 subjects.
Study JE049 #2002	Safety, tolerance, and proof-of-concept study for clinical activity of icatibant in patients with cirrhosis and refractory ascites with or without hepatorenal syndrome after multiple intravenous infusion in 41 patients (37 in Panel A, 4 in Panel B).

Study JE049 #2101	Proof-of-concept study to investigate, in patients with hereditary angioedema, the efficacy and safety of icatibant administered intravenously at various infusion rates and subcutaneously at different doses • (0.4 mg/kg i.v. (2 h infusion) for Group I • 0.4 mg/kg i.v. (30 min infusion) for Group II • 0.8 mg/kg i.v. (30 min infusion) for Group III • 30 mg s.c. for Group IV • 45 mg s.c. for Group V

The characteristics of the subjects included in the analysis are shown in Table 2.

Table 2. Characteristics of the subjects included in population pharmacokinetic analysis

Continuous Covariates				
Covariate	**Mean (SD)**	**Median**	**Range**	**Symbol**
Age (years)	41.84 (16.49)	38.5	19-82	AGE
Weight (kg)	73.89 (13.24)	74.1	40-121.1	WT
Creatinine Clearance (ml/min)	102.8 (32.18)	106.2	18.8-169.2	CRCL
Categorical Covariates				
Gender (Male/Female)	98/42			SEX
Study	0 – Study 1001 (n= 24 male subjects) 1 – Study 1101 (n=8 male subjects) 2 – Study 1102 (n=24 male subjects) 3 – Study 1103 (n=12 male and 12 female subjects) 4 – Study 2001 (n=10 male and 6 female subjects) 5 – Study 2002 (n=14 male and 10 female subjects) 6 – Study 2101 (n=6 male and 14 female subjects)			STUD
Race	1 – African 2 – Caucasian 3 – Metis 4 – Asian			RACE
Route of administration	1 – intravenous 2 – subcutaneous			ROUT

Source: Table 2 on Page 26 from csr-je049-5120-study-report.pdf

Table 3 shows the estimates of pharmacokinetic parameters for the basemodel (without any covariates) and final model (with age as covariate).

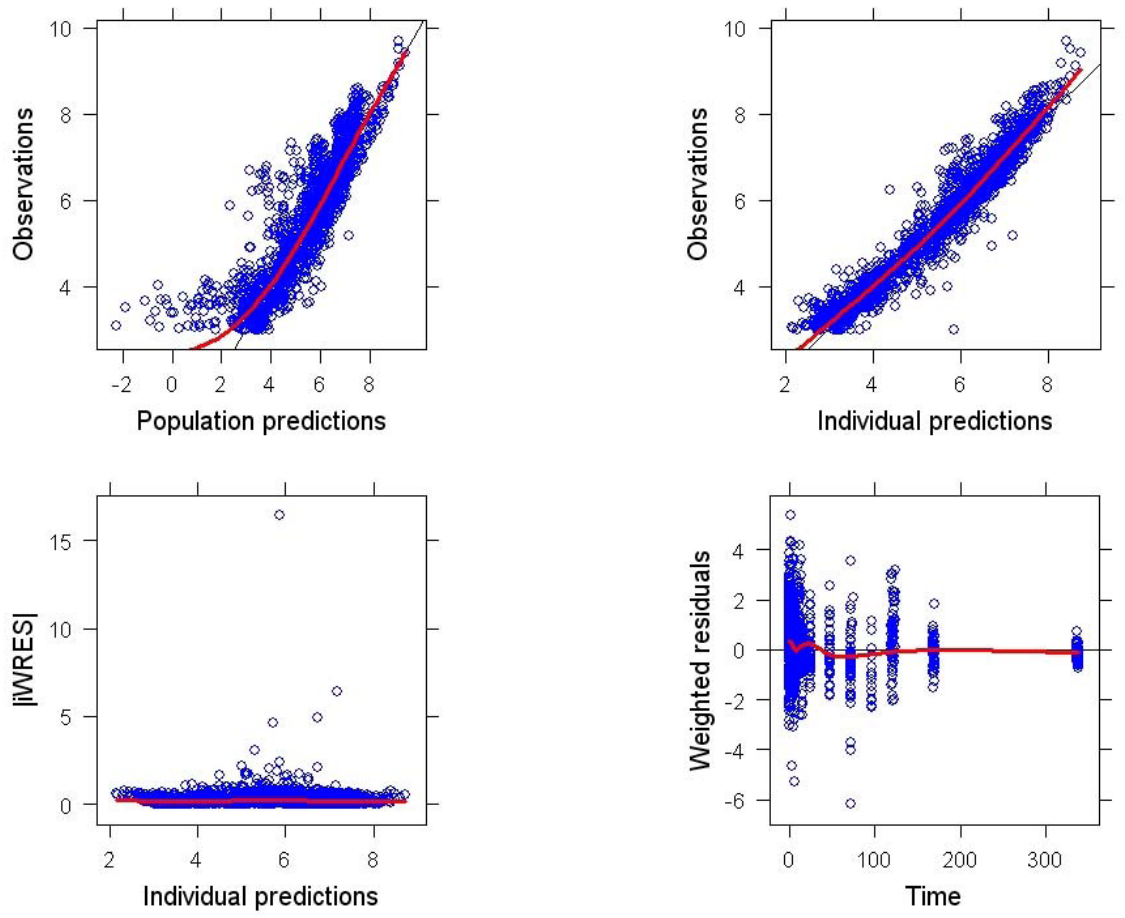
Table 3. Final parameter estimates of base and final models

Estimates	Base Model	Final Model
OBJF	-1037.874	-1091.011
ΔOBJF		53.14
p-value		<0.001
Significance		Yes
CL (L/hr)	11.00	11.50
V (L)	14.70	15.20
KA (h^{-1})	2.45	2.42
θ_{AGE} (CL)		-0.011
ω_{CL}	0.204	0.165
ω_{V1}	0.207	0.218
ω_{KA}	0.093	0.109
$CL_{(se\ \%)}$	4.15	3.65
$V_{(se\ \%)}$	4.69	4.53
$KA_{(se\ \%)}$	7.10	7.11
$\theta_{AGE\ (se\ \%)}$		10.3
$\omega_{CL(se\ \%)}$	21.90	22.30
$\omega_{V(se\ \%)}$	52.20	44.60
$\omega_{KA(se\ \%)}$	36.50	34.60
σ	0.142	0.142
$\sigma_{(se\ \%)}$	9.86	9.93

Source: Table 8 on Page 33 from csr-je049-5120-study-report.pdf

Figure 3 shows goodness of fit plots for the final model (with age as covariate).

Figure 3. Goodness of fit plots for final population pharmacokinetic model



Source: Figure 1 on Page 34 from csr-je049-5120-study-report.pdf

Reviewer's Comments: The sponsor's population pharmacokinetic analysis did not identify body weight as a significant covariate. However, analysis of 2 new studies (HGT-FIR-061 and HGT-FIR-065 as shown in Table 4) showed that changes in clearance and volume of distribution are dependent on body weight (Figure 4).

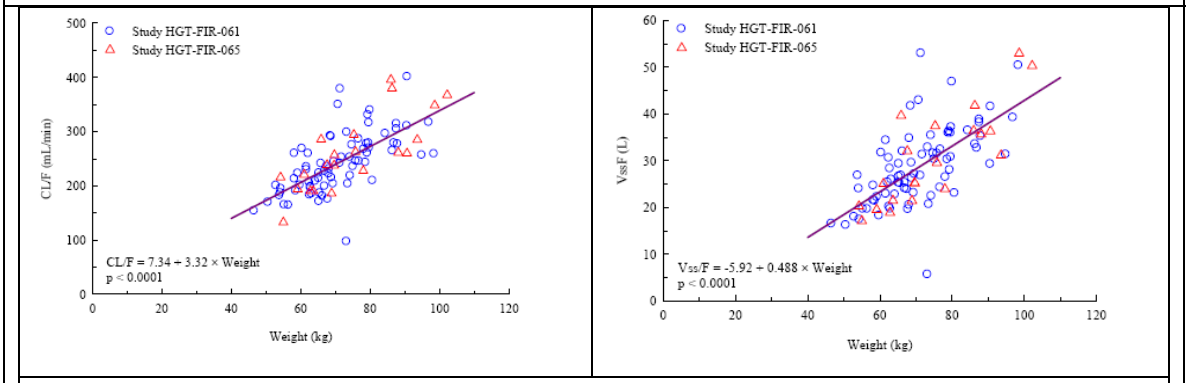
Table 4. Healthy volunteer studies to explore the effect of gender on pharmacokinetics of icatibant (Report: post-hoc-pk-analyses-report.pdf).

Study No.	Type of Subject	Dose (mg) and Regimen	No. of Subjects
HGT-FIR-061*	Healthy volunteer	30 mg Single Dose 90 mg Single Dose	82
HGT-FIR-065†	Healthy volunteer	30 mg Q6H × 3	21

*Only data from the 30 mg treatment, the clinical dose, will be used so that each subject will contribute only one value for each pharmacokinetic parameter.
†Only data from the first 30 mg SC dose will be used so that each subject will contribute only one value for each pharmacokinetic parameter.

Source: Table 1 on Page 10 from post-hoc-analyses-report.pdf

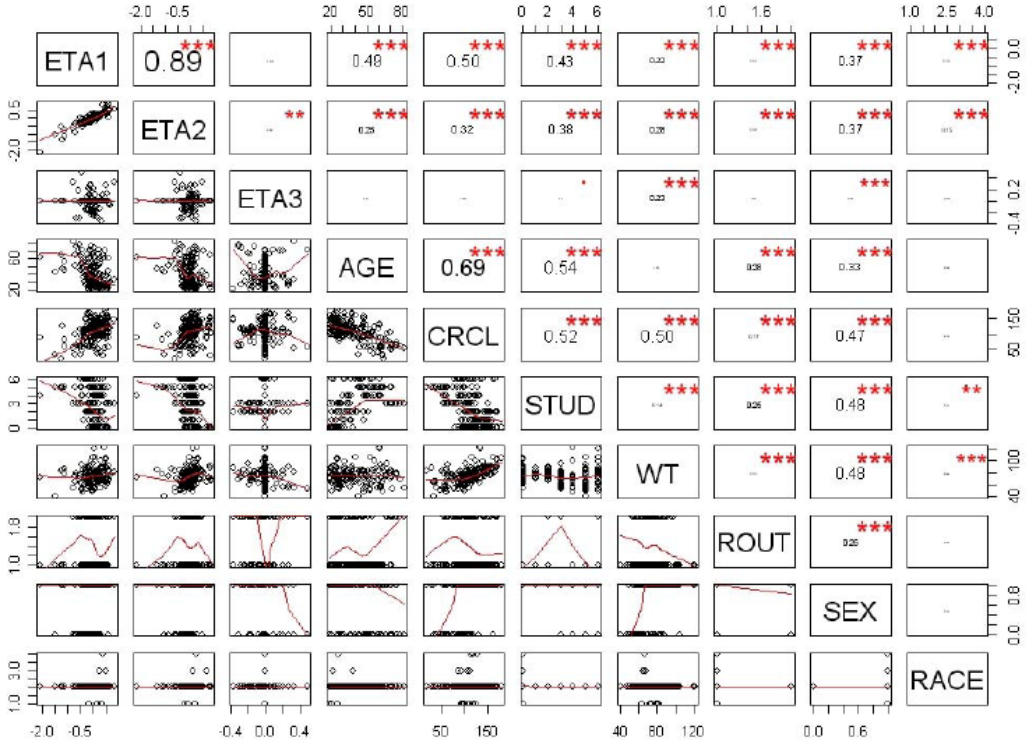
Figure 4. Relationship between icatibant clearance (CL/F), volume of distribution (Vss/F) and body weight after administration of a single 30 mg subcutaneous dose of icatibant.



Source: Figure 8 and 10 on Page 18, 19 from post-hoc-analyses-report.pdf

Figure 5 shows the relationship between interindividual variability in clearance, volume of distribution, absorption rate constant and covariates such as age, body weight (wt) etc. The sponsor should explore if the lack of relationship between ETA1(Interindividual variability for clearance) and body weight (wt) is due to any outliers (ETA1 less than -2). For description of body weight, age and gender effects in the label, the sponsor must use results from studies HGT-FIR-061 and HGT-FIR-065.

Figure 5. Correlation between covariates and etas (ETA1- Interindividual variability on clearance, ETA2- Interindividual variability on volume of distribution, ETA3- Interindividual variability on absorption rate constant). Refer to Table 2 for description of covariates.



REVIEWER'S ANALYSIS

NA

Introduction

NA

Objectives

NA

Methods

NA

Data Sets

Data sets used are summarized in **Table 5**.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR

Software
NA

Models
NA

Results
NA

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PARTHA ROY
07/14/2011

YANING WANG
07/14/2011

SURESH DODDAPANENI
07/14/2011

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-150
Type:	Original
Brand Name (proposed):	FIRAZYR®
Generic Name:	Icatibant; HOE140
Indication:	Treatment of Hereditary Angioedema (HAE) in adults ≥18 years.
Dosage Form:	Solution for injection
Strength:	10 mg / mL
Route of Administration:	Subcutaneous Injection
Dosing regimen:	30 mg (3 mL) sub-cutaneous injection: repeat at intervals NLT 6 hrs; do not exceed 3 doses/ 24 hrs
Applicant:	Jerini AG
OCP Division:	DCP2
Clinical Division:	DPAP (OND-570)
Submission Date:	October 22, 2007
Primary Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Wei Qiu, Ph. D.
Pharmacometric (PM) Reviewer:	Nitin Mehrotra, Ph.D.
PM Team leader:	Yaning Wang, Ph.D.

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1 EXECUTIVE SUMMARY

Jerini AG submitted a 505(b)(1) application for Firazyr® (Icatibant) (b) (4) to treat Hereditary Angioedema (HAE) in patients 18 years of age and older. HAE is a rare, inherited condition characterized by intermittent, unpredictable attacks of angioedema that are potentially life-threatening, particularly in cases of airway compromise. Currently, there are no drug products approved for the treatment of acute attacks of HAE.

Icatibant is a first-in-class new molecular entity that has never been a part of another approved drug product. It is a novel synthetic decapeptide that is a competitive antagonist at the bradykinin type 2 (B2) receptor. The Agency granted icatibant fast track designation and a priority review. Firazyr® (b) (4), a pre-filled syringe, contains 30 mg icatibant (free base) and presented as an acetate salt in 3 mL solution. The proposed dosing regimen is 30 mg icatibant subcutaneous injection repeated at intervals of not less than 6 hours and not to exceed 3 injections in 24 hours.

Clinical pharmacology program consists of four studies in healthy subjects (including QT evaluation in one study), one open-label proof-of-concept study in HAE patients, two studies in patients with hepatic and/or renal impairment, and one report of population PK and PK/PD modeling in selection of dosing regimen. The pharmacokinetic results are summarized as follows:

Icatibant is rapidly and completely absorbed (absolute bioavailability of 97%) after single 30 mg subcutaneous (SC) administration. Icatibant displays linear pharmacokinetics with regards to both dose and time. The mean volume of distribution is 0.25 L/kg in young healthy male subjects. The binding of icatibant to human serum proteins is low (~44%). Icatibant is rapidly eliminated from the body with mean $T_{1/2}$ values ranging from 0.6 to 1.5 hours. Clearance is predominantly non-renal with about 5-6% being excreted in the urine as parent drug. No accumulation was observed following SC administration of 30 mg icatibant every 6 hours for 3 doses in healthy subjects. Icatibant is extensively metabolized to two principal inactive metabolites, M1 and M2 by P450-independent pathways, likely by proteolytic enzymes such as peptidases.

Following SC administration of 0.4 mg/kg icatibant, elderly subjects (>65 years) showed an approximately 66% to 116% higher AUC values than young subjects aged between 18-45 years with only minor differences in C_{max}. The apparent clearance was decreased and half-life was prolonged in elderly compared to young subjects. Young female subjects showed an approximately 2.3-fold increase in both C_{max} and AUC values than young males. Elderly females exhibited a similar increase in C_{max} (~2.3-fold) while AUC was increased by about 1.8-fold compared to elderly males. Since both apparent clearance and volume of distribution were decreased to similar extent in females compared to males, the half-life values were nearly similar. Therefore, it appears that age and gender have significant effects on Icatibant pharmacokinetics. This needs to be further investigated, possibly at the metabolic pathway level to understand these differences in exposure.

The PK parameters of icatibant were found to be generally comparable between healthy subjects and mild to moderate hepatic impaired patients. No correlation was found between icatibant

systemic clearance and renal function consistent with only a minor role of renal clearance towards overall drug elimination. The pharmacokinetics of icatibant in patients with HAE is similar to those in healthy subjects.

In vitro studies suggest that icatibant does not inhibit any relevant drug metabolizing CYP450s or induce CYP450 enzymes (CYP1A2 and CYP3A4), implying that there is a low potential for metabolic drug-drug interactions with icatibant.

PK/PD modeling and simulation results predicted that at doses beyond 30 mg the duration of effect was relatively insensitive to a change in the administered dose. Therefore, the 30 mg dose was used in the phase III trials. However, in the placebo controlled Phase III trial, the 30 mg dose failed to show statistically significant efficacy. Pharmacometric review by Dr. Mehrotra (refer to Appendix 4.3) identified major deficiencies in the PK/PD modeling exercise conducted by the sponsor to support dose selection. It was pointed out that the efficacious dose based on biomarker (bradykinin challenge in healthy subjects) may not be efficacious for the clinical endpoint (Visual Analogue Scale (VAS) for HAE) due to (1) the uncertainty about the relationship between the biomarker and the clinical endpoint and (2) larger variability in the clinical endpoint than the biomarker, leading to an underpowered study. In addition, the plasma bradykinin level (15 pM – 30 pM) after bradykinin challenge in healthy subject was lower than that in a patient during an acute HAE attacks (~50 pM). Thus, the selected dose based on this PK/PD modeling and simulation may be an underestimate of the correct dose for HAE patients.

The QT-IRT review of a QT study without positive control arm concluded that the ECGs from the study suggested icatibant acetate was associated with ST/T wave changes and QT prolongation. The QT-IRT recommended that a thorough QT study would not be required and QT prolongation issues could be addressed in the labeling. Periodic monitoring of on-treatment electrocardiograms and electrolytes was recommended in future studies with icatibant.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) has reviewed NDA 22-150's Clinical Pharmacology information submitted on October 22, 2007 and finds it acceptable. Preliminary review of the label is conducted at this time. Formal line-by-line labeling review will be conducted in the future if the drug is being considered for favorable action.

Comments to the Sponsor:

1. Data from study JE049 #1103 indicate that both age and gender have profound effects on Icatibant pharmacokinetics. Address the scientific basis for these large differences in systemic exposure and possible role of proteolytic enzymes. Also provide justification for proposing the same dose regardless of age and gender.
2. Dose selection should be further defined in sufficient patients based on the clinical endpoint or other biomarkers that are validated to be related to the clinical endpoint.
3. Consider the merit of conducting age and gender specific dose exploration in future clinical trials.

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The Applicant submitted clinical pharmacology data generated from 4 studies in healthy subjects (JE049-1001, JE049-1101, JE049-1102, and JE049-1103) and one open-label proof-of-concept study in HAE patients (JE049-2101). Pharmacokinetics in patients with hepatic and/or renal impairment were evaluated in Studies JE049-2001 and JE049-2002 as part of the development programs for other indications. In addition, this application also included 3 preliminary PK/safety studies using continuous IV infusion while seeking to develop the drug candidate for other indications (Studies JE049-9101, JE049-9103, and JE049-9106). These initial 3 studies were not reviewed because non-validated analytical assay was used in 2 studies and all the PK information had been replicated in more recent studies with more sensitive and specific validated assays. The sponsor also submitted one stand alone report (JE049-5108), which presents the results of population PK and PK/PD modeling in selection of optimal dosing regimen. As part of the clinical database, results from two pivotal well-controlled studies in HAE patients with open-label extensions were submitted.

Pharmacokinetics:

Icatibant is rapidly absorbed after single 30 mg subcutaneous (SC) administration with peak plasma concentration achieving within 30 minutes of dosing. Absorption (i.e. bioavailability) is nearly complete (~97%) following SC administration of 0.4 mg/kg using 10 mg/mL solution for injection. Icatibant displays linear pharmacokinetics with regards to both dose and time. Following IV infusion of icatibant 0.4 mg/kg over 30 minutes, the mean volume of distribution is 0.25 L/kg in young healthy males. The binding of icatibant to human serum proteins is low (~44%). Icatibant is rapidly eliminated from the body with mean $T_{1/2}$ values ranging from 0.6 to 1.5 hours. Clearance of icatibant is predominantly non-renal with about 5-6% being excreted in the urine as parent drug. No accumulation was observed following SC administration of 30 mg icatibant every 6 hours for 3 doses in healthy subjects (Table below).

Icatibant is extensively metabolized to two principal inactive metabolites, M1 and M2. While the exact pathway is undetermined, *in vitro* studies suggest that the metabolism of icatibant is P450-independent.

Pharmacokinetic parameters of icatibant following 30 mg subcutaneous injection after single (Dose I) and repeated (3 doses every 6 hours, Dose III) administration in young male (Group I) and young female (Group II) and elderly male (Group III) and elderly female (Group IV) healthy subjects.

Dose[a]	Parameter		Group[b] [Geom. Mean ±Geom. SD / Range[c]]			
			I	II	III	IV
I	$AUC_{0-\infty}$	[ng·h/mL]	1197.3 ±1.20 (948.5; 1525.9)	2920.9 ±1.16 (2368.1; 3385.2)	2709.2 ±1.21 (1944.6; 3251.9)	4756.6 ±1.29 (3133.4; 6508.4)
	$AUC_{0-\infty}/D$	[g·h/L][d]	2833.6 ±1.28 (1960.3; 4196.3)	5782.0 ±1.23 (4207.4; 7819.8)	7253.2 ±1.24 (4874.4; 8484.6)	10433.8 ±1.31 (7411.1; 14710.0)
	C_{max}	[ng/mL]	739.7 ±1.26 (519.8; 1025.4)	1657.3 ±1.26 (1244.9; 2463.9)	843.8 ±1.19 (698; 1103.6)	1862.0 ±1.36 (1091.2; 2639.4)
	C_{max}/D	[g/L][d]	1750.6 ±1.25 (1310.3; 2121.7)	3280.7 ±1.26 (2211.8; 4500.7)	2259.0 ±1.25 (1749.7; 3082.7)	4084.4 ±1.28 (2673.4; 5405.5)
	t_{max}	[h][e]	0.75 (0.08; 1.00)	0.50 (0.50; 0.50)	1.00 (0.50; 1.00)	0.50 (0.50; 1.00)
	$t_{1/2}$	[h]	0.51 ±1.20 (0.45; 0.73)	0.56 ±1.30 (0.38; 0.76)	1.46 ±1.36 (1.05; 2.32)	1.11 ±1.13 (0.95; 1.29)
	CL/F	[L/h]	25.1±1.20 (19.6; 31.7)	10.3 ±1.16 (8.86; 12.68)	11.1 ±1.20 (9.32; 15.45)	6.31 ±1.29 (4.62; 9.58)
	V_{ss}/F	[L]	18.3 ±1.16 (14.6; 20.7)	8.34 ±1.45 (5.5; 13.8)	23.4 ±1.28 (15.7; 31.9)	10.1±1.25 (8.2; 15.3)
III	$AUC_{0-\infty}$	[ng·h/mL]	1406.3 ±1.18 (1049.9; 1611.0)	2963.3 ±1.18 (2396.4; 3530.3)	3529.1 ±1.15 (2735.0; 3949.9)	5543.6 ±1.21 4163.2; 7256.8)
	$AUC_{0-\infty}/D$	[g·h/L][d]	3328.1 ±1.10 (2852.1; 3638.3)	5866.0 ±1.25 (4377.4; 7631.7)	9448.2 ±1.21 (6855.7; 11845.5)	12160.1 ±1.26 (8578.1; 16372.0)
	C_{max}	[ng/mL]	878.4 ±1.23 (663.5; 1177.0)	1666.5±1.24 (1252.2; 2239.2)	1245.0 ±1.13 (1128.3; 1581.2)	1944.4 ±1.36 (1162.3; 2838.3)
	C_{max}/D	[g/L][d]	2078.8 ±1.1 (1802.5; 2322.6)	3299.0 ±1.24 (2224.7; 4224.6)	3333.1 ±1.19 (2929.8 ; 4416.8)	4265.2 ±1.26 (2847.6; 5411.4)
	t_{max}	[h][e]	0.50 (0.25; 0.50)	0.50 (0.25; 1.00)	0.50 (0.50; 0.50)	0.50 (0.25; 1.00)
	$t_{1/2}$	[h]	0.46 ±1.31 (0.36; 0.77)	0.53 ±1.17 (0.44; 0.64)	1.60 ±1.04 (1.52; 1.66)	1.41 ±1.03 (1.36; 1.49)
	CL/F	[L/h]	21.3 ±1.18 (18.6; 28.6)	10.1 ±1.18 (8.5; 12.5)	8.50 ±1.15 (7.6; 10.9)	5.4±1.21 (4.1; 7.2)
	V_{ss}/F	[L]	14.2 ±1.42 (10.8; 25.3)	7.77 ±1.11 (7.0; 9.3)	19.60 ±1.17 (16.6; 25.3)	11.0 ±1.25 (8.2; 15.5)

[a] Dose I and III: both doses were administered on Day 1, 12 h apart
[b] N per treatment group = 6
[c] Range (mininum; maximum)
[d] $AUC_{0-\infty}$ and C_{max} per dose and body weight
[e] Median (minimum; maximum)
Groups: I - male, 18-45 years; II - female, 18-45 years; III - male, >65 years; IV - female, >65 years

Pharmacokinetics in Special Populations:

Age:
Elderly subjects (>65 years) showed an approximately 66% to 116% higher AUC values than young subjects aged between 18-45 years (Table above). However, only minor differences (~12-14%) between C_{max} of gender–matched elderly and young subjects were observed.

