14 September 2017
EMA/702004/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Firazyr

International non-proprietary name: icatibant

Procedure No. EMEA/H/C/000899/II/0034/G

Note

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

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1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Shire Orphan Therapies GmbH submitted to the European Medicines Agency on 30 August 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Extension of Indication to include adolescents and children over 2 years old for the use of Firazyr for symptomatic treatment of