The apparent clearance was decreased in elderly compared to younger subjects for both males (~60%) and females (~40%). The half-life ($T_{1/2}$) estimates were prolonged approximately 2.6-fold in elderly males and 1.6-fold in elderly females compared to their younger counterparts.

Gender:
Young female subjects showed approximately 2.3-fold increase in both C_{max} and AUC values than young males. Elderly females exhibited a similar increase in C_{max} (~2.3-fold) while AUC was increased by about 1.8-fold compared to elderly males. Since both apparent clearance and volume of distribution are decreased to similar extent in females compared to males, the half-life values were nearly similar.

Hepatic Impairment:
The PK parameters including AUC, C_{max}, $T_{1/2}$, CL and V_z were found to be generally comparable between healthy subjects (n=8) and mild to moderate hepatic impaired patients (n=8) following a dose of 0.15 mg/kg/day or as continuous intravenous infusion over 3 days (3 x 24 hours).

Renal Impairment:
Since renal clearance of the drug is a minor eliminating pathway, renal impairment is not expected to affect the PK of icatibant. A dedicated renal impairment study was not conducted for icatibant, however such study is not needed as the drug is primarily cleared non-renally. Patients with hepatorenal syndrome (with mild to moderate renal impairment) did not show any observable differences in the plasma levels of Icatibant or its metabolites compared to subjects with normal renal function. No correlation was observed between icatibant clearance and GFR values >30 mL/min as measured by sinistrine clearance. Therefore dose adjustment is not warranted in patients with renal impairment.

HAE patients:
The pharmacokinetics of icatibant in patients with HAE is similar to those in healthy subjects.

Drug-Drug Interaction:

In vitro studies suggest that icatibant does not inhibit any relevant drug metabolizing CYP450s (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) or induce CYP450 enzymes such as CYP1A2 and CYP3A4, implying that there is a low potential for metabolic drug-drug interactions with Icatibant. Formal drug-drug interaction studies were not performed for icatibant due to absence of any significant inhibition or induction of drug metabolizing CYP450 enzymes.

The Applicant has postulated a theoretical pharmacodynamic interaction between icatibant and ACE inhibitors, suggesting that icatibant may compromise the antihypertensive effects of ACE inhibitors via bradykinin antagonism. Clinical trials excluded subjects taking ACE inhibitors. The possibility that short term administration of icatibant will alter significantly the chronic antihypertensive effect of an ACE inhibitor is presently unknown.

PK/PD Relationship Utilized to Select Dose/Dosing Regimen for Phase III:

Icatibant is a competitive antagonist of the bradykinin type 2 (B2) receptor. It is hypothesized that inhibition of endogenous bradykinin (BK) is required to control key symptoms elicited by overproduction of BK during an acute angioedema attack. Therefore, an exogenous IV BK challenge was used as a pharmacological tool in healthy subjects to investigate the dose range and regimen for later trials. It was hypothesized that near complete BK antagonism would be required to establish the optimal dose, dose regimen, and time window for a clinically relevant inhibition. IV route was chosen for this initial exploration as it would provide the least uncertainty of the exposure-time profile of the drug.

PK/PD modeling and simulation predicted that for the relevant dose of 30 mg, icatibant has a 75% probability of being at least 50% effective for at least 6.5 h. Doubling the icatibant dose from 30 mg to 60 mg results in an increase of duration of effect by 1 to 1.5 h regardless of the confidence level. These data suggested that at doses beyond 30 mg the duration of effect is relatively insensitive to a change in the administered dose. Thus, the 30 mg dose was used in the phase III trials. However, in the placebo controlled Phase III trial, the 30 mg dose failed to show statistically significant efficacy compared to placebo.

Pharmacometric review by Dr. Mehrotra (refer to Appendix 4.3) concluded that the PK/PD approach for dose selection is generally reasonable. However, in this case, the efficacious dose based on biomarker (bradykinin challenge in healthy subjects) may not be efficacious for the clinical endpoint (Visual Analogue Scale (VAS) for HAE) due to: 1) uncertainty about the relationship between the biomarker and the clinical endpoint; 2) larger variability in the clinical endpoint than the biomarker, leading to an underpowered study. Given the lower plasma bradykinin level (15 pM – 30 pM) after bradykinin challenge in healthy subject compared to that in a patient during an acute HAE attacks (~50 pM), the dose based on this PK/PD relationship may be an underestimate of the correct dose for HAE patients. These concerns may well contribute to the non-significant results obtained in the placebo-controlled Phase 3 clinical trial. The observation of relatively faster onset of action in females (1.6 hours) compared to males (3.5 hours) in one of the Phase III studies (JE049-2102) suggests that a higher exposure may have a chance to beat placebo. Due to injection site reactions with higher dose/concentration of icatibant solution, raising the dose beyond 30 mg with the proposed formulation and route of administration may not be practically feasible.

QT/QTc prolongation:

The QT-IRT review of a QT study without positive control arm concluded that the ECGs from the study suggest icatibant acetate is associated with ST/T wave changes and QT prolongation. However, a thorough QT study is not required and QT prolongation issues can be addressed in the labeling. Periodic monitoring of on-treatment electrocardiograms and electrolytes is recommended in future studies with icatibant acetate. The 30 mg SC dose studied may be adequate based on the clinical pharmacology profile of icatibant.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the general attributes of FIRAZYR®?

Firazyr® is the trade name for the drug product. The established name, Icatibant will be used throughout this review to refer to the product.

Icatibant (b) (4) is a synthetic decapeptide that has a structure similar to that of the hormone bradykinin and is an effective bradykinin type 2 (B2) receptor antagonist. Icatibant acetate is a peptide consisting of 10 amino acids in the following sequence: H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH, acetate salt

(b) (4)

The structural formula is presented in Figure 1 below.

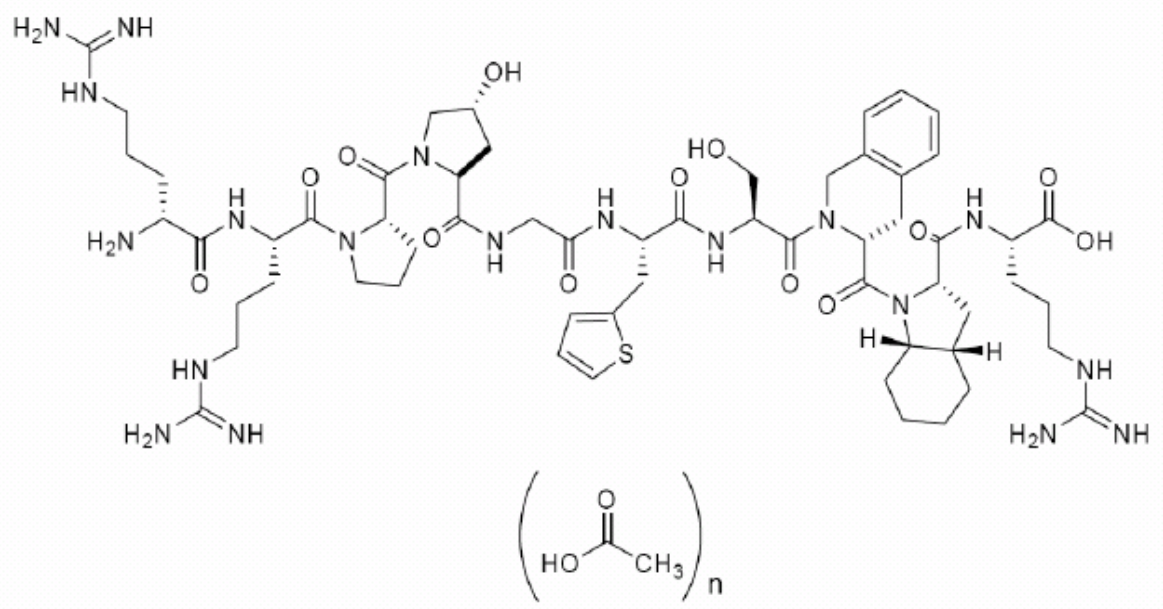


Figure 1. Structural formula of Icatibant acetate

Molecular formula: $C_{59}H_{89}N_{19}O_{13}S$ (net) · n CH_3COOH
Molecular weight: 1304.55 g/mol (b) (4)
Solubility: freely soluble in water, isotonic saline, phosphate buffer (b) (4) acetate buffer (pH 3.5), (b) (4) ethanol, and methanol.
Melting Point: (b) (4)

(b) (4)

Salt form: Icatibant exist as an acetate salt. (b) (4)

(b) (4)

FORMULATION
Icatibant 30 mg solution for injection is a parenteral drug product for subcutaneous administration. It is presented as a sterile, isotonic and buffered solution. The formulation consists of 10.00 mg/mL icatibant (free base) in water for injection (WFI), buffered at pH 5.5 with acetic acid and sodium hydroxide with sodium chloride (b) (4) The product is presented as a 3 (b) (4) mL single-dose disposable pre-filled syringe designed to deliver 3.0 mL of the product.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Icatibant is a competitive antagonist at the bradykinin type 2 (B2) receptor. Icatibant is a synthetic decapeptide with a similar structure to BK, but with 5 non proteinogenic amino acids. It is hypothesized that inhibition of endogenous bradykinin (BK) is required to control key symptoms elicited by overproduction of BK during an acute angioedema attack. Various *in vitro* binding studies exhibited IC_{50} values ranging between 1 and 10 nM towards B2 receptor antagonism.

The proposed indication (b) (4) for icatibant is "the treatment of hereditary angioedema" in patients 18 years of age and older.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

DOSAGE AND ADMINISTRATION (as per proposed label)
The recommended dose of Icatibant is one subcutaneous injection of 30 mg administered, preferably in the abdominal area for the treatment of a HAE attack.

In the majority of cases, a single injection is sufficient to treat an attack. In case of insufficient relief or recurrence of symptoms, a second injection can be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of can be administered after a further 6 hours. No more than 3 injections should be administered in a 24 hour period.

2.2 General Clinical Pharmacology

2.2.1 What is known about the single and multiple dose pharmacokinetics of Icatibant solution for injection?

Icatibant is rapidly absorbed after single 30 mg subcutaneous (SC) administration and drug levels are measurable in plasma as early as 5 minutes post-dose (section 2.2.2, Figure 2). The peak plasma concentration is achieved within 30 minutes of dosing. Absorption is nearly complete (~97%) following SC administration of 0.4 mg/kg using 10 mg/mL solution for injection. Icatibant displays linear pharmacokinetics with both dose and time. Icatibant is rapidly eliminated from the body with mean $T_{1/2}$ values ranging from 0.6 to 1.5 hours. Clearance of Icatibant is predominantly non-renal with about 6% being excreted in the urine as parent drug. The systemic clearance is found to be widely variable, on average, ranging between 0.34 L/h/kg

in young males, 0.17 L/h/kg in young females, 0.14 L/h/kg in elderly males and 0.10 L/h/kg in elderly females following SC administration of 30 mg Icatibant.

Almost no accumulation was observed following SC administration of 30 mg Icatibant every 6 hours for 3 doses in healthy young male, and both young and elderly female subjects. Slight accumulation is observed for elderly males (1.25-fold) with concomitant ~30% decrease in volume of distribution in this subject group. All other key PK parameters including T_{max}, $T_{1/2}$, CL/F, Vss/F remain essentially unchanged between single and multiple doses (Table 9, section 2.3.1) for all age and gender subgroups.

2.2.2 What is the absolute bioavailability following SC administration?

An open-label, randomized, cross-over absolute bioavailability study was conducted in 24 healthy male subjects between 18 and 50 years of age. The subjects received a single dose of 0.4 mg/kg Icatibant as a SC injection into the right upper quadrant of the abdomen using either 10 mg/mL or 20 mg/mL solution in one treatment period, and the same dose (0.4 mg/kg) as a 30 min IV infusion using 1 mg/mL solution in the other treatment period.

Mean (±SD) plasma concentrations of Icatibant and following IV infusion and SC injections are plotted in Figure 2. Pharmacokinetic data are listed in Table 1. The C_{max} was reached at the end of the IV infusion i.e. 30 minutes, as expected. SC injection also resulted in the T_{max} of 30 minutes regardless of the concentration of the administered Icatibant formulation. The IV infusion led to a higher maximum plasma concentrations than the SC injections as expected, but the AUC data of the SC injections were comparable to IV infusion. Mean absolute bioavailability ($AUC_{0-\infty}$) for Icatibant 20 mg/mL and 10 mg/mL by SC injections were found to be 86.1% (95% CI: 70.88; 98.20) and 97.2% (95% CI: 87.72; 106.43), respectively, based on geometric mean ratios (Table 2). The mean half lives of the SC injections and the IV infusions were comparable, ranging from 1.21 h to 1.46 h.

Figure 2. Mean (SD) plasma concentration-time plots of icatibant in healthy males following a 0.4 mg/kg dose administered as a 30 min intravenous infusion (n=24), a SC injection with a drug concentration of 20 mg/mL (n=12) and a SC injection with a drug concentration of 10 mg/mL (n=12).

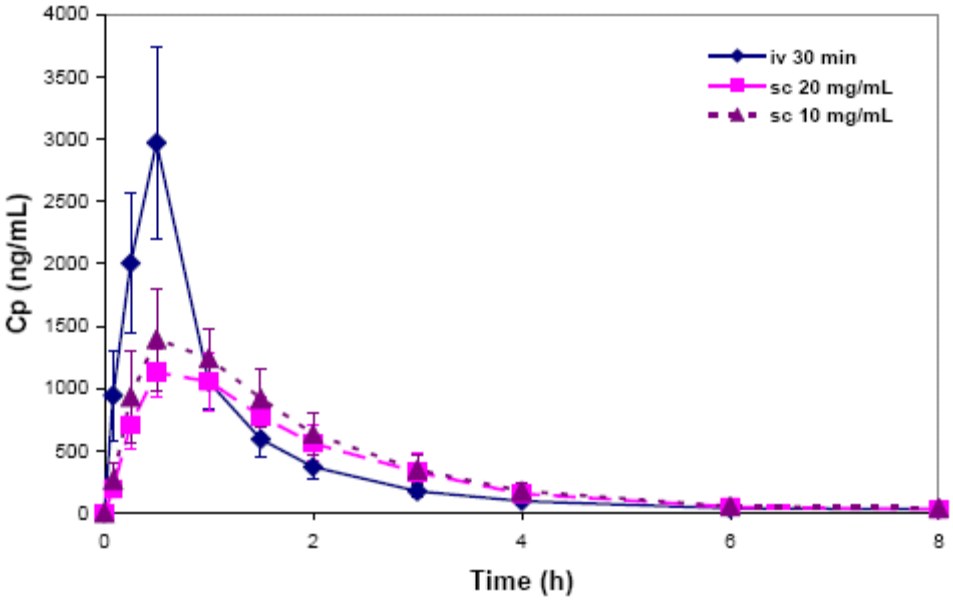


Table 1. Mean (CV%) pharmacokinetic parameters of Icatibant and its metabolite, M2 following administration of 0.4 mg/kg Icatibant solution as single intravenous (IV) infusion and single subcutaneous (SC) injections of 10 mg/mL and 20 mg/mL.

Treatments	**N**	**Analyte**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-t} (ng*hr/mL)**	**$AUC_{0-\infty}$ (ng*hr/mL)**	**$T_{1/2}$ (hr)**
0.4 mg/kg SC 20 mg/mL	12	Icatibant	0.50 (0.5-1.0)	1149 (18)	2557 (24)	2615 (23)	1.24 (17)
		M2	2.00 (1.5-3.0)	362 (24)	2130 (29)	2289 (31)	2.66 (22)
0.4 mg/kg SC 10 mg/mL	12	Icatibant	0.50 (0.5-1.0)	1429 (26)	3040 (20)	3114 (20)	1.21 (20)
		M2	2.00 (1.5-4.0)	387 (29)	2040 (28)	2192 (29)	2.82 (25)
0.4 mg/kg IV 1 mg/mL over 0.5h	24	Icatibant	0.5 (0.5-0.5)	2971 (26)	3120 (24)	3208 (24)	1.46 (45)
		M2	1.50 (1.0-3.0)	476 (24)	2148 (26)	2268 (26)	2.62 (16)

Table 2. C_{max} and AUC ratios between SC injections (right upper quadrant of the abdomen) and IV infusion of 0.4 mg/kg Icatibant

		0.4 mg/kg SC, 20 mg/mL [%]			0.4 mg/kg SC, 10 mg/mL [%]		
		C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
N		12	12	12	12	12	12
Icatibant	Mean (%)	39.96	86.22	86.10	50.84	97.61	97.20
	SD	11.58	23.24	23.76	12.07	14.65	15.28
	CV%	29.0	27.0	27.6	23.7	15.0	15.7
	Median (%)	38.6	81.0	81.1	55.1	99.7	98.0
M2	Mean (%)	77.74	98.68	100.20	87.56	101.4	102.9
	SD	15.27	19.40	19.87	37.72	33.34	32.29
	CV%	19.6	19.7	19.8	43.1	32.9	31.4
	Median (%)	81.9	95.2	96.7	74.4	89.9	92.2

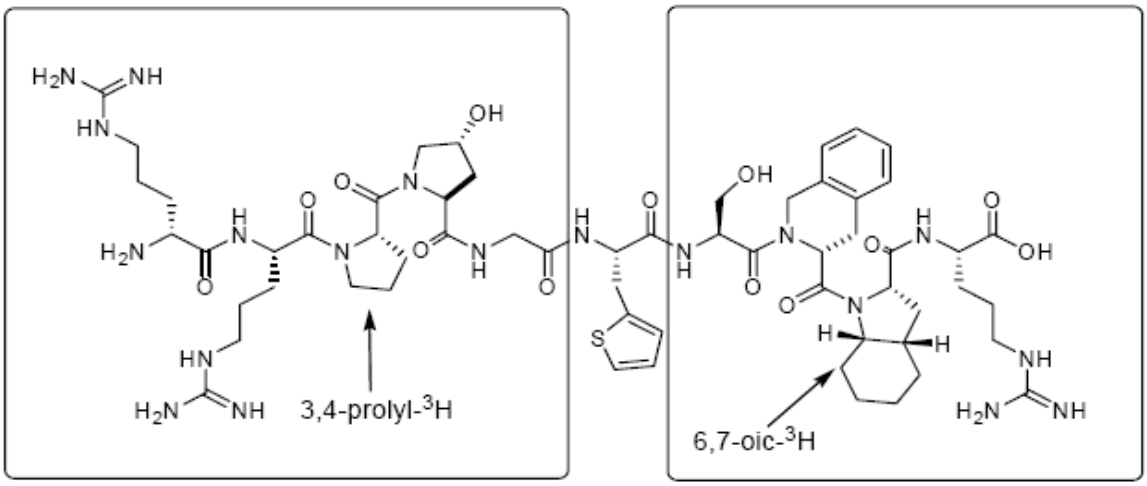
2.2.3 What are the characteristics of Icatibant distribution?

Following a single administration of Icatibant 0.4 mg/kg as an IV infusion over 30 minutes, the mean (SD) volume of distribution is 0.25 (0.43) L/kg in males, remaining unchanged after the same dose of SC administration of 10 mg/mL solution. The mean steady-state volume of distribution estimates following 3 doses of 30 mg Icatibant SC administration every 6 hours were found to be 0.35±0.04 L/kg in young males, 0.24±0.05 in young females, 0.26±0.05 in elderly males and 0.19±0.04 in elderly females. Upon multiple dosing of 30 mg SC doses in males, mean volume of distribution exhibited a slight reduction (20-30%) relative to single administration while it remains unchanged in females. The binding of Icatibant to human serum proteins is low (~44%).

2.2.4 What are the characteristics of Icatibant metabolism?

Icatibant is extensively metabolized to two principal metabolites, M1 and M2 (see Figure 3 for structures of M1 and M2), which have been shown to be relatively weak bradykinin 2 receptor anatagonists compared to Icatibant. It is assumed to be unlikely to contribute to the antagonism of bradykinin effects clinically. While the exact pathway is undetermined, i*n vitro* studies suggest that the metabolism of icatibant is P450-independent. *In vitro* studies suggest that Icatibant does not inhibit relevant drug metabolizing P450s (**CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4**) or induce CYP450 enzymes such as CYP1A2 and CYP3A4, implying that there is a low potential for drug-drug interactions with substrates of CYP1A2 and 3A4.

Figure 3. Structures of Icatibant and its two principal metabolites M1 and M2



Metabolite M1 **Metabolite M2**

2.2.5 What are the characteristics of Icatibant excretion?

Mean excretion data of Icatibant and its metabolites M1 and M2 in urine following IV infusion of escalating doses of Icatibant are listed in Table 3. The recovery of icatibant in urine was low compared to the recovery of the metabolites M1 and M2, reflecting a high degree of Icatibant metabolism and excretion of these metabolites via urine. The percentage of unchanged drug recovered in urine relative to dose administered is only about 5-6%, indicating that the drug is primarily cleared by non-renal mechanisms.

The geometric mean renal clearance of Icatibant across all doing regimens ranged between 0.4 and 2.3 L/h, while 0.4 mg/kg IV infusion over 4 hours yielded geometric mean renal clearance of 0.780 L/hr (Table 4) in healthy young male adults, i.e. calculated to be about 3% of the average total body clearance typically seen in this population (Table 9, section 2.3.1.). The renal clearance of M1 ranged between 6.5 and 9.6 L/h and that of M2 ranged between 4.4 and 9.1 L/h.

Table 3. Urinary excretion of Icatibant and its metabolites, M1 and M2 following IV infusion of various dose and dosing rates of Icatibant in healthy subjects

	Dose level (mg/kg)	Dose administered (µM)	N	Geometric mean (µM)			Geometric mean (% of dose administered)		
				Icatibant	M1	M2	Icatibant	M1	M2
Part I Panels A & B	0.005 [a]	0.339	4	0.060	0.414	0.476	18%	122%	141%
	0.01 [a]	0.773	4	0.192	-	0.901	25%	-	117%
	0.025 [a]	1.712	4	0.143	1.358	1.236	8%	79%	72%
	0.05 [a]	3.851	4	0.299	3.652	3.575	8%	95%	93%
	0.4 [a]	31.109	4	1.865	22.992	21.542	6%	74%	69%
	0.8 [a]	54.627	4	1.675	38.758	38.729	3%	71%	71%
Part I Panel C	0.8 [b]	49.411	4	1.555	43.404	39.028	3%	88%	79%
	1.6 [b]	98.229	4	3.219	94.541	91.505	3%	96%	93%
	3.2 [b]	196.770	4	4.874	173.101	163.131	2%	88%	83%
Part II	0.15 [c]	9.795	6	0.506	6.523	6.098	5%	67%	62%
	0.5 [d]	95.229	6	5.476	80.366	75.211	6%	84%	79%
Part III	0.45 [e]	26.558	6	2.142	15.504	15.815	8%	58%	60%

[a] Icatibant administered over 4 hours, urine collected over 24 hours.

[b] Icatibant administered over one hour, urine collected over 48 hours.

[c] Icatibant administered over 24 hours, urine collected over 28 hours.

[d] Icatibant administered t.i.d. for one day, urine collected over 28 hours.

[e] Icatibant administered over 24 hours for 3 days, urine collected over 72 to 96 hours.

Table 4. Renal clearance of Icatibant and its metabolites, M1 and M2 following IV infusion of various dose and dosing rates of Icatibant in healthy subjects.

	Dose level (mg/kg)	N	Geometric mean (L/h)		
			Icatibant	M1	M2
Part I, Panels A & B	0.005 [a]	4	-	6.928	-
	0.01 [a]	4	2.282	-	9.140
	0.025 [a]	4	0.811	9.613	6.249
	0.05 [a]	4	1.131	7.158	6.975
	0.4 [a]	4	0.780	7.682	7.710
	0.8 [a]	4	0.446	6.962	6.500
Part II	0.15 [b]	6	0.793	7.671	4.392
Part III	0.45 [c]	6	1.175	6.520	4.369

[a] Icatibant administered over 4 hours, urine collected over 24 hours.

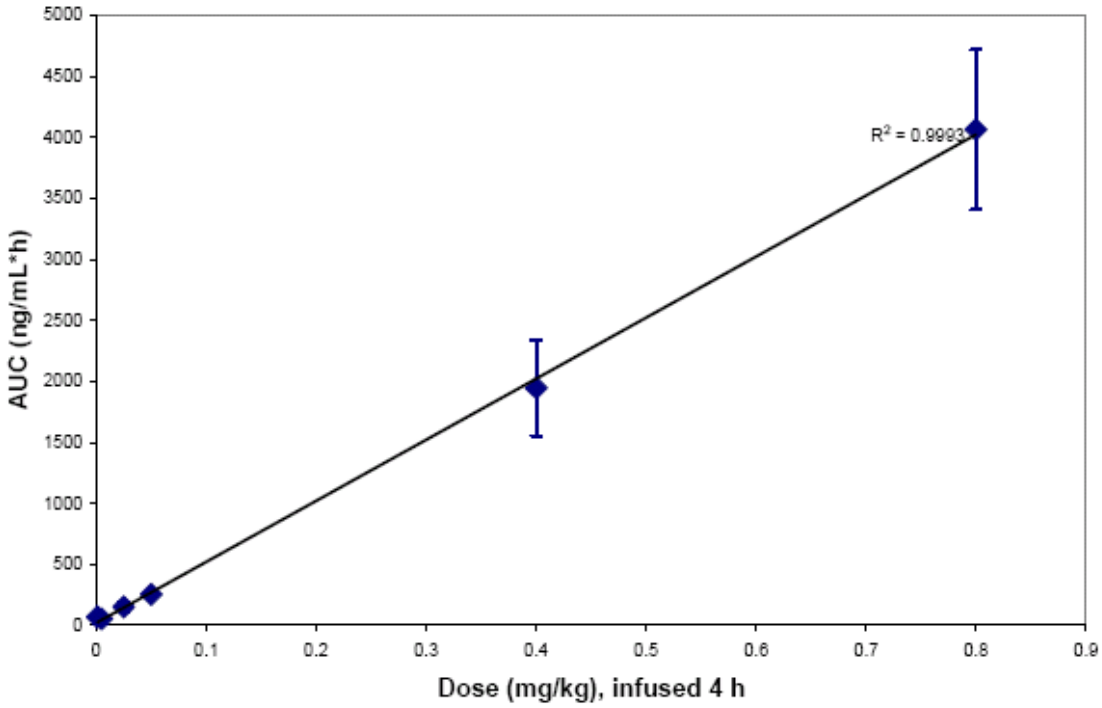
[b] Icatibant administered over 24 hours, urine collected over 28 hours.

[c] Icatibant administered over 24 hours for 3 days, urine collected over 72 to 96 hours.

2.2.6 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Dose proportional increase in systemic exposure ($AUC_{0-\infty}$) of icatibant is observed across single IV doses of 0.005 µg/kg to 0.8 mg/kg (Figure 4). The increase in AUC is less than dose proportional when higher doses escalating to 3.2 mg/kg are employed.

Figure 4. Dose proportional increase in Icatibant systemic exposure (AUC) following IV infusion.



2.2.7 What was the rationale for route of administration and dose regimen selection of Icatibant for evaluation of clinical efficacy and safety?

The Pharmacometric (PM) team within the OCP has been consulted to review the sponsor's population PK, population PK/PD, simulation studies which form the basis of dose selection for confirmatory trials. For details, refer to the PM review by Dr. Nitin Mehrotra included as an (Appendix 4.3) within this review.

Icatibant is a competitive antagonist of the bradykinin type 2 (B2) receptor. It is hypothesized that inhibition of endogenous bradykinin (BK) is required to control key symptoms elicited by overproduction of BK during an acute angioedema attack. Therefore, an exogenous IV BK challenge was selected as a pharmacological tool in a phase I study to investigate the dose range and regimen required to ensure near complete BK antagonism in order to establish the optimal dose, dose regimen, and time window for a clinically relevant inhibition. IV route was chosen for

this initial exploration as it provides the least uncertainty of the exposure-time profile of the drug.

A preliminary exploration of PK-PD relationships was conducted using the inhibitory profile of Icatibant following the BK challenge. 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. The relationship between log-transformed concentration-time points (PK) and effect (PD) data could be described using a sigmoidal E_{max}-model. Table 5 lists the EC_{50} values estimated for each PD response associated with the BK challenge.

Table 5. EC50 values for Icatibant

	Systolic blood pressure	Diastolic blood pressure	Mean blood pressure	Heart rate	Cutaneous blood flow
EC_{50} [nM]	6.55	7.49	7.08	7.11	7.19

EC_{50} values for all responses were similar, ranging from 6.55 to 7.49 nM, comparable to IC_{50} values ranging between 1 and 10 nM obtained from *in vitro* studies. Based on these data, an EC_{50} value of 7.3 nM (9.5 ng/mL) was used in the PK/PD simulations to assess duration of clinical response. In addition, EC_{85} values were also considered for this evaluation. Using the same model above, the EC_{85} value for icatibant was estimated as 54 ng/mL (41 nM). From the phase II study (JE049-2101), all patients maintained plasma concentrations above an expected effect level of over 90% for each of the response parameters up to 4 h after administration, and 67% of the patients maintained levels above EC85 for 6 h.

Table 6 summarizes the results of the estimated duration of effect of icatibant for each of the five responses and doses administered. For the relevant dose of 30 mg, icatibant has a 75% probability of being at least 50% effective for at least 6.5 h. Doubling the icatibant dose from 30 mg to 60 mg results in an increase of duration of effect by 1 to 1.5 h regardless of the confidence level. From these data it could be concluded that at doses beyond 30 mg the duration of effect is relatively insensitive to a change in the administered dose.

Table 6. Estimated duration (hours) of Icatibant effect for a given dose, response, effect level, and confidence interval

		Confidence level								
		90%			75%			50%		
Response	Effect level	15 mg	30 mg	60 mg	15 mg	30 mg	60 mg	15 mg	30 mg	60 mg
Diastolic blood pressure	85%	0	0	0	0	0	0	4.5	5.5	6.5
	50%	3	4.5	5.5	4.5	6	7	6.5	7.5	8.5
Mean blood pressure	85%	0	0	0	0	0	0	4.5	5.5	6.5
	50%	3	4.5	5.5	5	6	7	6.5	7.5	9
Heart Rate	85%	1.5	3	3.5	3	4.5	5	4.5	5.5	6.5
	50%	4	5.5	6	5	6.5	7.5	6.5	8	9
Cutaneous blood flow	85%	2.5	3.5	4.5	3.5	4.5	5.5	4.5	6	7
	50%	4	5.5	6	5	6.5	7.5	7	8	9.5

According to the PM reviewer, the sponsor's PK/PD approach for dose selection is reasonable. However, the efficacious dose based on biomarker (bradykinin challenge in healthy subjects) may not be efficacious for the clinical endpoint (Visual analogue scale, VAS, for hereditary angioedema, HAE) due to: 1) uncertainty about the relationship between the biomarker and the clinical endpoint; 2) larger variability in the clinical endpoint than the biomarker, leading to an underpowered study. Given the lower plasma bradykinin level (15 pM – 30 pM) after bradykinin challenge in healthy subject compared to that in a patient during an acute HAE attacks (~50 pM), the dose based on PK/PD may be an underestimate of the dose for HAE patients. Additionally, the PD data in the Phase 2 study JE049-2101, revealed that Icatibant 30 mg SC dose has been able to bring the BK level down to an average of 38 pM from the baseline level of 63 pM but not enough to get BK down to 2.2-7.1 pM typically found in disease-free subjects. These concerns may well contribute to the non-significant results obtained in one of the Phase 3 clinical trials. The observation of relatively faster onset of action in females (1.6 hours) compared to males (3.5 hours) in one of the Phase III studies (JE049-2102) suggested that higher exposure may work better.

A concentration of 20 mg/mL produced more severe injection site reactions than a solution with a concentration of 10 mg/mL. A SC dose of 0.4 mg/kg (concentration of 10 mg/mL) resulted in good tolerability. Additionally, an injection volume of 3 mL containing the proposed dose of 30 mcg is a large volume and probably approaching the limit of patient convenience. Therefore, increasing the dose beyond 30 mg may not be practically feasible with the proposed formulation and route of administration.

2.2.8 Does Icatibant prolong the QTc interval?

A randomized, double-blind, placebo-controlled study was conducted to explore the PK, safety (including QTc analysis) and tolerability of multiple subcutaneous doses (3 doses every 6 hr and single doses on day 8 and 15) of Icatibant administered to healthy young and elderly, male and female subjects. Study results were previously submitted under IND 68,214 and had been reviewed by the QT-IRT team within the Agency. This study does not qualify to be a thorough

QT study due to lack of positive control. Specific conclusions and recommendations from this review (see Dr. Hick's review dated 1/27/2007) include:

- **The ECGs from the study suggest icatibant acetate is associated with ST/T wave changes and QT prolongation.**
- Since icatibant acetate is associated with QT prolongation, a thorough QT study is not required. QT prolongation issues can be addressed in the labeling.
- Periodic monitoring of on-treatment electrocardiograms and electrolytes is recommended in future studies with Icatibant acetate.
- The 30 mg SC dose studied may be adequate because (a) there are no identified intrinsic or extrinsic factors that are known to increase exposures; (b) less than 5% of the administered dose is renally excreted and lack of increase in exposure in subjects with moderate renal impairment; (c) generally there was no difference in exposure in subjects with hepatic impairment; (d) icatibant has a short half-life and is not expected to accumulate with repeat dosing; and (e) icatibant will be given often as a single dose to treat acute attacks of HAE.

One liver cirrhosis patient with moderate hepatic impairment exhibited about 21-fold higher C_{max} and 13-fold greater AUC compared to other hepatic impaired patients in study JE049-2001. If this is true for a sub-set of subjects, then close monitoring of ECGs for such patients during Icatibant treatment may be needed.

2.2.9 Injection site reactions are observed with SC injections of Icatibant. Is this related to the drug or the formulation?

An attempt has been made by this reviewer to evaluate the incidence of injection site reactions within the study JE049 #1102. The incidence of local reactions at the injection site was reportedly higher for the SC treatment compared to the placebo treatment in Part 1 (Table 7) . Similarly, the incidence of local reactions at the injection site was noticeably higher for the SC treatment compared to the IV treatment in Part 2 (Table 8). The intensity of these reactions was mild. No subject had to be withdrawn due to these site reactions. It appears that the number of site reactions dropped (9 vs. 6) when drug concentration in the solution for SC injection was lowered from 40 mg/mL to 20 mg/mL. Also, the incidence of site reaction increased (6 vs. 11) when higher dose (i.e. more volume of solution) of the drug was administered using the same concentration solution compared to administration of lower dose (hence lower volume). Therefore from this small study, this reviewer concluded that the site reaction may possibly be due to the drug concentration and not so much the formulation. This is further substantiated by the fact that the number of injection site reactions was comparable between the two treatments of 0.2 mg/kg using 40 mg/mL solution and 0.4 mg/kg using 20 mg/mL solution, i.e. in spite of using substantially larger volume for the later treatment in part 1 (Table 7). In part 2 also, incidence of site reactions was slightly higher (37 vs. 33) from the 20 mg/mL solution compared to 10 mg/mL (Table 8).

Table 7. Frequency of adverse events by system organ class, MedDRA term, and treatment in Part 1.

Route of administration		Subcutaneous injection					
Icatibant dose		Placebo	0.05 mg/kg	0.2 mg/kg		0.4 mg/kg	
Concentration		0	40 mg/mL	20 mg/mL	40 mg/mL	20 mg/mL	Total
N		4	3	3	3	3	16
MedDRA SOC Term	MedDRA LL Term	n	n	n	n	n	n
General disorders and administration site conditions	Flu-like illness	1	-	-	-	-	1
	Injection site burning	1	-	1	2	3	7
	Injection site erythema	-	2	3	3	3	11
	Injection site pruritus	-		1	2	-	3
	Injection site warmth	-	-	-	2	2	4
	Swelling of injection site	-	1	1	-	3	5
Investigations	CK increased	1	-	-	1	1	3
Skin and subcutaneous tissue disorders	Localized erythema	-	-	-	1	-	1
Total adverse events		3	3	6	11	12	35
Total subjects with adverse events		3	2	3	3	3	14

Table 8. Frequency of adverse events by system organ class, MedDRA term, and treatment in Part 2.

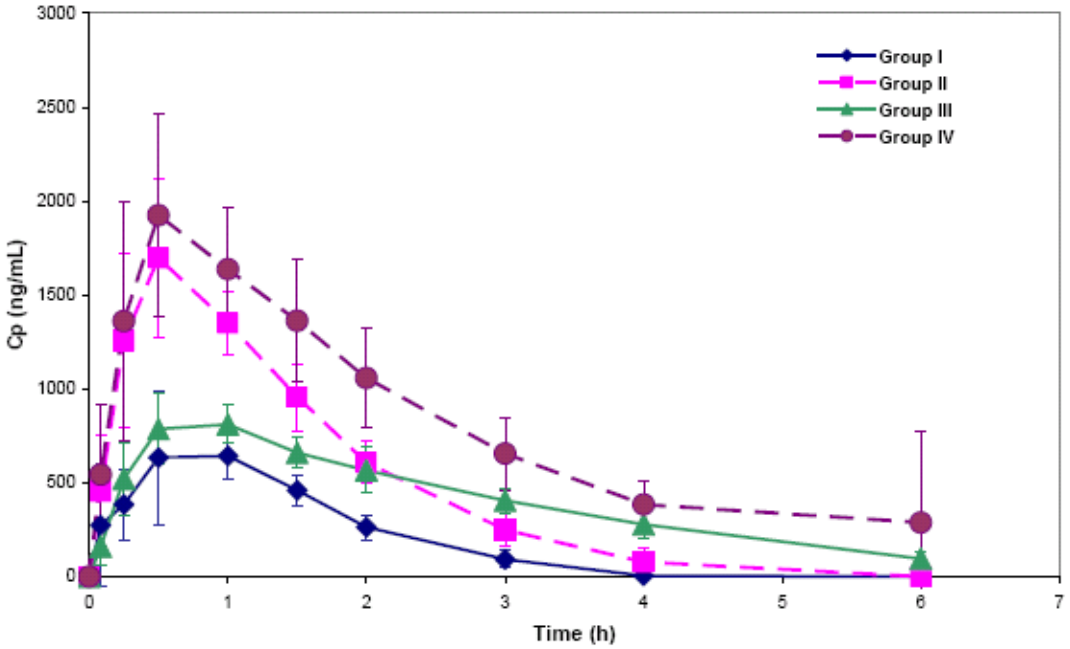
Route		Intravenous	Subcutaneous		Total
Icatibant dose		0.4 mg/kg			
Concentration		1 mg/mL	10 mg/mL	20 mg/mL	
N		24	12	12	24
MedDRA SOC Term	MedDRA LL Term	n	n	n	n
Gastrointestinal disorders	Dysphagia	-	-	1	1
General disorders and administration site conditions	Application site pain	1	-	-	1
	Application site pruritus	3	-	-	3
	Flu-like symptoms	1	-	-	1
	Infusion site erythema	5	-	-	5
	Injection site bruising	-	-	1	1
	Injection site burning	-	11	11	22
	Injection site erythema	-	12	12	24
	Injection site hematoma	1	-	-	1
	Injection site hypesthesia	-	-	1	1
	Injection site pressure sensation	-	2	-	2
	Injection site pruritus	-	3	3	6
	Injection site warmth	-	4	2	6
	Swelling of injection site	-	1	7	8
	Tiredness	-	-	1	1
Infections and infestations	Bronchitis	1	-	-	1
Investigations	CK increased	1	-	-	1
	GOT increased	1	-	-	1
	Red blood cells urine positive	2	-	1	3
Nervous system disorders	Headache	4	2	1	7
Respiratory, thoracic and mediastinal disorders	Rhinitis	-	-	1	1
Total adverse events		20	35	42	97
Total subjects with adverse events		13	12	12	17

2.3 Intrinsic Factors

2.3.1 Is there any age and/or gender effect on Icatibant pharmacokinetics?

Plasma Icatibant concentration-time plots after single SC injection (Day 1) to healthy young (18-45y) males, young (18-45y) females, elderly (>65y) males and elderly (>65y) females are illustrated in Figure 5.

Figure 5. Mean (SD) Icatibant following single SC 30 mg dose in healthy young males (18-45y, Group I), young females (18-45y, Group II), elderly males (>65y, Group III) and elderly females (>65y, Group IV), n=6/group.



Icatibant PK parameters following single-dose (Dose I) and multiple-dose (Dose III) of 30 mg SC injection were grouped by age (18-45y vs. >65y) and gender in Table 9.

Age:

Elderly subjects (>65 years) showed a considerably higher systemic exposure to Icatibant than young subjects aged between 18-45 years. For elderly males (Group III), $AUC_{0-\infty}$ increased by about 2.3- and 2.5-fold (Doses I and III, respectively) compared to young males. Likewise, elderly females (Group IV) exhibited an increase of 1.6- and 1.9-fold of $AUC_{0-\infty}$ (Dose I and III, respectively) compared to young female subjects. However, only minor differences (~12-14%) between C_{max} of gender–matched elderly and young subjects were observed. The age effect was further tested by comparing the $AUC_{0-\infty}$ and C_{max} data normalized by dose and body weight (Table 9). Elderly males showed a 2.6- and 2.8-fold (Dose I and III) higher $AUC_{0-\infty}$ /D than young males. Similarly, elderly females showed a 1.8- and 2.1-fold (Dose I and III) higher $AUC_{0-\infty}$ /D than young females. The differences of C_{max}/D for gender–matched elderly vs. young subjects were 1.3- and 1.6-fold for males and both about 1.3-fold (Dose I and III) for females.

While the general trend for significant age effect for Icatibant remained unchanged, the age effect was slightly more pronounced compared to those observed prior to dose and body weight normalization. Clearance is decreased in elderly compared to younger subjects. Both the elimination rate constant and volume of distribution show similar changes with age that are not readily explained by differences in body weight. The half-life ($t_{1/2}$) estimates were prolonged 2 to 3 fold in elderly compared to young subjects.

Gender:

Young females aged 18-45 years exhibited a 2.4- and 2.1-fold higher $AUC_{0-\infty}$ compared to the age-matched young males following single-dose (Dose I) and multiple-dose (Dose III) SC administration, respectively. Likewsie, elderly females aged >65 years exhibited a 1.8- and 1.6-fold increase of $AUC_{0-\infty}$ compared to elderly males. Correspondingly, C_{max} was 2.2- and 1.9-fold higher in the young females and 2.2- and 1.6-fold higher in elderly females compared with the respective age-matched males following single and multiple dose SC injection, respectively (Table 9).

The gender effect was further explored by comparing the $AUC_{0-\infty}$ and C_{max} data normalized by dose and body weight (Table 9). Young females demonstrated 2.0- and 1.8-fold (Dose I and III) higher $AUC_{0-\infty}$ /D and 1.9- and 1.6-fold higher C_{max}/D compared to young males. For elderly females, $AUC_{0-\infty}$ /D was about 1.4- and 1.3-fold and C_{max}/D 1.8- and 1.3-fold (Doses I and III) higher than for elderly males. While the general trend for significant gender effects for Icatibant remained unchanged, the gender effect was slightly less pronounced compared to those observed prior to dose and body weight normalization. Clearance shows an approximately 2-fold decrease in women compared to men irrespective of age. Both the elimination rate constant and volume of distribution show similar changes with gender that are not readily explained by differences in body weight. The half-life ($T_{1/2}$) estimates appeared generally unchanged with gender.

Table 9. Icatibant PK parameters after single and multiple-dose (3 doses q6 hr) 30 mg SC injection of Icatibant solution (10 mg/ml) in healthy young males, young females, elderly males and elderly females.

Dose[a]	Parameter		Group[b] [Geom. Mean ±Geom. SD / Range[c]]			
			I	II	III	IV
I	$AUC_{0-\infty}$	[ng·h/mL]	1197.3 ±1.20 (948.5; 1525.9)	2920.9 ±1.16 (2368.1; 3385.2)	2709.2 ±1.21 (1944.6; 3251.9)	4756.6 ±1.29 (3133.4; 6508.4)
	$AUC_{0-\infty}/D$	[g·h/L][d]	2833.6 ±1.28 (1960.3; 4196.3)	5782.0 ±1.23 (4207.4; 7819.8)	7253.2 ±1.24 (4874.4; 8484.6)	10433.8 ±1.31 (7411.1; 14710.0)
	C_{max}	[ng/mL]	739.7 ±1.26 (519.8; 1025.4)	1657.3 ±1.26 (1244.9; 2463.9)	843.8 ±1.19 (698; 1103.6)	1862.0 ±1.36 (1091.2; 2639.4)
	C_{max}/D	[g/L][d]	1750.6 ±1.25 (1310.3; 2121.7)	3280.7 ±1.26 (2211.8; 4500.7)	2259.0 ±1.25 (1749.7; 3082.7)	4084.4 ±1.28 (2673.4; 5405.5)
	t_{max}	[h][e]	0.75 (0.08; 1.00)	0.50 (0.50; 0.50)	1.00 (0.50; 1.00)	0.50 (0.50; 1.00)
	$t_{1/2}$	[h]	0.51 ±1.20 (0.45; 0.73)	0.56 ±1.30 (0.38; 0.76)	1.46 ±1.36 (1.05; 2.32)	1.11 ±1.13 (0.95; 1.29)
	CL/F	[L/h]	25.1±1.20 (19.6; 31.7)	10.3 ±1.16 (8.86; 12.68)	11.1 ±1.20 (9.32; 15.45)	6.31 ±1.29 (4.62; 9.58)
	V_{ss}/F	[L]	18.3 ±1.16 (14.6; 20.7)	8.34 ±1.45 (5.5; 13.8)	23.4 ±1.28 (15.7; 31.9)	10.1±1.25 (8.2; 15.3)
III	$AUC_{0-\infty}$	[ng·h/mL]	1406.3 ±1.18 (1049.9; 1611.0)	2963.3 ±1.18 (2396.4; 3530.3)	3529.1 ±1.15 (2735.0; 3949.9)	5543.6 ±1.21 4163.2; 7256.8)
	$AUC_{0-\infty}/D$	[g·h/L][d]	3328.1 ±1.10 (2852.1; 3638.3)	5866.0 ±1.25 (4377.4; 7631.7)	9448.2 ±1.21 (6855.7; 11845.5)	12160.1 ±1.26 (8578.1; 16372.0)
	C_{max}	[ng/mL]	878.4 ±1.23 (663.5; 1177.0)	1666.5±1.24 (1252.2; 2239.2)	1245.0 ±1.13 (1128.3; 1581.2)	1944.4 ±1.36 (1162.3; 2838.3)
	C_{max}/D	[g/L][d]	2078.8 ±1.1 (1802.5; 2322.6)	3299.0 ±1.24 (2224.7; 4224.6)	3333.1 ±1.19 (2929.8 ; 4416.8)	4265.2 ±1.26 (2847.6; 5411.4)
	t_{max}	[h][e]	0.50 (0.25; 0.50)	0.50 (0.25; 1.00)	0.50 (0.50; 0.50)	0.50 (0.25; 1.00)
	$t_{1/2}$	[h]	0.46 ±1.31 (0.36; 0.77)	0.53 ±1.17 (0.44; 0.64)	1.60 ±1.04 (1.52; 1.66)	1.41 ±1.03 (1.36; 1.49)
	CL/F	[L/h]	21.3 ±1.18 (18.6; 28.6)	10.1 ±1.18 (8.5; 12.5)	8.50 ±1.15 (7.6; 10.9)	5.4±1.21 (4.1; 7.2)
	V_{ss}/F	[L]	14.2 ±1.42 (10.8; 25.3)	7.77 ±1.11 (7.0; 9.3)	19.60 ±1.17 (16.6; 25.3)	11.0 ±1.25 (8.2; 15.5)

[a] Dose I and III: both doses were administered on Day 1, 12 h apart
[b] N per treatment group = 6
[c] Range (minimum; maximum)
[d] $AUC_{0-\infty}$ and C_{max} per dose and body weight
[e] Median (minimum; maximum)
Groups: I - male, 18-45 years; II - female, 18-45 years; III - male, >65 years; IV - female, >65 years

From this particular study, it is abundantly clear that there is significant age and gender effects on Icatibant pharmacokinetics. The sponsor has not provided or evaluated any scientific mechanisms to explain the marked differences in drug exposure related to age and gender. This difference in exposure may arise from the differences in absorption and/or elimination between these age and gender subgroups. The site of injection in this study was right upper quadrant of the abdomen, which was the same site used in the absolute bioavailability study (JE049 #1102) which enrolled only males in the age range of 18 to 50 years. This suggests that it is highly unlikely that the exposure difference between various subgroups is due to absorption difference.

Rather, this age and gender-specific differences are more likely due to differences in drug clearance. Therefore, it may be worthwhile to understand the mechanistic basis for these differences in subpopulations that may help develop optimal dosing to achieve desired efficacy and safety of this drug and label the drug appropriately.

One of the Phase 3 studies, Study JE049 #2102 revealed that the time to onset of symptom relief was relatively greater in male patients (3.5 hours) compared to female (1.6 hours) patients treated with Icatibant. Although small sample size (12 males and 24 females) in this study limits definitive conclusions regarding gender effect on efficacy but this general trend is supported by differences in systemic exposure observed between males and females. The efficacy differences between the two genders were further supported by responder analysis. The response rate at 4 hours after the start of treatment was 54.5% for the male patients and 91.7% for the female patients in the Icatibant treatment group from the same study. For further details, refer to Medical Officer Dr. Limb's NDA 22150 review dated 2/29/08.

2.3.2 Does the renal function affect Icatibant pharmacokinetics?

A dedicated renal impairment study was not conducted for Icatibant, however such study is not needed as the drug is primarily cleared non-renally. Study JE049-2002 conducted in patients with hepatorenal syndrome (with mild to moderate renal impairment) did not show any observable differences in the plasma levels of Icatibant or its metabolites compared to subjects with normal renal function. No correlation was observed between icatibant clearance and GFR values >30 mL/min as measured by sinistrine clearance. Therefore dose adjustment is not warranted in patients with renal impairment.

2.3.3 Does the hepatic function affect Icatibant pharmacokinetics?

A single centre, multiple-dose, double blind, 2-way crossover, randomized, placebo controlled study (JE049-2001) was conducted with Panel A: 8 patients with hepatic insufficiency (6 with mild impairment with Child Pugh scores of 5-6 and 2 with moderate impairment with Child Pugh scores of 7-8) and Panel B: 8 normal healthy volunteers matched for gender, race, body mass index (BMI), and age. All subjects received either a dose of 0.15 mg/kg/day Icatibant or placebo given as continuous intravenous infusion over 3 days (3 x 24 hours) in one period and then crossed over to receive the alternate treatment in the next period.

The PK parameters summarized as descriptive statistics from both panels of treated subjects are presented in Table 10 and are found to be generally comparable between healthy subjects and moderate to mild hepatic impaired patients. In one patient (subject no. 207, Panel A), a very high plasma Icatibant concentrations were measured up to 48 hr after the start of infusion, with C_{max} and AUC of this subject calculated to be about 21- and 13-fold higher than the other 7 subjects in the same panel (Tables 10-11). The plasma concentrations of the metabolites, M1 and M2 were comparable to the rest of the hepatic impaired subjects as evident from summary tables with (Table 12) and without (Tables 13) the outlier subject. No clear explanation was provided. Possible explanations presented by the sponsor included incorrect handling of blood samples or sampling close to Icatibant infusion site, although a severe impairment of Icatibant metabolism (Child Pugh score of 7 for this subject) can not be completely ruled out. It is important to look out for such outlier in future trials enrolling hepatic impaired patients.

Table 10. Summary statistics of PK parameters of Icatibant in patients with hepatic impairment and healthy subjects

Panels ↓	Parameter →	Dose mg	Cmax µg/L	Tmax hr	AUCtot µg.h/L	T ½ hr	CL L/hr	Vz L
Panel A Cirrhosis patients n = 8	Mean	31978	154.64	19.535	5778.2	2.767	12.749	45.131
	GeoMean	31498	61.586	9.3779	3142.2	2.5826	10.024	37.348
	SD	6214.9	312.68	19.923	9695.3	1.1176	6.7412	21.269
	Median	31590	40.9	14.25	2483	2.4709	12.246	47.573
	Min	24885	30.7	1.0833	1369.5	1.4892	1.1095	5.7827
	Max	45000	927.4	48.167	29730	4.8417	25.071	74.938
Panel B healthy volunteer n = 8	Mean	32822	41.84	37.192	2362	2.5822	13.926	51.373
	GeoMean	31776	39.617	17.255	2349.3	2.4666	13.526	48.132
	SD	9638.6	16.169	32.702	258.25	0.74427	3.5092	16.943
	Median	31725	33.784	36.208	2360.9	2.6755	13.682	54.896
	Min	21600	29.8	1.35	1917.4	1.1908	8.1237	20.532
	Max	54495	70.3	72.25	2684.2	3.4135	20.302	69.654

Table 11. Summary statistics of PK parameters in patients with hepatic impairment (without subject 207)

Panels ↓	Parameter →	Dose mg	Cmax µg/L	Tmax hr	AUCtot µg.h/L	T ½ hours	CL L/hr	Vz L
Panel A Cirrhosis patients n = 7	Mean	31834	44.243	21.731	2356.5	2.6462	14.412	50.753
	GeoMean	31291	41.805	10.53	2279.4	2.4617	13.728	48.754
	SD	6698.4	17.846	20.448	624.93	1.1493	5.2166	15.259
	Median	30195	38.5	24.0	2286.2	2.3723	12.427	53.862
	Min	24885	30.7	1.0833	1369.5	1.4892	8.6562	30.862
	Max	45000	81.1	48.167	3181.5	4.8417	25.071	74.938

Table 12. Summary statistics of PK parameters of Icatibant metabolites, M1 and M2 in patients with hepatic impairment and healthy subjects

Panels ↓		Parameter →	Cmax µg/L	Tmax hr	AUCtot µg.h/L	Lz L/hr
M1	Panel A Cirrhosis patients	N	8	8	7	7
		Mean	35.043	32.99	2064.1	0.23281
		GeoMean	34.47	29.987	2032.8	0.22046
		SD	7.1147	17.943	397.25	0.074882
		Median	32.733	24.042	2089	0.24363
		Min	28.499	23.583	1537	0.1102
		Max	46.32	72.167	2813.8	0.30892
	Panel B Healthy volunteers	N	8	8	8	8
		Mean	36.254	54.327	2031.2	0.24759
		GeoMean	34.411	49.658	1933.4	0.23888
		SD	14.103	21.591	751.91	0.068765
		Median	33.838	60.258	1749.8	0.2591
		Min	23.654	24	1365.4	0.14745
		Max	68.706	73	3685.4	0.35557
M2	Panel A Cirrhosis patients	N	8	8	7	7
		Mean	48.155	42.104	3000.2	0.22185
		GeoMean	46.869	37.622	2951	0.21599
		SD	12.34	21.415	615.48	0.055668
		Median	45.877	36.083	2961.8	0.18474
		Min	34.153	23.917	2351	0.16143
		Max	69.811	72.5	4220.3	0.29214
	Panel B Healthy volunteers	N	8	8	8	8
		Mean	46.955	60.327	2628.3	0.23399
		GeoMean	42.98	54.927	2438.9	0.22937
		SD	24.093	22.47	1293.1	0.047761
		Median	38.931	72.233	2180.6	0.24305
		Min	28.527	23.85	1668.7	0.15936
		Max	101.22	73	5703.8	0.29957

Table 13. Summary statistics of PK parameters of Icatibant metabolites, M1 and M2 in patients with hepatic impairment (without subject 207)

		Parameter →	Cmax µg/L	Tmax hr	AUCtot µg.h/L	Lz L/hr	T½M1 hr
M1	Panel A Cirrhosis patients	N	7	7	6	6	6
		Mean	35.179	30.833	2058.9	0.23713	3.3623
		GeoMean	34.524	28.031	2022.6	0.22281	3.111
		SD	7.6736	18.227	434.91	0.081069	1.5938
		Median	32.254	24	2086.4	0.26597	2.6246
		Min	28.499	23.583	1537	0.1102	2.2438
		Max	46.32	72.167	2813.8	0.30892	6.2897
M2		N	7	7	6	6	6
		Mean	48.323	41.25	2982.2	0.22843	3.2088
		GeoMean	46.852	36.326	2925.5	0.22218	3.1198
		SD	13.319	22.983	672.2	0.057919	0.82959
		Median	45.833	24.083	2921	0.22941	3.1406
		Min	34.153	23.917	2351	0.16143	2.3727
		Max	69.811	72.5	4220.3	0.29214	4.2937

2.3.4 Is the PK in HAE patients similar to healthy subjects?

The PK parameters of Icatibant in male and female HAE patients after various doses and dosing regimen are tabulated below (Table 14) from the Phase II study JE049-2102. These parametrs are highly comparable to the parameters listed in Table 9 in section 2.3.1. Therefore, it appears PK in patients are similar to healthy subjects.

Table 14. Pharmacokinetic parameters for Icatibant after single SC injection and IV infusion in male and female HAE patients.

Group		C_{max} [ng/mL] n = 4	AUC_{0-t} [h*ng/mL] n = 4	$AUC_{0-\infty}$ [h*ng/mL] n = 4	t_{max} * [h] n = 4	$t_{1/2}$ [h] n = 4
I 0.4 mg/kg *i.v.* (2 h)	Mean	1158.0	3126.6	3249.0	1.750	1.508
	SD	355.3	842.0	831.8	0.500	0.916
	CV%	30.7	26.9	25.6	2.00	60.8
	Geometric mean	1113.8	3037.2	3162.1	1.00-2.00	1.346
II 0.4 mg/kg *i.v.* (0.5 h)	Mean	2569.0	3196.2	3370.5	0.375	1.023
	SD	857.0	1110.7	1182.1	0.144	0.192
	CV%	33.4	34.8	35.1	0.37	18.8
	Geometric mean	2470.5	3062.4	3222.5	0.25-0.50	1.007
III 0.8 mg/kg *i.v.* (0.5 h)	Mean	4683.2	5011.5	5217.3	0.380	1.013
	SD	222.9	1753.1	1835.1	0.000	0.147
	CV%	4.8	35.0	35.2	0.38	14.5
	Geometric mean	4679.2	4806.7	4999.5	0.38-0.38	1.005
IV 30 mg *s.c.*	Mean	1278.3	2555.1	2718.2	0.750	1.057
	SD	160.4	535.0	650.3	0.289	0.238
	CV%	12.5	20.9	23.9	0.75	22.5
	Geometric mean	1271.0	2505.8	2649.2	0.50-1.00	1.037
V 45 mg *s.c.*	Mean	2229.8	4886.1	5686.6	0.875	1.317
	SD	399.9	563.3	1133.3	0.250	0.185
	CV%	17.9	11.5	19.9	1.00	14.1
	Geometric mean	2201.8	4862.8	5603.3	0.50-1.00	1.307

* For T_{max}: Median and Min–Max are given instead of CV% and geometric mean

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

Formal drug-drug interaction studies were not performed for Icatibant. *In vitro* study did not show any significant inhibition of drug metabolizing CYP450 enzymes (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) or induction of CYP450 enzymes such as CYP1A2 and CYP3A4. The Applicant has postulated a theoretical interaction between icatibant and ACE inhibitors, suggesting that icatibant may compromise the antihypertensive effects of ACE inhibitors via bradykinin antagonism. Clinical trials excluded subjects taking ACE inhibitors.

The possibility that short term administration of icatibant will alter significantly the chronic antihypertensive effect of an ACE inhibitor is presently unknown.

2.5 General Biopharmaceutics

2.5.1 Was the formulation used in clinical trial the same as to-be-marketed?

Yes. The same formulation is used for both IV infusion and SC injection.

2.6 Analytical Section

2.6.1 Were the analytical procedures used in this NDA acceptable?

For the early studies conducted by (b) (4) (JE049-9101, and JE049-9103), icatibant was measured using a radioimmunoassay developed and used at the (b) (4) (b) (4) This was a non-validated assay. For study JE049-9106 the radioimmunoassay had been improved and validated. The detection limit was (b) (4) icatibant with minimal cross-reaction from the M1 metabolite (b) (4). These studies were not reviewed.

Subsequently, a new analytical method (LC-MS/MS) to measure icatibant and the M1 and M2 metabolites was developed to use in studies JE049 #1001 and JE049 #2001. This was a validated LC-MS/MS method developed at the (b) (4) This has been applied for both plasma and urine analysis with different limits of quantitation.

Calibration curves were linear from 4.3 to 683 µg/L for icatibant, from 1.8 to 295 µg/L and from 2.2 to 353 µg/L for M1 and M2, respectively. The coefficients of variation (CV%) for intra-assay precision were 2.9% to 3.9% for icatibant, 4.7% to 9.9 for M1 and 3.4% to 12% for M2. Inter-assay precision (CV%) was 2.4% to 5.8% for icatibant, 3.2% to 10.4% for M1, and 7.0% to 10.1% for M2.

The same LC-MS/MS assay was applied to measure urine concentrations of icatibant, M1 and M2 in a single run. Calibration curves were linear from 0.25 to 15 µg/mL for icatibant, and from 0.5 to 30 µg/mL for M1 and M2. The inter-assay precision (CV) was 4.5% to 17.5% for icatibant, 6.7% to 10.7% for M1, and 6.9% to 9.9% for M2 signifying poor precision and not acceptable based on FDA recommendation of not exceeding 15% for precision. Therefore, urine data is less reliable but still not enough to prevent making broad conclusions about renal clearance and its contribution towards overall systemic clearance.

A new LC-MS/MS assay was subsequently developed at (b) (4) (b) (4) which allowed measurement of plasma Icatibant and its metabolite, M2 in studies JE049 #1101, JE049 #1102, JE049 #2101, JE049 #2002 and JE049 #1103. The M2 metabolite of Icatibant could also be quantified by this method. LLOQs are shown below:

Icatibant: LOQ range 2.53-45.4 ng/mL
M2: LOQ range 0.912-21.5 ng/mL

The bioanalytical assays in plasma fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance.

3 LABELING RECOMMENDATIONS

As the intended regulatory action of this review from the Medical Reviewer is Not Approvable, a broad overview of the two major changes needed for the proposed labeling is presented below. A line-by-line review is not included in this review.

1. QT/QTc effects need to be addressed in section 12.2 (Pharmacodynamics) of the label.
2. Clearance and volume estimates need to be included in section 12.3 (Pharmacokinetics) of the label.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 INDIVIDUAL STUDY REVIEWS

4.2.1 Study JE049 #1102

Title: Tolerability and Absolute Bioavailability of a Single Subcutaneous Dose of Icatibant Compared to a Single Intravenous Infusion of Icatibant in Healthy Subjects.

Objectives: The primary objective of the study was to evaluate the absolute bioavailability of icatibant after s.c. injection in comparison to an i.v. infusion of the drug. The secondary objective was to assess the safety and tolerability of icatibant after s.c. injection in healthy subjects.

Design: The study was performed in 2 parts. In Part 1, 16 subjects, 18 to 49 years of age, received ascending doses of s.c. icatibant or placebo (0.05 mg/kg, 0.2 mg/kg (repeated once), and 0.4 mg/kg) in a double-blind fashion. The concentration of icatibant used for the first two dose levels (40 mg/mL) resulted in mild skin reactions. Accordingly, the second dose level (0.2 mg/kg) was repeated in an additional 4 healthy subjects using a concentration of 20 mg/mL. This concentration was subsequently used for the next dose level (0.4 mg/kg). After safety and tolerability of the 0.4 mg/kg dose of icatibant had been demonstrated in Part 1, the second part of the study was conducted. In Part 2, which was a randomised, open-label, crossover design in 24 healthy subjects 20 to 50 years of age, each subject received a 0.4 mg/kg dose of icatibant as a subcutaneous injection at one of two dose concentrations (10 or 20 mg/mL) and a 0.4 mg/kg dose of icatibant as a i.v. infusion (1 mg/mL solution) over 30 minutes with a 7-day washout period in between the doses.

Main Outcome Measure: In Part 2, blood samples for the measurement of plasma concentrations of icatibant and its M2 metabolite were taken pre-dose and at 5, 15, 30, 60, and 90 min, 2, 3, 4, 6, 8, 10, 12, 24 and 36 h post-dose. The single dose pharmacokinetics of icatibant and M2 were calculated, including t_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, CL, and V from the plasma concentration-time profiles using noncompartmental analysis. Absolute bioavailability was assessed by comparing the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of SC versus IV icatibant.

Results: Mean (±SD) plasma concentrations of Icatibant following IV infusion and SC injections are plotted in Figure 4.2.1. Pharmacokinetic data are listed in Table 4.2.1. The C_{max} was reached at the end of the IV infusion i.e. 30 minutes and was higher than that from SC injections, as expected, but the AUC data of the SC injections were comparable to the IV infusion. SC injection also resulted in the T_{max} of 30 minutes regardless of the concentration of the administered Icatibant formulation. Mean absolute bioavailability ($AUC_{0-\infty}$) for Icatibant 20 mg/mL and 10 mg/mL by SC injections were found to be 86.1% (95% CI: 70.88; 98.20) and 97.2% (95% CI: 87.72; 106.43), respectively, based on geometric mean ratios (Table 4.2.2). The mean half lives of the SC injections and the IV infusions were comparable, ranging from 1.21 h to 1.46 h.

For the M2 metabolite, the mean C_{max} values from the SC injections were slightly lower than the mean C_{max} observed following the i.v. infusion. The median t_{max} values for M2 were found to be 2.0 (1.5-3.0), 2.0 (1.4-4.0) and 1.5 (1.0-3.0) hours following 20 mg/mL and 10 mg/mL SC

injections and the IV infusion, respectively. The mean $AUC_{0-\infty}$ and $t_{1/2}$ estimates were comparable between the three treatments.

Regarding the bioavailability of M2, there was little difference between the two SC injections and they in turn were no different from the IV infusion. Therefore, bioavailability estimates between the three treatments are essentially comparable.

Figure 4.2.1. Mean (SD) plasma concentration-time plots of icatibant in healthy males following a 0.4 mg/kg dose administered as a 30 min intravenous infusion (n=24), a SC injection with a drug concentration of 20 mg/mL (n=12) and a SC injection with a drug concentration of 10 mg/mL (n=12).

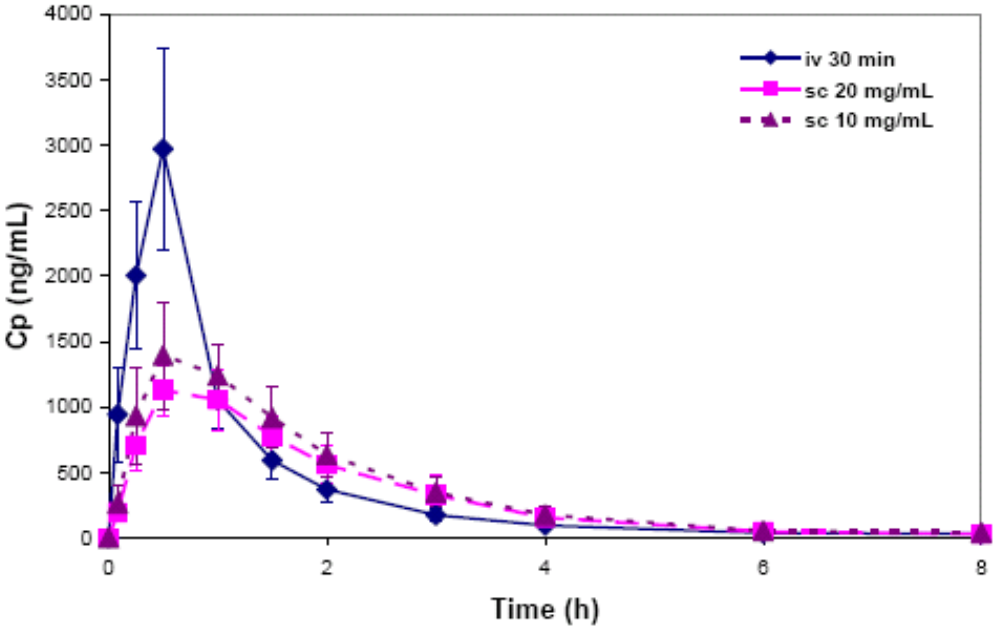


Table 4.2.1. Mean (CV%) pharmacokinetic parameters of Icatibant and its metabolite, M2 following administration of 0.4 mg/kg Icatibant solution as single intravenous (IV) infusion and single subcutaneous (SC) injections of 10 mg/mL and 20 mg/mL.

Treatments	N	Analyte	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	$T_{1/2}$ (hr)
0.4 mg/kg SC 20 mg/mL	12	Icatibant	0.50 (0.5-1.0)	1149 (18)	2557 (24)	2615 (23)	1.24 (17)
		M2	2.00 (1.5-3.0)	362 (24)	2130 (29)	2289 (31)	2.66 (22)
0.4 mg/kg SC 10 mg/mL	12	Icatibant	0.50 (0.5-1.0)	1429 (26)	3040 (20)	3114 (20)	1.21 (20)
		M2	2.00 (1.5-4.0)	387 (29)	2040 (28)	2192 (29)	2.82 (25)
0.4 mg/kg IV 1 mg/mL over 0.5h	24	Icatibant	0.5 (0.5-0.5)	2971 (26)	3120 (24)	3208 (24)	1.46 (45)
		M2	1.50 (1.0-3.0)	476 (24)	2148 (26)	2268 (26)	2.62 (16)

Table 4.2.2. C_{max} and AUC ratios between SC injections and IV infusion of 0.4 mg/kg Icatibant

		0.4 mg/kg SC, 20 mg/mL [%]			0.4 mg/kg SC, 10 mg/mL [%]		
		C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$
N		12	12	12	12	12	12
Icatibant	Mean (%)	39.96	86.22	86.10	50.84	97.61	97.20
	SD	11.58	23.24	23.76	12.07	14.65	15.28
	CV%	29.0	27.0	27.6	23.7	15.0	15.7
	Median (%)	38.6	81.0	81.1	55.1	99.7	98.0
M2	Mean (%)	77.74	98.68	100.20	87.56	101.4	102.9
	SD	15.27	19.40	19.87	37.72	33.34	32.29
	CV%	19.6	19.7	19.8	43.1	32.9	31.4
	Median (%)	81.9	95.2	96.7	74.4	89.9	92.2

Safety (Injection site reactions):
All 30 AEs in Part 1 which were rated as probably related to treatment were injection site reactions, of which 11 were injection site erythema, 7 were injection site burning, 5 were injection site swelling, 4 were injection site warmth, and 3 were injection site pruritus (Table 4.2.3). All AEs in Part 2 rated as probably or possibly related to treatment were injection or infusion site reactions. Of the 70 treatment related local reactions observed after SC injections, 24 were erythema, 22 were burning, 8 were swelling, 6 were pruritus, 6 were warmth, 2 were pressure sensation, 1 was bruising, and 1 was hypoesthesia at the injection site (Table 4.2.4). Of the 9 treatment-related local reactions observed with IV infusions, 5 were infusion site erythema, 3 were pruritus, and 1 was pain at the injection site (Table 4.2.4). The local reactions usually began shortly after infusion/injection, and most of the local reactions resolved within an hour or less. All local reactions were mild in intensity.

Reviewer's Comments: The incidence of local reactions at the injection site was reportedly higher for the SC treatment compared to the placebo treatment in Part 1. Similarly, the incidence of local reactions at the injection site was noticeably higher for the SC treatment compared to the IV treatment in Part 2. The intensity of these reactions was mild. No subject had to be withdrawn due to these site reactions. It appears that the number of site reactions dropped (9 vs. 6) when drug concentration in the solution for SC injection was lowered from 40 mg/mL to 20 mg/mL. Also, the incidence of site reaction increased (6 vs. 11) when higher dose (i.e. more volume of solution) of the drug was administered using the same concentration solution compared to administration of lower dose (hence lower volume). Therefore from this small study, this reviewer concluded that the site reaction may possibly be due to the drug concentration and not the formulation. This is further substantiated by the fact that the number of injection site reactions was comparable between the two treatments of 0.2 mg/kg using 40 mg/mL solution and 0.4 mg/kg using 20 mg/mL solution, i.e. in spite of using substantially larger volume for the later treatment in part 1 (Table 4.2.3). In part 2, incidence of site reactions was slightly higher (37 vs. 33) from the 20 mg/mL solution compared to 10 mg/mL (Table 4.2.4).

Table 4.2.3. Frequency of adverse events by system organ class, MedDRA term, and treatment in Part 1.

Route of administration		Subcutaneous injection					
Icatibant dose		Placebo	0.05 mg/kg	0.2 mg/kg		0.4 mg/kg	
Concentration		0	40 mg/mL	20 mg/mL	40 mg/mL	20 mg/mL	Total
N		4	3	3	3	3	16
MedDRA SOC Term	MedDRA LL Term	n	n	n	n	n	n
General disorders and administration site conditions	Flu-like illness	1	-	-	-	-	1
	Injection site burning	1	-	1	2	3	7
	Injection site erythema	-	2	3	3	3	11
	Injection site pruritus	-		1	2	-	3
	Injection site warmth	-	-	-	2	2	4
	Swelling of injection site	-	1	1	-	3	5
Investigations	CK increased	1	-	-	1	1	3
Skin and subcutaneous tissue disorders	Localized erythema	-	-	-	1	-	1
Total adverse events		3	3	6	11	12	35
Total subjects with adverse events		3	2	3	3	3	14

Table 4.2.4. Frequency of adverse events by system organ class, MedDRA term, and treatment in Part 2.

Route		Intravenous	Subcutaneous		Total
Icatibant dose		0.4 mg/kg			
Concentration		1 mg/mL	10 mg/mL	20 mg/mL	
N		24	12	12	24
MedDRA SOC Term	MedDRA LL Term	n	n	n	n
Gastrointestinal disorders	Dysphagia	-	-	1	1
General disorders and administration site conditions	Application site pain	1	-	-	1
	Application site pruritus	3	-	-	3
	Flu-like symptoms	1	-	-	1
	Infusion site erythema	5	-	-	5
	Injection site bruising	-	-	1	1
	Injection site burning	-	11	11	22
	Injection site erythema	-	12	12	24
	Injection site hematoma	1	-	-	1
	Injection site hypesthesia	-	-	1	1
	Injection site pressure sensation	-	2	-	2
	Injection site pruritus	-	3	3	6
	Injection site warmth	-	4	2	6
	Swelling of injection site	-	1	7	8
	Tiredness	-	-	1	1
Infections and infestations	Bronchitis	1	-	-	1
Investigations	CK increased	1	-	-	1
	GOT increased	1	-	-	1
	Red blood cells urine positive	2	-	1	3
Nervous system disorders	Headache	4	2	1	7
Respiratory, thoracic and mediastinal disorders	Rhinitis	-	-	1	1
Total adverse events		20	35	42	97
Total subjects with adverse events		13	12	12	17

Conclusions: As expected, the mean Icatibant C_{max} after IV infusion was two-fold higher compared to after SC injection, regardless of the concentration of the SC injection. There were no major differences found for the AUC between the different administration routes and between the two SC injections. The study showed high mean absolute bioavailability of the SC injection compared to the IV infusion. The pharmacokinetics of the M2 metabolite was comparable for the SC injection and the IV infusion. Injections site reactions was the most common treatment related adverse event associated with SC injection and the incidence may be related to the drug concentration in the solution for injection.

4.2.2 Study JE049 #1103

Title: Randomized, Double-Blind, Placebo-controlled Study to Explore the Pharmacokinetics, Safety (including QTc analysis) and Tolerability of Several Single Subcutaneous Doses of Icatibant Administered to Healthy Young and Elderly, Male and Female Subjects.

Objectives: The primary objective of the study was to evaluate the pharmacokinetics of a 30 mg SC dose of icatibant administered to male and female, young and elderly healthy subjects. The secondary objectives were to assess the safety and tolerance of icatibant administered as a SC injection, to thoroughly assess any effect of icatibant on the QTc interval, and, since multiple single intermittent doses were given, to determine if antibodies to icatibant were formed.

Design: This was a randomized, double-blind, placebo controlled study conducted at a single investigational center. A total of 32 subjects were enrolled into 4 treatment groups-8 males and 8 females aged 18-45 years (Groups I and II, respectively), and 8 males and 8 females aged >65 years (Groups III and IV, respectively). A total of 5 doses of 30 mg icatibant or placebo were administered as s.c. injections (3 mL of a 10 mg/mL solution) as follows: Day 1 - 3 injections every 6 hours, Days 8 and 15 - 1 injection each day. In each group, 2 subjects received placebo injections and 6 subjects received injections of icatibant.

Main Outcome Measure: Blood samples were taken for determination of plasma concentrations of icatibant pre-dose on Day 1 and at 5, 15, 30, 60, 90 min, 2. 3, 4, 6, 6.5, 8, 12 h, 12 h 5 min, 12 h 25 min, 12.5, 13, 13.5, 14, 15, 16, 18, 24 and 36 h post-first dose. Similarly, blood samples for drug concentrations were obtained on Days 8 and 15 pre-dose and at 0.5 and 2 hours post-dose. In addition to serial 12-lead ECGs, a 12-lead Holter recording was obtained for detailed analysis of QT/QTc using central reading by a cardiologist.

Results: A total of 32 healthy subjects were randomized into the study and all completed the study. There were differences in the baseline mean demographic variables between placebo and icatibant subjects within each Group, this being due to only two subjects being in the placebo sub-group.

Table 4.2.5. Demographic data of subjects in Group 1 (young males), Group 2 (young females), Group 3 (elderly males) and Group 4 (elderly females)

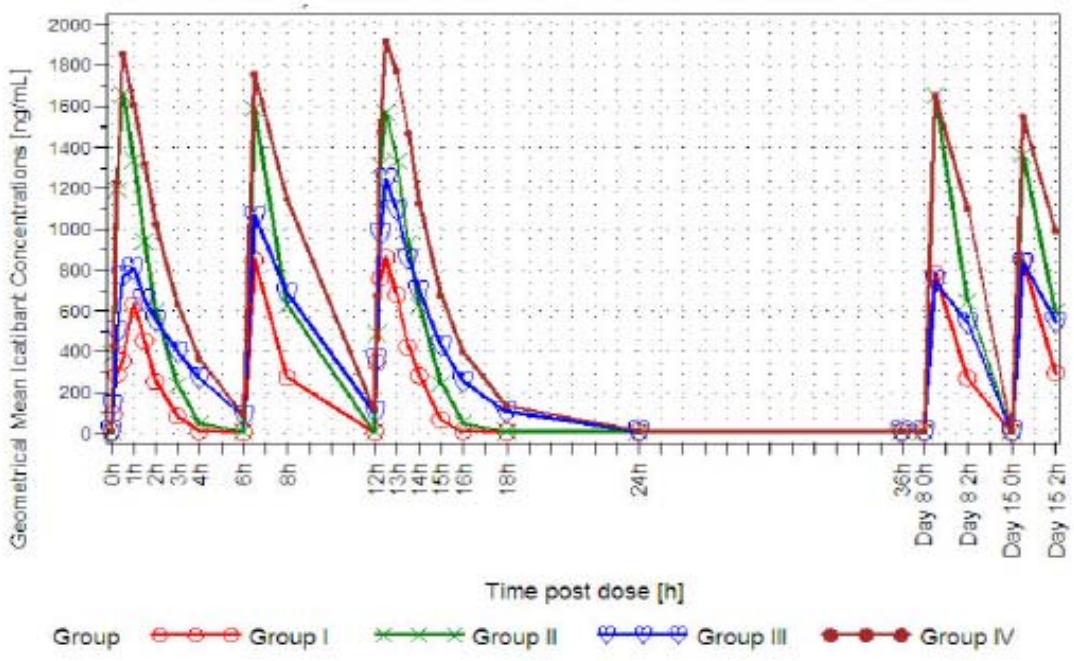
Variable	Group I		Group II		Group III		Group IV		
	P	I	P	I	P	I	P	I	Total
N	2	6	2	6	2	6	2	6	32
Sex [%]									
Female	0%	0%	100%	100%	0%	0%	100%	100%	50%
Male	100%	100%	0%	0%	100%	100%	0%	0%	50%
Ethnic origin [N]									
Asian	0	0	1	0	0	0	0	0	1
Caucasian	2	6	1	6	2	6	2	6	31
Age [years]									
Mean	39.5	28.0	35.5	26.5	69.0	70.0	68.5	73.2	50.3
SD	0.7	4.6	0.7	5.6	4.2	3.8	3.5	5.8	21.6
Minimum	39	21	35	19	66	66	66	66	19
Median	39.5	28.0	35.5	26.0	69.0	69.5	68.5	72.5	53.0
Maximum	40	33	36	36	72	75	71	82	82
Height [cm]									
Mean	175.5	183.0	173.5	166.0	167.0	175.7	166.0	161.5	171.3
SD	4.9	3.6	3.5	7.2	0.0	3.9	2.8	5.6	8.8
Minimum	172	179	171	154	167	172	164	153	153
Median	175.5	182.5	173.5	166.0	167.0	174.5	166.0	164.0	171.5
Maximum	179	188	176	175	167	181	168	167	188
Weight [kg]									
Mean	82.55	71.58	65.65	59.63	77.10	80.65	73.70	66.53	70.89
SD	8.98	9.95	9.69	6.04	5.66	8.30	4.67	10.52	10.88
Minimum	76.2	59.2	58.8	53.3	73.1	73.9	70.4	52.8	52.8
Median	82.55	72.15	65.65	58.40	77.10	77.45	73.70	69.70	72.80
Maximum	88.9	82.5	72.5	69.3	81.1	96.1	77.0	78.9	96.1
BMI [kg/m^2]									
Mean	26.75	21.32	21.75	21.68	27.65	26.13	26.75	25.37	24.15
SD	1.34	2.42	2.33	2.36	2.05	2.42	2.62	2.61	3.21
Minimum	25.8	18.5	20.1	19.4	26.2	23.0	24.9	21.7	18.5
Median	26.75	21.70	21.75	20.90	27.65	26.15	26.75	25.60	23.90
Maximum	27.7	23.6	23.4	25.4	29.1	29.7	28.6	29.0	29.7

Abbreviations: I = Icatibant; N = number of subjects; P = placebo

Icatibant was rapidly absorbed after SC administration and drug levels were detectable in plasma as early as 5 minutes post-dose in almost all subjects. There was a clear difference in plasma concentrations between males and females and young and

elderly subjects (Figure 4.2.2).

Figure 4.2.2. Geometric mean Concentration-Time Profiles on Days 1, 8, and 15



Icatibant PK parameters following single-dose (Dose I) and multiple-dose (Dose III) of 30 mg SC injection were grouped by age (18-45y vs. >65y) and gender in Table 4.2.6.

Age:
Elderly subjects (>65 years) showed a considerably higher systemic exposure to Icatibant than young subjects aged between 18-45 years. For elderly males (Group III), $AUC_{0-\infty}$ increased by about 2.3- and 2.5-fold (Doses I and III, respectively) compared to young males. Likewise, elderly females (Group IV) exhibited an increase of 1.6- and 1.9-fold of $AUC_{0-\infty}$ (Dose I and III, respectively) compared to young female subjects. However, only minor differences (~12-14%) between C_{max} of gender–matched elderly and young subjects were observed.

The age effect was further tested by comparing the $AUC_{0-\infty}$ and C_{max} data normalized by dose and body weight (Table 4.2.6). Elderly males showed a 2.6- and 2.8-fold (Dose I and III) higher $AUC_{0-\infty}$ /D than young males. Similarly, elderly females showed a 1.8- and 2.1-fold (Dose I and III) higher $AUC_{0-\infty}$ /D than young females. The differences of C_{max}/D for gender–matched elderly vs. young subjects were 1.3- and 1.6-fold for males and both about 1.3-fold (Dose I and III) for females.

Clearance is decreased in elderly compared to younger subjects. Both the elimination rate constant and volume of distribution show similar changes with age that are not readily explained by differences in body weight. The half-life (t1/2) estimates were prolonged 2 to 3 fold in elderly compared to young subjects.

Gender:
Females aged 18-45 years exhibited a 2.4- and 2.1-fold higher $AUC_{0-\infty}$ compared to the age-matched males following single-dose (Dose I) and multiple-dose (Dose III) SC administration, respectively. Likewsie, elderly females aged >65 years exhibited a 1.8- and 1.6-fold increase of AUC0–∞ compared to elderly males. Correspondingly, C_{max} was 2.2- and 1.9-fold higher in the young females and 2.2- and 1.6-fold higher in elderly females compared with the respective age-matched males following single and multiple dose SC injection, respectively (Table 4.2.6).

The gender effect was further explored by comparing the $AUC_{0-\infty}$ and C_{max} data normalized by dose and body weight (Table 4.2.6). Young females demonstrated 2.0- and 1.8-fold (Dose I and III) higher $AUC_{0-\infty}$ /D and 1.9- and 1.6-fold higher C_{max}/D compared to young males. For elderly females, $AUC_{0-\infty}$ /D was about 1.4- and 1.3-fold and C_{max}/D 1.8- and 1.3-fold (Doses I and III) higher than for elderly males. Clearance shows an approximately 2-fold decrease in women compared to men irrespective of age. Both the elimination rate constant and volume of distribution show similar changes with gender that are not readily explained by differences in body weight. The half-life ($T_{1/2}$) estimates appeared generally unchanged with gender.

Table 4.2.6. Icatibant PK parameters after single and multiple-dose (3 doses q6 hr) 30 mg SC injection of Icatibant solution (10 mg/ml) in healthy young males, young females, elderly males and elderly females.

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Dose[a]	Parameter		Group[b] [Geom. Mean ±Geom. SD / Range[c]]			
			I	II	III	IV
I	$AUC_{0-\infty}$	[ng·h/mL]	1197.3 ±1.20 (948.5; 1525.9)	2920.9 ±1.16 (2368.1; 3385.2)	2709.2 ±1.21 (1944.6; 3251.9)	4756.6 ±1.29 (3133.4; 6508.4)
	$AUC_{0-\infty}/D$	[g·h/L][d]	2833.6 ±1.28 (1960.3; 4196.3)	5782.0 ±1.23 (4207.4; 7819.8)	7253.2 ±1.24 (4874.4; 8484.6)	10433.8 ±1.31 (7411.1; 14710.0)
	C_{max}	[ng/mL]	739.7 ±1.26 (519.8; 1025.4)	1657.3 ±1.26 (1244.9; 2463.9)	843.8 ±1.19 (698; 1103.6)	1862.0 ±1.36 (1091.2; 2639.4)
	C_{max}/D	[g/L][d]	1750.6 ±1.25 (1310.3; 2121.7)	3280.7 ±1.26 (2211.8; 4500.7)	2259.0 ±1.25 (1749.7; 3082.7)	4084.4 ±1.28 (2673.4; 5405.5)
	t_{max}	[h][e]	0.75 (0.08; 1.00)	0.50 (0.50; 0.50)	1.00 (0.50; 1.00)	0.50 (0.50; 1.00)
	$t_{1/2}$	[h]	0.51 ±1.20 (0.45; 0.73)	0.56 ±1.30 (0.38; 0.76)	1.46 ±1.36 (1.05; 2.32)	1.11 ±1.13 (0.95; 1.29)
	CL/F	[L/h]	25.1±1.20 (19.6; 31.7)	10.3 ±1.16 (8.86; 12.68)	11.1 ±1.20 (9.32; 15.45)	6.31 ±1.29 (4.62; 9.58)
	V_{ss}/F	[L]	18.3 ±1.16 (14.6; 20.7)	8.34 ±1.45 (5.5; 13.8)	23.4 ±1.28 (15.7; 31.9)	10.1±1.25 (8.2; 15.3)
III	$AUC_{0-\infty}$	[ng·h/mL]	1406.3 ±1.18 (1049.9; 1611.0)	2963.3 ±1.18 (2396.4; 3530.3)	3529.1 ±1.15 (2735.0; 3949.9)	5543.6 ±1.21 4163.2; 7256.8)
	$AUC_{0-\infty}/D$	[g·h/L][d]	3328.1 ±1.10 (2852.1; 3638.3)	5866.0 ±1.25 (4377.4; 7631.7)	9448.2 ±1.21 (6855.7; 11845.5)	12160.1 ±1.26 (8578.1; 16372.0)
	C_{max}	[ng/mL]	878.4 ±1.23 (663.5; 1177.0)	1666.5±1.24 (1252.2; 2239.2)	1245.0 ±1.13 (1128.3; 1581.2)	1944.4 ±1.36 (1162.3; 2838.3)
	C_{max}/D	[g/L][d]	2078.8 ±1.1 (1802.5; 2322.6)	3299.0 ±1.24 (2224.7; 4224.6)	3333.1 ±1.19 (2929.8 ; 4416.8)	4265.2 ±1.26 (2847.6; 5411.4)
	t_{max}	[h][e]	0.50 (0.25; 0.50)	0.50 (0.25; 1.00)	0.50 (0.50; 0.50)	0.50 (0.25; 1.00)
	$t_{1/2}$	[h]	0.46 ±1.31 (0.36; 0.77)	0.53 ±1.17 (0.44; 0.64)	1.60 ±1.04 (1.52; 1.66)	1.41 ±1.03 (1.36; 1.49)
	CL/F	[L/h]	21.3 ±1.18 (18.6; 28.6)	10.1 ±1.18 (8.5; 12.5)	8.50 ±1.15 (7.6; 10.9)	5.4±1.21 (4.1; 7.2)
	V_{ss}/F	[L]	14.2 ±1.42 (10.8; 25.3)	7.77 ±1.11 (7.0; 9.3)	19.60 ±1.17 (16.6; 25.3)	11.0 ±1.25 (8.2; 15.5)

[a] Dose I and III: both doses were administered on Day 1, 12 h apart
[b] N per treatment group = 6
[c] Range (minimum; maximum)
[d] $AUC_{0-\infty}$ and C_{max} per dose and body weight
[e] Median (minimum; maximum)
Groups: I - male, 18-45 years; II - female, 18-45 years; III - male, >65 years; IV - female, >65 years

Repeated administration

Almost no accumulation was observed following SC administration of 30 mg Icatibant every 6 hours for 3 doses in healthy young male, and both young and elderly female subjects. Slight accumulation is observed for elderly males (1.25-fold) with concomitant ~30% decrease in volume of distribution in this subject group. All other key PK parameters including T_{max}, $T_{1/2}$, CL/F, Vss/F remain essentially unchanged between single and multiple doses for all age and gender subgroups (Table 4.2.6).

Safety

A total of 28 TEAEs were reported in 15 subjects during the study – 12 subjects receiving icatibant and 3 subjects receiving placebo. The majority of TEAEs were mild in severity. For icatibant-treated subjects, the incidences of AEs seemed to be evenly distributed across treatment groups, although incidences were slightly higher in Groups II and III and most AEs were observed in young females. No SAEs were reported during the study and no TEAE resulted in subject discontinuation.

The majority of SC injections resulted in a reaction at the injection site, mainly characterized by erythema, swelling, and a sensation of warmth. The ISRs were regarded mainly as mild in severity and lasted a few minutes to a few hours, resolving spontaneously without sequelae. There was no trend for a difference in ISRs based on gender or age or following injections on Days 8 and 15 compared to Day 1. There were no clinically significant changes or trends identified in laboratory parameters, coagulation factors, LH and FSH, and vital signs either within a Group or between Groups.

Conclusions: Three 30 mg s.c. doses of icatibant administered at 6-hourly intervals followed by a single dose 1 and 2 weeks later were safe and well tolerated by young and elderly, male and female healthy subjects. Females showed higher plasma levels than did males, with elderly females having approximately a 2.5-fold higher C_{max} and 4-fold higher $AUC_{0-\infty}$ than young males. Gender and age related differences in clearance and a gender difference in apparent volume of distribution were observed.

Reviewer's Comments: The sponsor did not address the scientific basis for this dramatic difference in drug exposure between males and females. This could be a rationale for gender specific dose exploration in the future.

4.2.3 Study JE049 #1001

Title: Renal Function, Safety and Tolerance, Pharmacokinetics and Pharmacodynamic Profile of Icatibant Following Single and Multiple IV Infusion

Objectives: The primary objectives of the study were to investigate the safety and tolerance given under various treatment regimes and doses. Secondary objectives included the investigation of the pharmacological profile of icatibant following a bradykinin challenge, identification of the maximum tolerated dose, and the pharmacokinetics of icatibant and its 2 major metabolites.

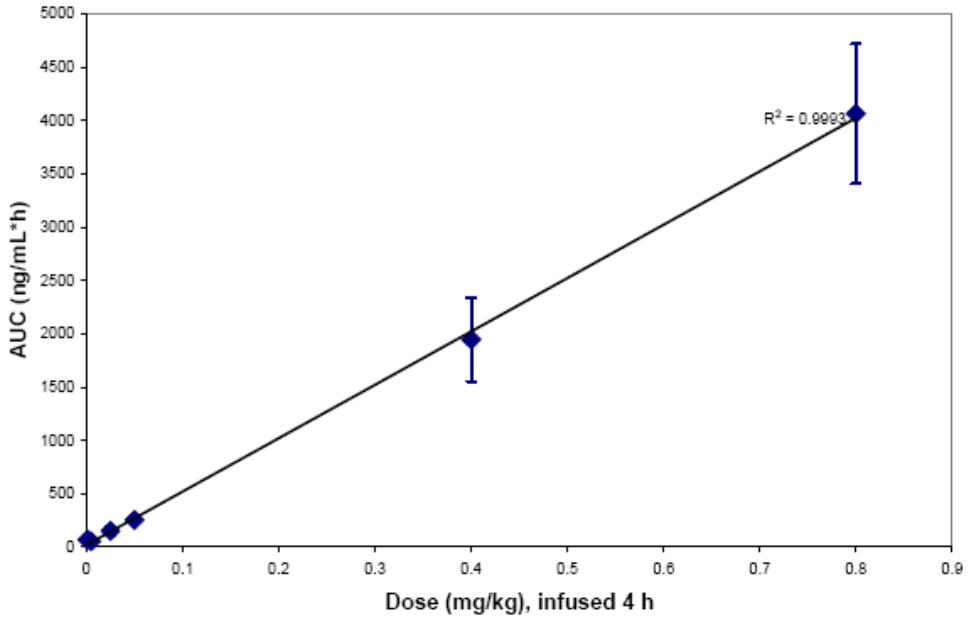
Design: The study was divided into 3 parts (I-III) and with 4 panels in part I. Parts I and II explored various doses and i.v. infusion dosing regimes of icatibant ranging from 0.005 mg/kg over 4 hours i.v. infusion to 3.2 mg/kg over a 1 hour i.v. infusion to 0.15 mg/kg over a 24-hour infusion and 0.5 mg/kg administered as 3 separate 1 hour infusions over 24 hours. A total of 20 healthy male subjects participated in parts I and II. In part III a total of 6 healthy male subjects participated in a randomised, double-blind, placebo controlled, 2-way crossover study of a continuous i.v. infusion of either placebo or icatibant 0.15 mg/kg over 24 hours for 3 days.

Main Outcome Measure: Blood and urine samples were collected pre-dose and at various times post-dose for the determination of plasma and urinary concentrations of icatibant and it two major metabolites (M1 and M2). Various pharmacodynamic measures were used to assess the inhibitory profile of icatibant following a bradykinin challenge.

Results:
Plasma PK

Dose proportional increase in systemic exposure ($AUC_{0-\infty}$) of icatibant is observed across single IV doses of 0.005 µg/kg to 0.8 mg/kg (Figure 4.2.3). The increase in AUC is less than dose proportional when higher doses escalating to 3.2 mg/kg are employed.

Figure 4.2.3. Dose proportional increase in Icatibant systemic exposure following IV infusion.



The PK results of Icatibant are summarized in Table 4.2.7.

Table 4.2.7. Geometric means of plasma pharmacokinetic parameters of Icatibant following escalating doses and various dosing rates of IV infusion of Icatibant.

Dose (mg/kg)	C_{max} (µg/L)	T_{max} (h)	AUC_{tot} (µg.h/L)	$T_{1/2}$ (h)	MRT (h)	Clearance (L/h)	V_{ss} (L)
Panels A & B							
0.005 [a]	10.40	2.75	52.98	2.5665	2.1839	8.3443	18.223
0.01 [a]	18.85	3.74	95.14	3.5506	2.7916	10.602	29.596
0.025 [a]	34.45	4.02	185.51	4.4932	3.421	12.043	41.198
0.05 [a]	66.07	3.50	307.79	4.9198	2.755	16.322	44.966
0.4 [a]	526.5	3.42	2124.4	2.9573	1.421	19.104	27.148
0.8 [a]	1023.7	3.45	4204.9	3.9735	1.4313	16.949	24.259
Panel C							
0.8 [b]	3908.4	1.00	5758.6	4.5082	2.2181	17.367	38.521
1.6 [b]	5614.4	0.96	7402.4	4.3348	1.7803	16.289	29
3.2 [b]	7493.3	0.99	10384	4.607	1.6701	16.934	28.282
Mean [c]	-	-	-	4.1	1.7	17.3	29.4

N = 4 subjects each in Panels A & B, and C.

[a] Icatibant administered over 4 hours, urine collected over 24 hours.

[b] Icatibant administered over one hour, urine collected over 48 hours.

[c] Mean values are calculated only for the higher doses (0.4 to 3.2 mg/kg).

AUC_{tot} = total AUC over observable period of time (to last quantifiable point).

The metabolites M1 and M2 had similar PK profiles and appeared to be formed from icatibant in a parallel fashion (Table 4.2.8-4.2.9). Systemic exposure of both M1 and M2 increases with increasing dose of icatibant in a fairly dose proportional manner up to 0.8 mg/kg dose beyond which saturation of exposure sets in (Panel C).

Table 4.2.8. Geometric means of plasma pharmacokinetic parameters of Icatibant metabolite M1 following escalating doses and various dosing rates of IV infusion of Icatibant.

	Dose (mg/kg)	C_{max}M1 (µg/L)	T_{max}M1 (h)	AUC_{tot}M1 (µg.h/L)	L_zM1 (1/h)	$T_{1/2}$M1 (h)	MRTM1 (h)
Panels A & B	0.005	5.68	4.19	29.60	0.34	2.04	5.09
	0.01	14.83	4.27	98.80	0.13	5.37	8.01
	0.025	18.21	4.39	111.66	0.22	3.20	6.34
	0.05	58.83	4.21	334.65	0.19	3.68	6.12
	0.4	386.26	4.42	2351.3	0.26	2.69	5.59
	0.8	683.6	4.13	3691.7	0.26	2.71	5.54
Panel C	0.8	1292.1	1.56	6755.7	0.21	3.09	4.11
	1.6	1434.9	1.49	6775.6	0.23		
	3.2	1754.5	1.46	8412.8	0.23		

N = 4 subjects each in Panels A & B, and C.

Table 4.2.9. Geometric means of plasma pharmacokinetic parameters of Icatibant metabolite M2 following escalating doses and various dosing rates of IV infusion of Icatibant.

	Dose (mg/kg)	C_{max}M2 (µg/L)	T_{max}M2 (h)	AUC_{tot}M2 (µg.h/L)	L_zM2 (1/h)	$T_{1/2}$M2 (h)	MRTM2 (h)
Panels A & B	0.005	5.33	4.42	39.13	0.20	3.45	7.13
	0.01	11.83	4.67	95.30	0.16	4.45	8.34
	0.025	24.71	4.73	158.92	0.23	3.02	6.44
	0.05	62.66	4.32	393.01	0.17	4.02	7.06
	0.4	414.26	4.48	2703	0.25	2.82	6.57
	0.8	770.24	4.41	4614.7	0.25	2.76	6.10
Panel C	0.8	1474.2	1.56	7946.6	0.19	3.43	4.58
	1.6	1579.9	1.70	8179.8	0.21		
	3.2	1952.7	1.71	11416	0.20		

N = 4 subjects each in Panels A & B, and C.

Urine data

Mean excretion data of Icatibant and its metabolites M1 and M2 in urine following IV infusion of escalating doses of Icatibant are listed in Table 4.2.10. The recovery of icatibant in urine was low compared to the recovery of the metabolites M1 and M2, reflecting a high degree of Icatibant metabolism and excretion of these metabolites via urine. As a percentage of the icatibant dose administered, the geometric mean excretion of icatibant (across all dosing regimens) ranged between 2% and 25%, whereas the excretion of M1 ranged between 58% and 122% and the excretion of M2 ranged between 60% and 141%.

Table 4.2.10. Urinary excretion of Icatibant and its metabolites, M1 and M2 following IV infusion of various dose and dosing rates of Icatibant in healthy subjects

	Dose level (mg/kg)	Dose administered (µM)	N	Geometric mean (µM)			Geometric mean (% of dose administered)		
				Icatibant	M1	M2	Icatibant	M1	M2
Part I Panels A & B	0.005 [a]	0.339	4	0.060	0.414	0.476	18%	122%	141%
	0.01 [a]	0.773	4	0.192	-	0.901	25%	-	117%
	0.025 [a]	1.712	4	0.143	1.358	1.236	8%	79%	72%
	0.05 [a]	3.851	4	0.299	3.652	3.575	8%	95%	93%
	0.4 [a]	31.109	4	1.865	22.992	21.542	6%	74%	69%
	0.8 [a]	54.627	4	1.675	38.758	38.729	3%	71%	71%
Part I Panel C	0.8 [b]	49.411	4	1.555	43.404	39.028	3%	88%	79%
	1.6 [b]	98.229	4	3.219	94.541	91.505	3%	96%	93%
	3.2 [b]	196.770	4	4.874	173.101	163.131	2%	88%	83%
Part II	0.15 [c]	9.795	6	0.506	6.523	6.098	5%	67%	62%
	0.5 [d]	95.229	6	5.476	80.366	75.211	6%	84%	79%
Part III	0.45 [e]	26.558	6	2.142	15.504	15.815	8%	58%	60%

[a] Icatibant administered over 4 hours, urine collected over 24 hours.

[b] Icatibant administered over one hour, urine collected over 48 hours.

[c] Icatibant administered over 24 hours, urine collected over 28 hours.

[d] Icatibant administered t.i.d. for one day, urine collected over 28 hours.

[e] Icatibant administered over 24 hours for 3 days, urine collected over 72 to 96 hours.

The geometric mean renal clearance of icatibant across all dosing regimens ranged between 0.4 and 2.3 L/h in healthy young male adults (Table 4.2.11). Also shown in the same table, the renal clearance of M1 ranged between 6.5 and 9.6 L/h and that of M2 ranged between 4.4 and 9.1 L/h.

Table 4.2.11. Renal clearance of Icatibant and its metabolites, M1 and M2 following IV infusion of various dose and dosing rates of Icatibant in healthy subjects.

	Dose level (mg/kg)	N	Geometric mean (L/h)		
			Icatibant	M1	M2
Part I, Panels A & B	0.005 [a]	4	-	6.928	-
	0.01 [a]	4	2.282	-	9.140
	0.025 [a]	4	0.811	9.613	6.249
	0.05 [a]	4	1.131	7.158	6.975
	0.4 [a]	4	0.780	7.682	7.710
	0.8 [a]	4	0.446	6.962	6.500
Part II	0.15 [b]	6	0.793	7.671	4.392
Part III	0.45 [c]	6	1.175	6.520	4.369

[a] Icatibant administered over 4 hours, urine collected over 24 hours.

[b] Icatibant administered over 24 hours, urine collected over 28 hours.

[c] Icatibant administered over 24 hours for 3 days, urine collected over 72 to 96 hours.

PK/PD modeling and simulation for dose selection

Detailed review and analysis of the PK/PD data submitted is captured in the pharmacometric review by Dr. Mehrotra (Appendix 4.3). A preliminary exploration of PK-PD relationships was conducted using the inhibitory profile of icatibant following a bradykinin challenge. The plasma concentration data were log transformed and a sigmoid dose-response with PD parameters was attempted using the E_{max} model. The fit converged for all datasets although there were large standard errors in some cases. A high degree of concordance on EC_{50} was obtained for each of the PD parameters, with the majority of values being between 8.54 and 9.77 µg/L. Thus, a mean EC_{50} value of 9.5 µg/L was used for the PK-PD simulation. Figures 4.2.4-4.2.5 show two representative PK-PD relationship plots.

Exploratory PK-PD simulation was conducted using the EC_{50} concentration derived from the above analysis. Based on the PK-PD estimations on plasma concentrations at EC_{50} and the BK challenge response, icatibant doses of 0.4 mg/kg and 0.8 mg/kg were predicted to provide duration of therapeutic effect of about 9 or 13 hours when infused over 0.5-1 h. Using the PK-PD modeling approach described above, the EC_{85} value for icatibant was estimated as 53.8 µg/L. In the context of targeting EC_{85} for desired pharmacological activity, the derived PK-PD curves showed that the 0.4 and 0.8 mg/kg doses administered over 0.5 hours should provide an appropriate duration of therapeutic effect of approximately 6 to 8 hours.

Figure 4.2.4. Pooled instantaneous relationship between plasma icatibant concentration and heart rate.

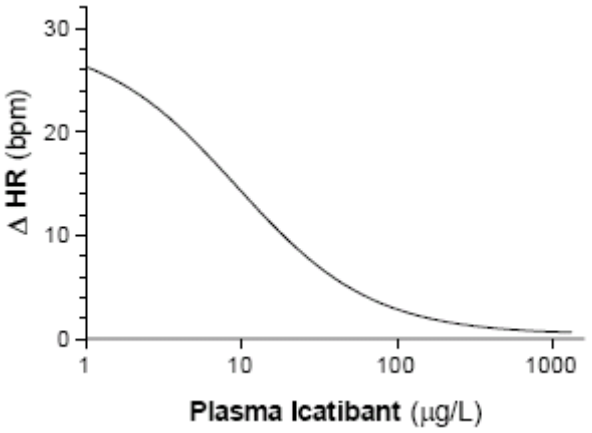
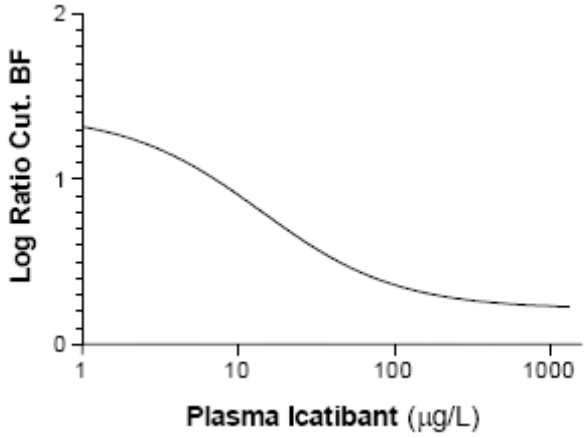


Figure 4.2.5. Pooled instantaneous relationship between plasma icatibant concentration and heart rate.



Conclusions: The plasma PK profile of icatibant is dose proportional and linear. The recovery of icatibant in urine was low compared to the recovery of the metabolites M1 and M2, reflecting a high degree of icatibant metabolism and excretion of these metabolites via the urine. Based on PK-PD estimations on plasma concentrations at EC_{85} and BK challenge response, icatibant doses of 0.4 and 0.8 mg/kg were predicted to provide a duration of therapeutic effect of about 6 to 8 hours when infused over 0.5 hours.

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4.2.4 Study JE049 #1101

Title: Randomized, Double-blind, Placebo-controlled Study to Explore Safety, Tolerability and Pharmacokinetics of Icatibant after Single Intravenous Infusions, Administered at Various Infusion Rates in Healthy Male Subjects

Objectives: The primary objectives of the study were to investigate the safety and tolerance of icatibant following single i.v. infusion of 0.4 mg/kg using decreasing infusion times (60, 30 and 15 minutes). The secondary objective was to explore the pharmacokinetics of icatibant at this dose and with varying infusion times.

Design: This was a randomized, double-blind, placebo controlled study with sequential administration of study treatments (Periods 1-3). In each study period, 8 healthy male subjects received an i.v. infusion of 0.4 mg/kg icatibant and 2 subjects received an i.v infusion of placebo. All subjects initially randomized to receive icatibant continued to receive the drug for each study period; equally placebo subjects continued to receive placebo. There was at least a 6-day washout between each dosing period.

Main Outcome Measure: Safety evaluations included adverse event reporting, local tolerance at the infusion site, vital signs (blood pressure and heart rate), pre- and post-dose usual safety labs. Pre- and post-dose 12-lead ECGs was also performed. Blood samples were collected pre-dose and up to 12 hours post-dose for the determination of plasma concentrations of icatibant and its M2 metabolite.

Results: A total of 10 healthy male subjects were enrolled and completed the study. The summary of demographic information is captured in Table 4.2.12. A total of 8 non-serious adverse events occurring in 5 subjects were reported during the study. Of these, 7 events in 4 subjects were infusion site reactions with the administration of icatibant. All AEs were mild in severity and resolved without treatment and without sequelae.

Table 4.2.12. Summary of demographic characteristics

	Placebo (N = 2)			**Active drug** (N = 8)			**Total** (N = 10)		
Parameter	**mean**	**SD**	**range**	**mean**	**SD**	**range**	**mean**	**SD**	**range**
Age [years]	38.0	12.7	29-47	30.8	9.0	20-47	32.2	9.5	20-47
Height [cm]	180.0	9.9	173-187	179.3	10.0	166-199	179.4	9.4	166-199
Weight [kg]	74.80	2.55	73.0-76.6	80.08	6.24	70.0-88.8	79.02	5.99	70.0-88.8
BMI [kg/m²]	23.15	1.76	21.91-24.40	24.99	1.90	22.21-27.40	24.62	1.94	21.91-27.40

A summary of the mean pharmacokinetic parameters of icatibant are shown in summary Table 4.2.13. There was an inverse relationship of C_{max} to the i.v. infusion time (Figure 4.2.6). The mean plasma elimination half life of icatibant was not related to infusion time and ranged from 1.3-2.0 hours. However, there was an inverse relationship between AUC and the infusion time with increasing exposure observed with shorter infusion times (Table 4.2.13).

For the M2 metabolite, a similar mean C_{max} and AUC estimates were observed following each of the different infusion times. The mean half-life was approximately 2.4 hours irrespective of infusion time (Table 4.2.14).

Figure 4.2.6. Concentration-time plots for Icatibant after 60, 30, and 15 minutes of infusion of a single dose of 0.4 mg/kg Icatibant.

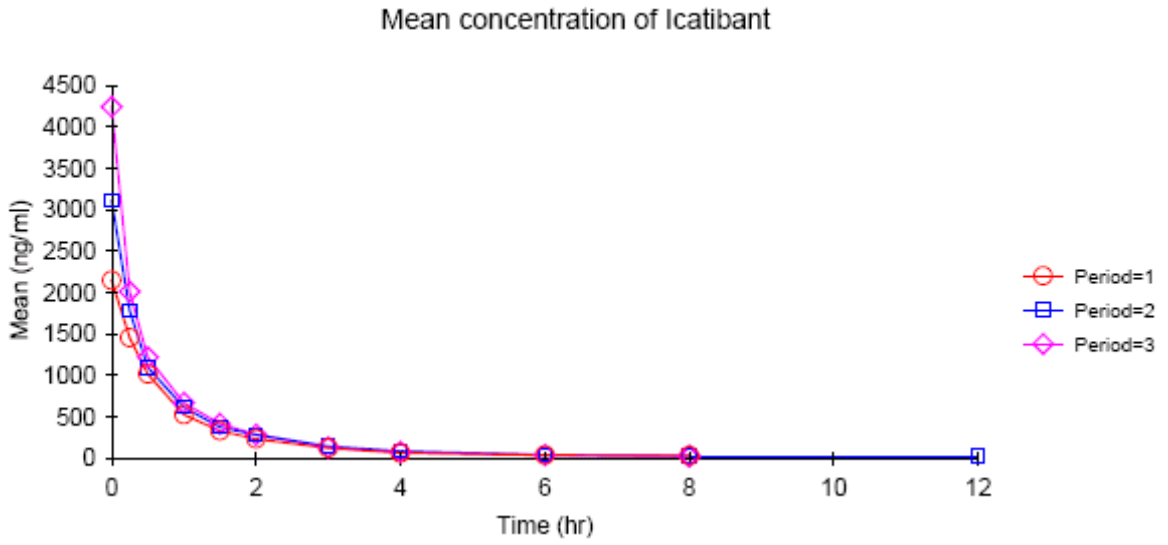

Table 4.2.13. Plasma pharmacokinetics of Icatibant following single intravenous infusion doses to healthy subjects.

		Cmax (ng/mL)	$AUC_{(0-t)}$ (h*ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	$t_{½}$ λz (h)
Period 1 (60 min)	N	8	8	8	8
	Mean	2171.987	1860.877	1922.338	1.319
	SE	127.270	145.379	146.098	0.032
	Median	2163.10	1806.01	1876.69	1.45
	CV%	16.6	22.1	21.5	6.8
Period 2 (30 min)	N	8	8	8	8
	Mean	3106.457	2302.110	2380.032	1.957
	SE	234.529	253.847	253.754	0.419
	Median	3019.35	2002.12	2048.92	1.68
	CV%	21.4	31.2	30.2	60.6
Period 3 (15 min)	N	8	8	8	8
	Mean	4242.508	2491.965	2552.785	1.308
	SE	334.587	297.489	294.793	0.122
	Median	4156.60	2344.05	2390.97	1.30
	CV%	22.3	33.8	32.7	26.3

Table 4.2.14. Plasma pharmacokinetics of Icatibant metabolite M2 following single intravenous infusion doses to healthy subjects.

		Cmax (ng/mL)	$AUC_{(0-t)}$ (h*ng/mL)	$AUC_{(0-\infty)}$ (h*ng/mL)	tmax (h)	$t_{½}\lambda z$ (h)
Period 1 (60 min)	N	8	8	8	8	8
	Mean	423.215	1891.990	1974.227	0.594	2.397
	SE	46.436	157.260	156.562	0.156	0.114
	Median	384.36	1761.06	1867.27	0.50	2.33
	CV%	30.2	23.5	22.4	74.4	13.4
Period 2 (30 min)	N	8	8	8	8	8
	Mean	434.501	2064.801	2147.221	0.969	2.366
	SE	53.520	257.115	258.358	0.243	0.087
	Median	391.64	1943.27	2025.87	0.75	2.31
	CV%	34.8	35.2	34.0	70.9	10.4
Period 3 (15 min)	N	8	8	8	8	8
	Mean	434.064	1952.632	2040.086	1.188	2.442
	SE	64.000	255.755	258.688	0.132	0.092
	Median	390.53	1858.39	1960.25	1.25	2.43
	CV%	31.3	37.0	35.9	31.3	10.6

Conclusions: The dose of 0.4 mg/kg icatibant administered as an i.v. infusion over 60, 30 and 15 minutes was safe and well tolerated with local infusion site reactions being the most commonly reported adverse event. These reactions were mild in severity and generally lasted from a few minutes to less than day. The intensity of the reaction appeared to be related to the infusion time with longer infusions causing more reaction.

The maximum plasma concentration measured at the end of each infusion period was inversely related to the infusion time. Other pharmacokinetic parameters were generally consistent irrespective of the infusion time. Icatibant has a relatively short elimination half life, ranging from 1.3 to 2.0 hours.

4.3 PHARMACOMETRICS REVIEW

Pharmacometrics Review

NDA	22150
Submission Date(s)	October 22, 2007
PDUFA Due Date	April 25, 2008
Brand Name	Firazyr®
Generic Name	Icatibant acetate
Dosage Form	Solution for Subcutaneous (s.c.) injection
Dosage Regimen	30 mg s.c. Repeat if required not less than q6 h. Not more than 3 injection in 24h
Pharmacometrics Reviewer	Nitin Mehrotra, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Reviewer	Partha Roy, Ph.D.
Clinical Pharmacology Team Leader	Wei Qiu, Ph. D.
Sponsor	Jerini
Submission Type	NDA
Proposed indication	Hereditary Angioedema

Executive Summary

The aim of the document is to review the sponsor's population PK, population PK/PD, simulation studies which form the basis of dose selection for Phase III trials.

The key question of the present review is:

1. Is sponsor's PK/PD approach for dose selection reasonable?

In general, it is a reasonable method. However, the efficacious dose based on biomarker (bradykinin challenge in healthy subjects) may not be efficacious for the clinical endpoint (Visual analogue scale, VAS, for hereditary angioedema, HAE) due to: 1) uncertainty about the relationship between the biomarker and the clinical endpoint; 2) larger variability in the clinical endpoint than the biomarker, leading to an underpowered design. Given the lower plasma bradykinin level (15 pM – 30 pM) after bradykinin challenge in healthy subject compared to that in a patient during an acute HAE attacks (53-82 pM), the dose based on PK/PD may be an underestimate of the dose for HAE patients. These concerns may have contributed to the non-significant results for one of the Phase 3 clinical trials.

Recommendation

Dose selection should be further defined in sufficient patients based on the clinical endpoint (VAS) or other biomarkers that are validated to be related to the clinical endpoint.

Signatures:

Nitin Mehrotra, Ph.D.
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Office of Clinical Pharmacology

Yaning Wang, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology

Labeling Statements

There are no labeling statements directly referring to population PK or population PK/PD. However, since the sponsor utilized exposure-response relationship from various studies for selection of dosage regimen, the study JE049-5108 which details the use of PK/PD modeling in dose selection is referred in the label in two sections.

2. FIRAZYR is intended for subcutaneous use. The recommended dose of FIRAZYR is one subcutaneous injection of 30 mg administered, preferably in the abdominal area for the treatment of a hereditary angioedema attack. 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.

8.2 Pharmacotherapeutic group: Bradykinin B2 receptor antagonist, ATC code: C11AA01 (applied for, not yet granted) In healthy young volunteers given doses of FIRAZYR (0.0025-0.8 mg/kg over 4 hours; 0.8-3.2 mg/kg over 1 hour, 1.5 mg/kg/day or 0.15 mg/kg/day for 3 days), reversal of bradykinin induced hypotension, vasodilation and reflex tachycardia was observed. Icatibant was shown to be a reversible antagonist when the bradykinin challenge dose was increased 4-fold. Icatibant had no impact on renal function (GFR, electrolyte excretion, renal plasma flow, and tubular function) or on endocrinological profile when administered as both single and multiple doses.

Introduction

Hereditary angioedema (HAE) is caused by either a quantitative (Type I) or qualitative (Type II) deficiency of C1 esterase inhibitor (C1-INH) caused by mutations of the C1-INH gene. A third type of HAE (Type III) is unrelated to C1-INH deficiency and its related genetic defect is unknown. C1-INH is a serine protease inhibitor mainly produced by hepatocytes, which acts as a "suicide inhibitor" by forming complexes with its target proteases. Its major functions include the prevention of C1 complement autoactivation, inactivation of coagulation factors XIIa, XIIf, XIa and direct inhibition of activated kallikrein. Under physiological conditions, plasma kallikrein and factor XIIa (activated Hageman factor), which converts prekallikrein to active kallikrein are inactivated by C1-INH. Following a triggering event, the deficiency in C1-INH results in an increased release of BK, which is the main recognized mediator responsible for the increased vascular permeability characteristic of HAE.
Icatibant is a potent and specific antagonist of the bradykinin type 2 (B2) receptor. It has
the same affinity for the B2 receptor as bradykinin (BK) itself. Icatibant is indicated for the treatment of all forms of attacks of HAE, including cutaneous, abdominal and laryngeal attacks.

Sponsor's Analysis

In the current submission, the sponsor submitted one stand alone report (JE049-5108) which describes the role of population PK and PK/PD modeling in selection of optimum dosing

regimen. In this report, the sponsor conducted a preliminary PK/PD exploratory analysis for the study JE049-1001 followed by a more sophisticated population pharmacokinetics (JE049-1102) using Bayesian modeling and exposure-response modeling (JE049-1001). Also, a Bayesian population PK/PD simulation utilizing the knowledge from above mentioned studies along with information from some other clinical studies guided the dose selection of icatibant for the Phase 3 studies.

Population Pharmacokinetics of Icatibant

Objectives

The objectives of this population pharmacokinetic analysis of concentration versus time data were:

• To characterize the pharmacokinetics of icatibant by developing a population pharmacokinetic model and further explore various scenarios using PK-PD simulation to aid in selection of suitable dosing regimen

Data

Data from 12 subjects from a Phase I clinical study receiving 30 mg s.c dose was utilized to develop a population pharmacokinetic model. Samples were collected post dose at 0.083, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 36 h.

Analysis Methods

PK analysis from study JE049 #1102 for 12 subjects that received 30 mg of the 10 mg/ml formulation of Icatibant via s.c. injection, and simulation to predict the distribution of concentrations, responses and effects within the population were carried out simultaneously using Markov chain Monte Carlo (MCMC). This was accomplished using the software WinBUGS (version 1.4), with the PKBugs add-on (version 1.1, note; works only in WinBUGS 1.3, but the generated model can be used in 1.4). Convergence was declared after 200,000 iterations, with a burn-in of 4,000 iterations. This procedure was repeated for each of the doses of interest: 15 mg, 30 mg and 60 mg.

Pharmacodynamics of Icatibant

The pharmacological effect of icatibant (inhibition of bradykinin (BK) effects) was investigated after administration of different doses and regimens to define an optimal dose range and dosing interval. The antagonistic effect of icatibant was assessed by measuring the degree of inhibition of exogenous BK-induced decrease in blood pressure (systolic, diastolic, and mean blood pressure), tachycardia (finger plethysmography), and cutaneous vasodilatation (laser Doppler flow meter) (Table 1). A dose response to escalating doses of BK was performed in each subject at screening to identify the appropriate BK challenge dose (ranging from 37.5 μg to 87.5 μg) to be used during the subsequent challenge days.

Table 1: Responses to bradykinin challenge used to define icatibant effect

	Description	Unit
Systolic blood pressure	Absolute decrease in systolic blood pressure	mmHg
Diastolic blood pressure	Absolute decrease in diastolic blood pressure	mmHg
Mean blood pressure	Absolute decrease in mean blood pressure	mmHg
Heart rate	Absolute increase in heart rate	bpm
Cutaneous blood flow	Ratio of cutaneous blood flow*	dimensionless

* The post-bradykinin cutaneous blood flow is divided by the pre-bradykinin blood flow level.

Data

This was a Phase 1 (JE049-1001) study primarily designed to assess the safety, tolerance, effect on renal function, PK, PD and maximum tolerated dose of icatibant. A wide range of 9 single doses (6 doses from 0.005 mg/kg to 0.8 mg/kg infused over 4 h and 3 doses, 0.8, 1.6, and 3.2 mg/kg infused over 1 h) were explored and compared to placebo. Data from Part I (Panel A to C) and Part II were utilized for exposure response analysis (Table 2)

Table 2: Subject Allocation and Treatment for study JE049-001

Part / Panel	Subject number (AN)	Dose (mg/kg)			
		Period 1	Period 2	Period 3	Period 4
Part I /Panel 0	001	0.2 x 4 hrs			
	002	0.2 x 4 hrs			
Part I / Panel A	101	0.05 x 4 hrs	Placebo	0.01 x 4 hrs	0.4 x 4 hrs
	102	0.05 x 4 hrs	0.01 x 4 hrs	Placebo	0.4 x 4 hrs
	103	Placebo	0.05 x 4 hrs	0.01 x 4 hrs	0.4 x 4 hrs
	104	0.05 x 4 hrs	0.01 x 4 hrs	0.4 x 4 hrs	Placebo
Part I / Panel B	105	0.025 x 4 hrs	0.005 x 4 hrs	0.8 x 4 hrs	Placebo
	106	0.025 x 4 hrs	0.005 x 4 hrs	Placebo	0.8 x 4 hrs
	107	Placebo	0.025 x 4 hrs	0.005 x 4 hrs	0.8 x 4 hrs
	108	0.025 x 4 hrs	Placebo	0.005 x 4 hrs	0.8 x 4 hrs
Part I / Panel C	109	Placebo	0.8 x 1 hr	1.6 x 1 hr	3.2 x 1 hr
	110	0.8 x 1 hr	Placebo	1.6 x 1 hr	3.2 x 1 hr
	111	0.8 x 1 hr	1.6 x 1 hr	3.2 x 1 hr	Placebo
	112	0.8 x 1 hr	1.6 x 1 hr	Placebo	3.2 x 1 hr
Part II	201	0.5 x 3 x 1 hr	0.15 x 24 hrs		
	202	0.15 x 24 hrs	0.5 x 3 x 1 hr		
	203	0.15 x 24 hrs	0.5 x 3 x 1 hr		
	204	0.5 x 3 x 1 hr	0.15 x 24 hrs		
	205	0.5 x 3 x 1 hr	0.15 x 24 hrs		
	206	0.15 x 24 hrs	0.5 x 3 x 1hr		
Part III	301	0.15 / 24 hrs x 3	Placebo		
	302	0.15 / 24 hrs x 3	Placebo		
	303	Placebo	0.15 / 24 hrs x 3		
	304	Placebo	0.15 / 24 hrs x 3		
	305	0.15 / 24 hrs x 3	Placebo		
	306	Placebo	0.15 / 24 hrs x 3		

Exposure-Response Analysis

Objectives

The objectives of the exposure-response analyses were:

- To characterize the relationship between icatibant and pharmacodynamic effects (Refer Table 1)
- To project the amount and duration of effect of alternative icatibant doses on pharmacodynamic responses using computer simulations to come up with an optimum dosing regimen.

Data

Data from 18 subjects from study JE049-1001 was utilized for the exposure response analysis. From 662 concentration measurements and 656 response measurements, set of 344 observations had both concentration and response at the same time point and thus were used to explore concentration-response relationships.

Analysis Methods

- ***Exposure-Response relationships (Refer to JE049-5108)***

The effect of Icatibant is defined in terms of its inhibition of the response to a bradykinin challenge (the lower the response the better). The exposure response relationships were performed in two parts:

1) A preliminary PK/PD analysis using these observations was performed by non linear regression using GraphicPad Prism and to predict an optimum infusion dosing regimen.
2) A more detailed PK/PD analysis on same data was performed using generalized nonlinear least squares (GNLS), implemented in the package nlme in R.

The relationship between log-concentration and response is modeled by a standard inhibitory model:

$$E = E_{\min} - \frac{(E_{\min} - E_{\max})C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}} + \epsilon \quad \text{------- Eq. 1}$$

where C is the concentration of Icatibant, E_{min} is the expected response when the concentration is 0, E_{max} is the limiting expected response as the concentration goes to infinity, EC_{50} is the concentration for which the response is half way between E_{min} and E_{max}, γ the hill factor, and ϵ is residual error. Residual error is assumed to be normally distributed with mean zero variance modeled by a power variance function—this accounts for heteroscedasticity. This can be expressed by

$$\mathrm{Var}(\epsilon) = \sigma^2 |f(x)|^{2\delta} \quad \text{----- Eq. 2}$$

where ϵ is residual error, and σ and δ are model parameters.

For technical reasons, the model is parameterized in terms of E_{min}, E_{max}, $\log EC_{50}$ and $\lambda = 1/\gamma$ rather than the parameterization given in equation (1). Since there was no a priori definition of percent-effectiveness for Icatibant, we defined percent effectiveness in terms of the parameter estimates obtained from fitting the logistic model. Specifically, we designated the expected limiting response for an infinite concentration of Icatibant (i.e. E_{max}) to be 100% effectiveness. Similarly, we designated the expected response for an Icatibant concentration of zero (E_{min}) to be 0% effectiveness. Note that since higher concentrations of Icatibant lead to lower responses (i.e. Icatibant inhibits the effect of bradykinin), we have $E_{max} < E_{min}$. With these definitions in place, any observed response x can be viewed in terms of percent-effectiveness as

$$(x - E_{\min})/(E_{\max} - E_{\min}). \qquad \text{----- Eq. 3}$$

A possible source of confusion is that the above model does not constrain an observed (or simulated) effect to be in the range 0% to 100%. Whereas the expected response is guaranteed by equation (1) to lie between E_{max} and E_{min} for any concentration, this is not so for the observed response once we add residual variability _. So, since we define 0% and 100% effect to correspond to E_{min} and E_{max} respectively and normalize observed effects according to this scale, it is a logical consequence of the model that observed effects may be less than 0% (i.e. negative), or greater than 100%. In particular, this is unrelated to the fact that we use fixed population average values (rather than subject specific ones) for the parameters E_{min}, E_{max}, EC_{50} and γ throughout the simulation. Including residual variability in the simulation rather than just modeling expected values makes the model more realistic, as it reflects the true range of variability in responses that we would expect to find in a patient population.
The four-parameter logistic model with power variance function was fit using generalized nonlinear least squares (GNLS), implemented in the package nlme in R (version 2.1.0). 344 concentration-response observations. It was assumed that the relationship between concentration and response was independent of the dose (ranged from 0.05 mg to 3.2 mg per kilogram body mass), formulation, and length of infusion (ranged from 1 hour to 24 hours). The model for systolic blood pressure did not converge, so no results for this particular response are available.

- **Simulation study**

Simulation in PKBugs is accomplished through the use of prediction events. For a fictitious individual (i.e. one with a special ID number), a dosing event was created specifying the administration of a specific dose of interest. Prediction events were then added at every half-hour up to 12 hours post-dose. The prediction events cause concentration measurements at the specified time points to be included in the model as random quantities. In particular, the posterior distribution is used to draw inference about these quantities, such as the computation of credible intervals. The posterior corporates all the information contained in the observed data—thus the distribution of the predicted concentration can be thought of as the distribution in a population for which the 12 subjects are a representative sample. For each random (i.e. predicted) concentration, a random response is generated according to the model in equation (1), and using the parameter estimates in Table 2 (these are considered fixed in the model). From the response, percent-effectiveness is calculated using equation (3). Inference about these quantities can then be drawn in the usual way, i.e. according to their posterior distributions.

Results (Sponsor's Analysis)

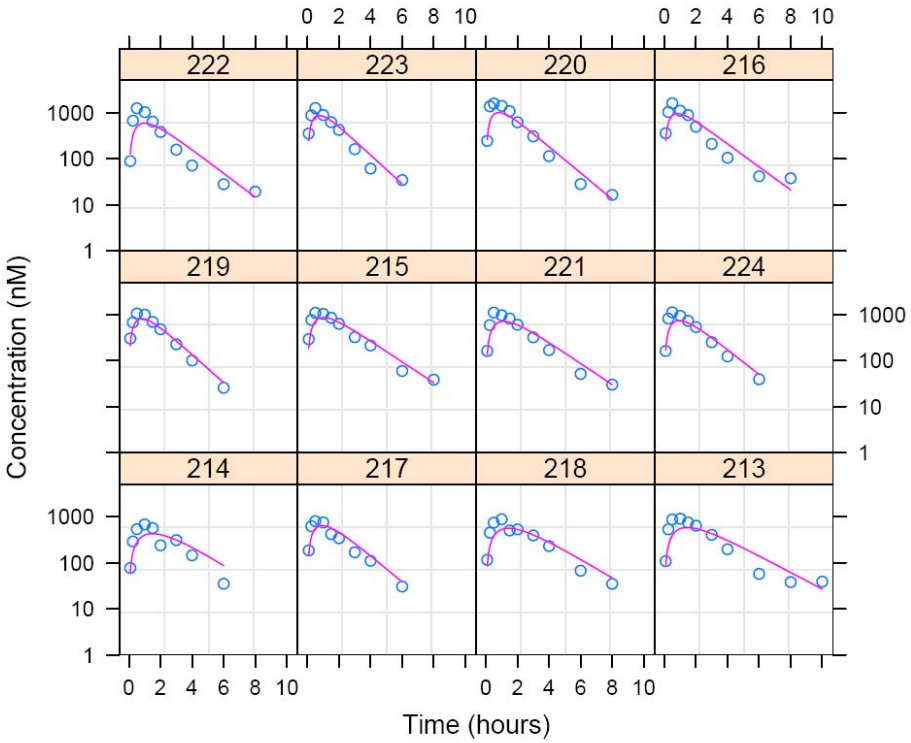
- ***Population Pharmacokinetics***

The model used to describe the PK of icatibant in 12 subjects receiving 30 mg s.c. injection was a one compartmental model with first order absorption. The population parameter estimates are listed below in Table 3 and fit to individual data is provided in Figure 1. The population estimates were similar when repeated for other dose levels also (15 and 60 mg s.c.).

Table 3: Population level PK parameter estimates obtained from PKBugs model

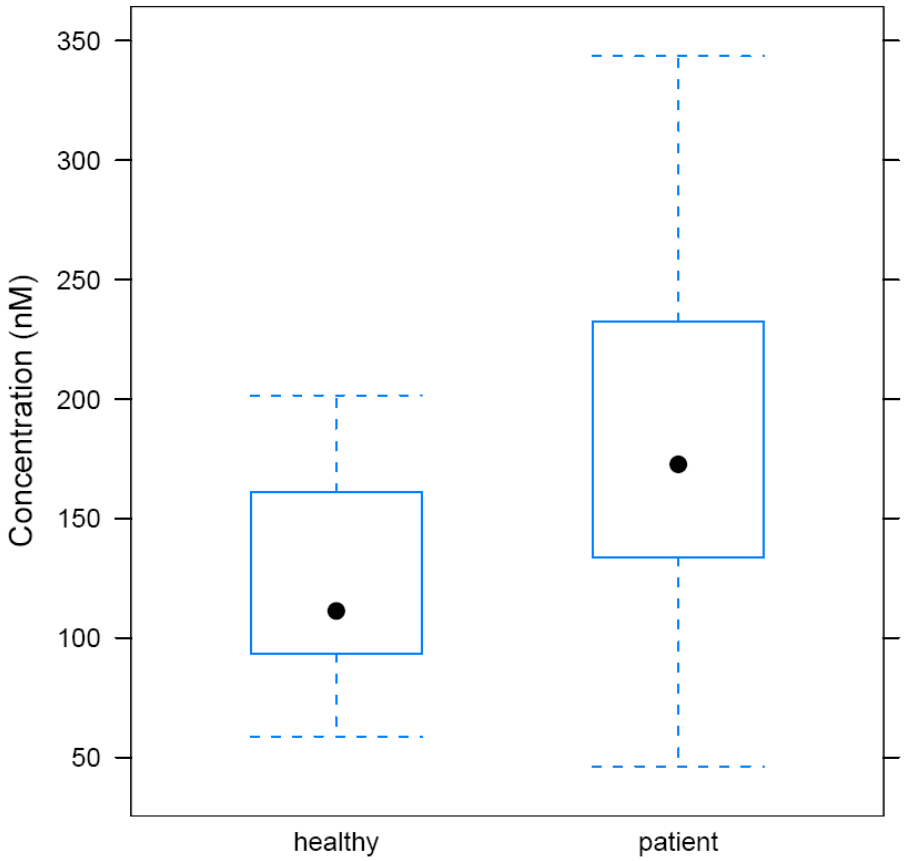
Parameter	Estimate (posterior mean)	95% Credible Interval
Cl (L/h)	11.5	[10.0, 13.1]
V (L)	19.6	[16.3, 23.4]
k_a (h^{-1})	2.75	[2.17, 3.45]
k_e (h^{-1})	0.587	[0.499, 0.691]

Figure 1: Semi-logarithmic plots of fitted concentration-time curves after parameter estimation with WinBUGS/PKBugs (one-compartment model).



Data from 8 patients (40 observations) with HAE receiving either 30 mg or 45 mg s.c. was also available, but due to such small set of data, population analysis was not performed rather the exposures achieved in healthy subjects and HAE patients. Dose adjusted concentrations at 4 h post dose 0.4 mg/kg (30 mg s.c.) were compared with HAE patients and were found to be insignificant (p=0.57) (Figure 2.). Thus, sponsor claim that the effect durations (which will be described in further sections) will be similar for healthy subjects and patients.

Figure 2: Box plot of the observed concentration 4 hours after administration for healthy subjects and HAE patients. Dot corresponds to median, box corresponds to interquartile range (25th to 75th percentile), whiskers extend to minimal and maximal data values.



Covariate assessment

There were no covariate assessments in the present population PK analysis.

Model evaluation

Sponsor did not perform model evaluation

Conclusion

- The pharmacokinetics of icatibant in healthy subjects was well described by a one compartmental model with first-order absorption.
- Based on comparison of exposures, the PK is similar between healthy and HAE patients.

Exposure-response analyses

Based on preliminary PK/PD analysis, it was found that 0.4 mg/kg administered i.v. by infusion should provide an effect around 6-9 h. The absolute bioavailability was >95% for 30 mg s.c. injection (10mg/ml) in study JE049-1102 which further supported the use of 30 mg s.c. as an appropriate dosing regimen. The parameter estimates from the exposure response analysis of 18 subjects from study JE049-1001 is presented in Table 4.

Table 4: Parameter estimates and corresponding approximate 95% confidence intervals (in brackets) for the concentration-response models

Response	E_{min}	E_{max}	EC_{50}	γ	σ	δ
Systolic BP*	NA	NA	NA	NA	NA	NA
	(NA, NA)	(NA, NA)	(NA, NA)	(NA, NA)	(NA, NA)	(NA, NA)
Diastolic BP	14.4	3.5	12.7	1.77	2.37	0.23
	(12.5, 16.3)	(2.75, 4.27)	(8.97, 16.5)	(1.05, 2.49)	(1.72, 3.25)	(0.0655, 0.391)
Mean BP	16.0	3.7	12.0	1.71	2.25	0.30
	(13.6, 18.4)	(2.92, 4.56)	(8.03, 15.9)	(0.998, 2.43)	(1.63, 3.07)	(0.149, 0.458)
Heart rate	24.3	1.7	12.5	1.57	1.75	0.47
	(20.9, 27.8)	(1.10, 2.38)	(9.19, 15.9)	(1.17, 1.97)	(1.41, 2.15)	(0.371, 0.566)
Cutaneous BF	3.6	1.4	14.1	1.94	0.11	2.2
	(3.06, 4.05)	(1.30, 1.41)	(9.81, 18.4)	(1.38, 2.50)	(0.0862, 0.127)	(1.94, 2.43)

Covariate assessment

There was no covariate assessment for the exposure response analysis.

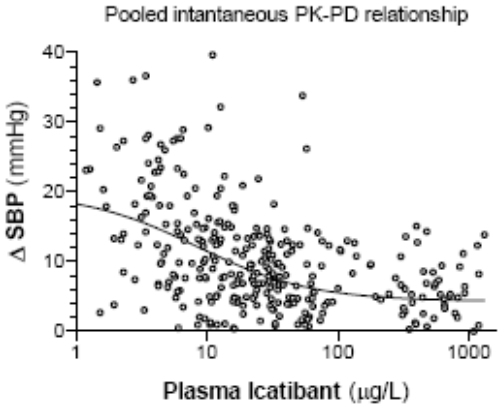
Model Evaluation

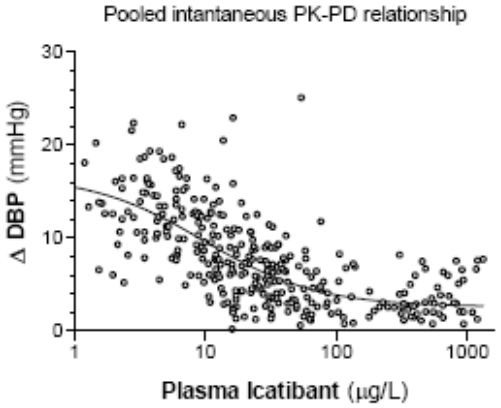
The sponsors did not evaluate the model

Model-based simulation

Plots of observed concentration-effect and simulated time course of % effect along with credible intervals for the four responses are shown in Figure 3-4 and 5-8 respectively.

Figure 3: Observed concentration-response (systolic blood pressure, diastolic blood pressure and mean blood pressure)





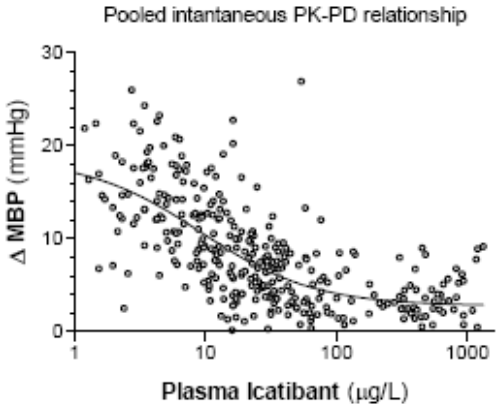


Figure 4: Observed concentration-response (heart rate, ratio cutaneous blood flow and log ratio cutaneous blood flow).

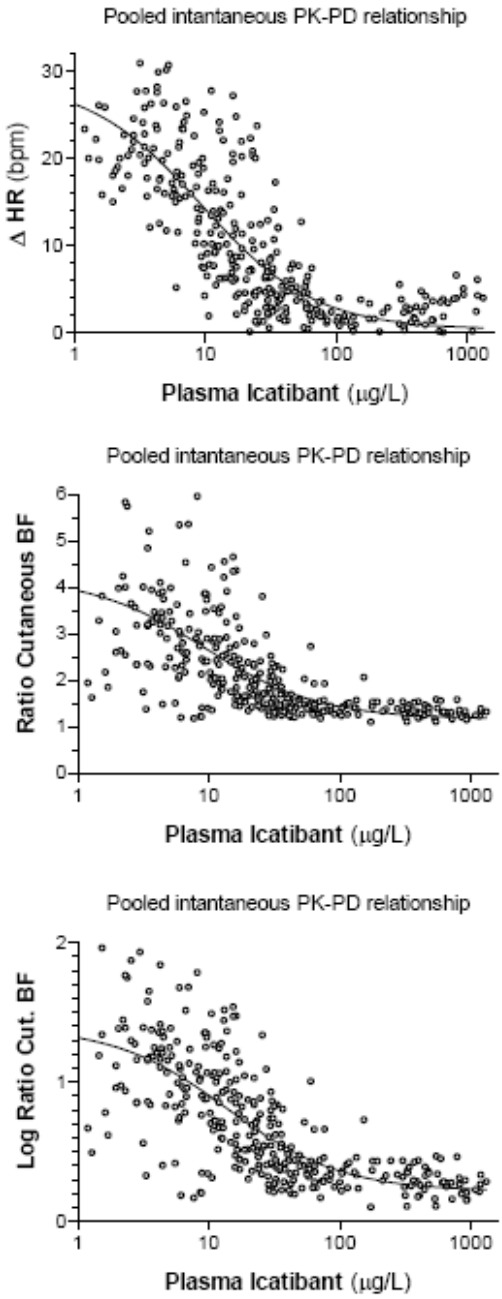


Figure 5: Bayesian Credible intervals defined in terms of diastolic blood pressure response. Darkest regions represent 50% (25th-75th percentile), intermediate regions 80% (10th-90th percentile), and lightest regions 90% (5th-95th percentile) probability.

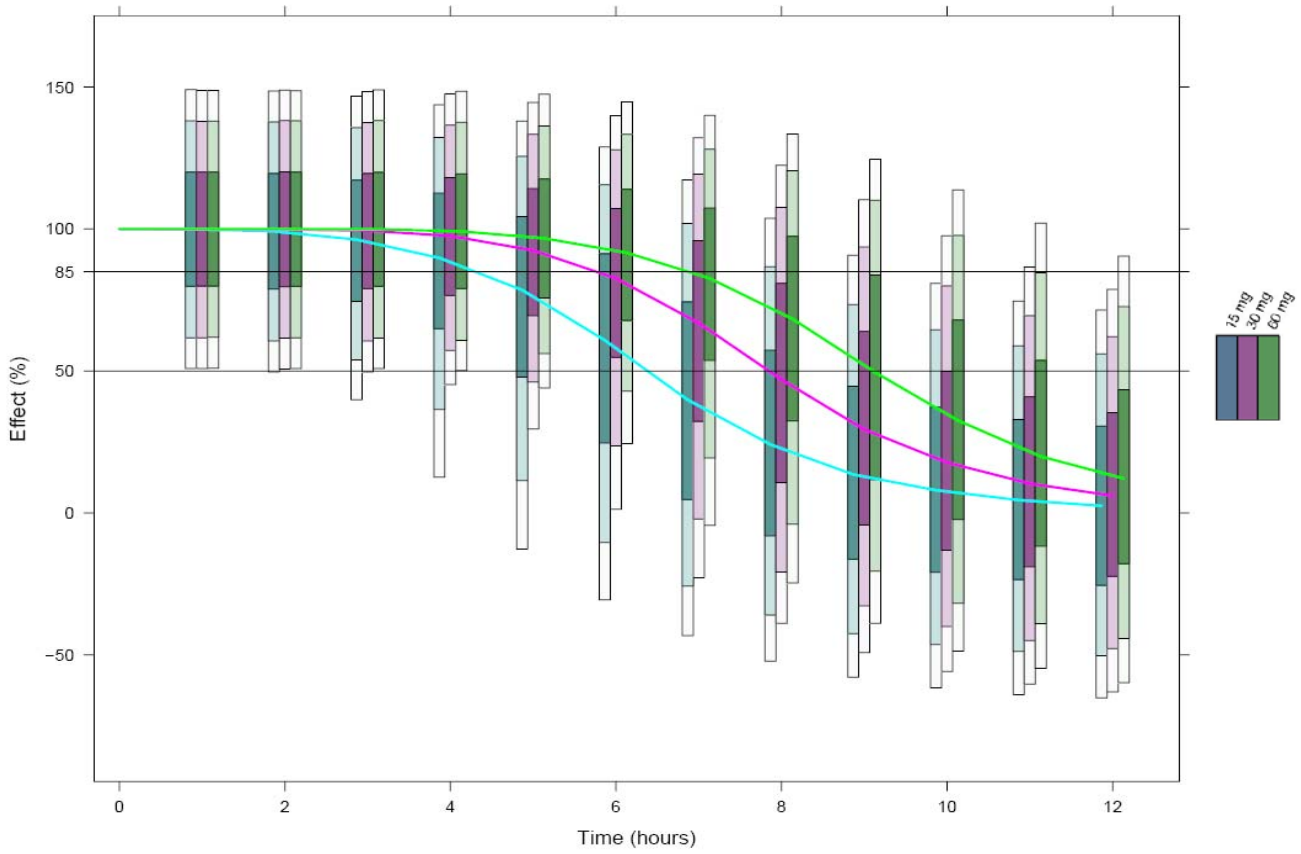


Figure 6: Bayesian Credible intervals defined in terms of mean blood pressure response. Darkest regions represent 50% (25th-75th percentile), intermediate regions 80% (10th-90th percentile), and lightest regions 90% (5th-95th percentile) probability.

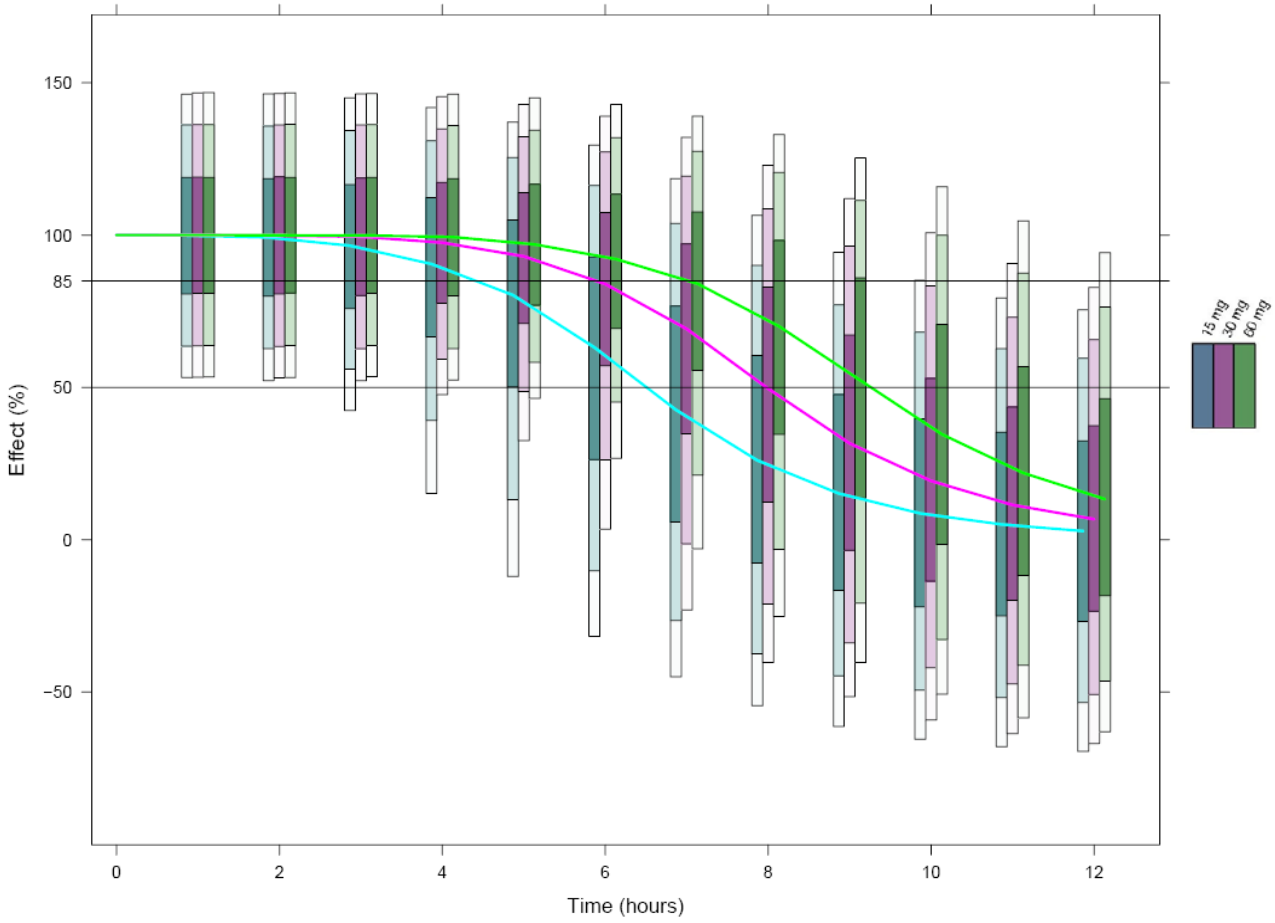


Figure 7: Bayesian Credible intervals defined in terms of heart rate response. Darkest regions represent 50% (25th-75th percentile), intermediate regions 80% (10th-90th percentile), and lightest regions 90% (5th-95th percentile) probability.

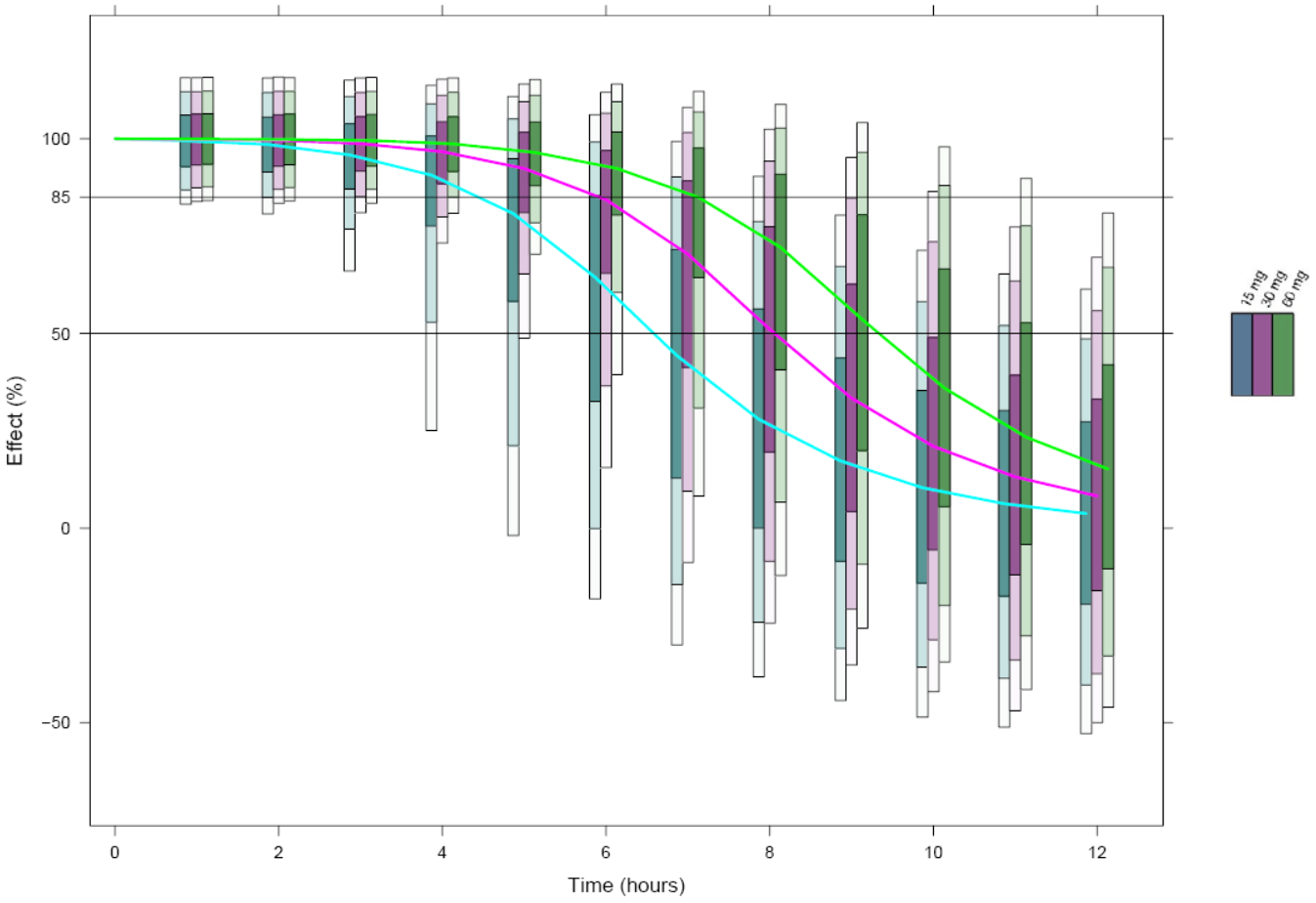


Figure 8: Bayesian Credible intervals defined in terms of cutaneous blood flow response. Darkest regions represent 50% (25th-75th percentile), intermediate regions 80% (10th-90th percentile), and lightest regions 90% (5th-95th percentile) probability.

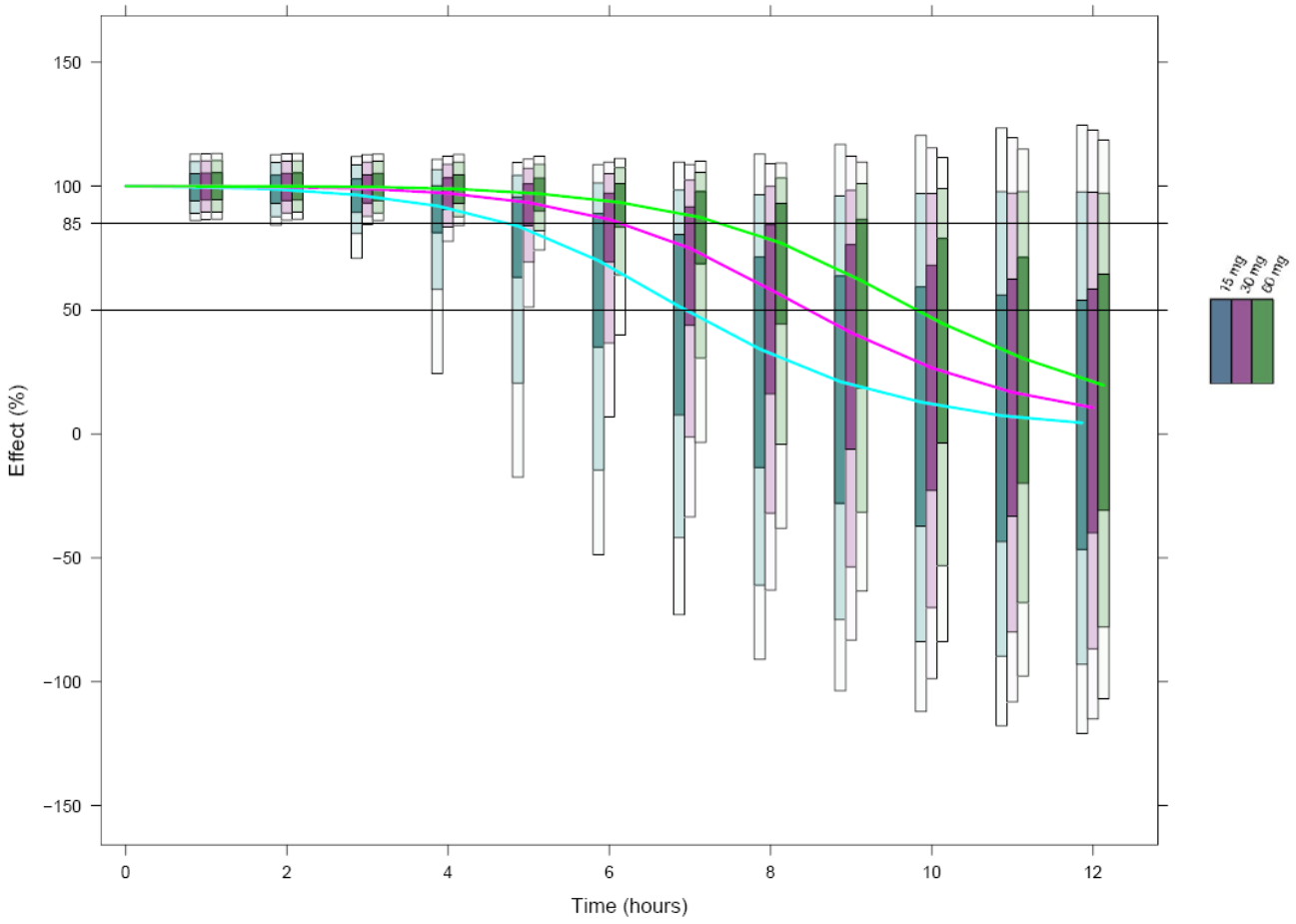


Table 5 summarizes the results of the estimated duration of effect of icatibant for each of the five responses and doses administered. The table combines different effect levels and confidence levels. Both EC_{50} versus EC_{85} levels were considered in the analysis. Duration of effect was determined by identifying the last time point at which an appropriate and credible interval contained the effect cut-off level. As an example, graphical representation of response (credible intervals) versus time is shown for cutaneous blood flow in Figure 8. For the relevant dose of 30 mg, icatibant has a 75% probability of being at least 50% effective for at least 6.5 h. Doubling the icatibant dose from 30 mg to 60 mg results in an increase of duration of effect by 1 to 1.5 h regardless of the confidence level. From these data it could be concluded that at doses beyond 30 mg the duration of effect is relatively insensitive to a change in the administered dose.

Table 5: Estimated duration (in hours) of icatibant effect for a given dose, response, effect level, and confidence level

		Confidence level								
		90%			75%			50%		
Response	Effect level	15 mg	30 mg	60 mg	15 mg	30 mg	60 mg	15 mg	30 mg	60 mg
Diastolic blood pressure	85%	0	0	0	0	0	0	4.5	5.5	6.5
	50%	3	4.5	5.5	4.5	6	7	6.5	7.5	8.5
Mean blood pressure	85%	0	0	0	0	0	0	4.5	5.5	6.5
	50%	3	4.5	5.5	5	6	7	6.5	7.5	9
Heart Rate	85%	1.5	3	3.5	3	4.5	5	4.5	5.5	6.5
	50%	4	5.5	6	5	6.5	7.5	6.5	8	9
Cutaneous blood flow	85%	2.5	3.5	4.5	3.5	4.5	5.5	4.5	6	7
	50%	4	5.5	6	5	6.5	7.5	7	8	9.5

Conclusion

Doses higher than 30 mg are unlikely to increase the duration of effect based on simulation based study. In order to maintain effective plasma concentrations over a longer period of time, the data suggest that it would be clinically more useful to repeat administration of the proposed dose of 30 mg when clinically needed instead of using a higher single dose of e.g. 60 mg for all patients. The reduction of dose to 15 mg would result in 75% of plasma concentration staying above EC_{50} for 4-4.5 h which is clinically less useful and result in high rates of re-treatments.

Reviewer's Comments

- ***Population Pharmacokinetics***

The PK/PD modeling and simulation used for dose selection by the sponsor is reasonably acceptable, however there are certain concerns with respect to the amount of data utilized for the population PK and the approach for PK/PD analysis. The specific comments of the reviewer are as follows:

1. Sponsor has rich source of PK data for both i.v. and s.c administration from various clinical studies. However, the sponsor only used data from 12 subjects from JE049-1102 study to develop a population PK model. Though the sponsor mentions that the population parameter estimates were obtained for all three s.c. doses (15, 30 and 60 mg) separately and they were similar, the results are not provided. It seems that the person who performed Bayesian population PK modeling believes that only 30 mg s.c. injection (the proposed therapeutic dose) data can be used to built the population PK model for a subcutaneous administration route. Considering the fact that population PK modeling approach allows all the relevant data to be pooled, irrespective of the doses or route of administration in building a model, the sponsor should have used other PK data for 15 and 60 mg s.c. from the present study and relevant data from other studies (for example

rich data from JE049-1001 with wide range of doses after i.v. and s.c. administration) in order to generate more confidence in model building and parameter estimation. More importantly, the estimated between subject variability on PK parameters will be closer to the target population. Despite the rich PK data in patients collected in a phase II study (N=20), the sponsor chose not to build a population PK model for patients because of small set of patient data while the sponsor built the population PK model for healthy subjects based on 12 subjects.

2. The sponsor should have performed model evaluation/qualification. Since the goal of modeling is to predict various scenarios beyond the current data to select phase III dose, a robust model evaluation is especially important.

- ***Exposure-Response analysis***

1. For concentration-response analysis, the sponsor chose a naive pooling approach, ignoring the correlation among the data collected on the same subject. Given the problems associated with naive pooling approach, the alternative is to develop a robust population PK model with the available rich PK data followed by mixed effect modeling approach to model PK/PD accounting for both interindividual variability and residual variability.
2. Since the dose of bradykinin challenge in healthy subjects ranged from 37.5 μg to 87.5 μg, the plasma bradykinin level is approximately in the range of 15 pM to 30 pM, assuming 3L for plasma volume and 3.2 pM for endogenous bradykinin (0.2-7.1 pM). In contrast, the plasma bradykinin level in a patient during an acute HAE attacks can increase to 53-82 pM (Refer, Page 53, JE049-2101). Therefore, the dose based on healthy subjects may be an underestimate of the dose for HAE patients.
3. The variability based on bradykinin challenge in a small group of highly homogenous healthy subjects is expected to be much smaller than that for the clinical endpoint in a highly heterogeneous patient population. Even among the 5 PD biomarkers after bradykinin challenge, the simulation results show that selected dose is less likely to be efficacious for those more variable biomarkers (blood pressure). These concerns should be incorporated into phase III trial design to avoid an underpowered study.

4.4 OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

4.4.1.1.1 General Information About the Submission

	Information		Information
NDA Number	**22-150**	**Brand Name**	**FIRAZYR®**
OCP Division	**DCP2**	**Generic Name**	**Icatibant**
Medical Division	**DPAP**	**Drug Class**	**Bradykinin 2 receptor antagonist**
OCP Reviewer	**Partha Roy**	**Indication(s)**	**HAE**
OCP Team Leader (Acting)	**Wei Qiu**	**Dosage Form**	**Solution for S.C. Injection**
		Dosing Regimen	**30 mcg/3 mL**
Date of Submission	**26 October 2007**	**Route of Administration**	**S.C. Injection**
Estimated Due Date of OCPB Review	**11 February 2008**	**Sponsor**	**Jerini AG**
PDUFA Due Date	**25 April 2008**	**Priority Classification**	**Priority**
Division Due Date	**26 March 2008**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**x**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**x**			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:	x			
Patients-				
single dose:	x			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	x			
Subpopulation studies -				
ethnicity:				
gender:	x			
pediatrics:				
geriatrics:	x			
renal impairment:	x			
hepatic impairment:	x			
PD:				
Phase 2:	**x**			
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x			
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				

Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	x			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	10			

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		None
QBR questions (key issues to be considered)	**1. Dose selection? Application of PK/PD for dose finding** **2. QT/QTc evaluation** **3. Is there a need for age or gender based dosing?**	
Other comments or information not included above	**QT/QTc evaluation for study JE049 #1103 already completed by the QT IRT group, review in DFS dated Jan 30, 2007 under IND 68214. AC Meeting scheduled for Feb 20, 2008. OCP Review due Feb 11, 2008.**	
Primary reviewer Signature and Date	**Partha Roy, Ph.D.**	
Secondary reviewer Signature and Date	**Wei Qiu, Ph.D.**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Partha Roy
3/21/2008 11:00:47 AM
BIOPHARMACEUTICS

Put signature comment that u r signing for Nitin also

Yaning Wang
3/21/2008 11:55:19 AM
BIOPHARMACEUTICS

Wei Qiu
3/21/2008 01:18:51 PM
BIOPHARMACEUTICS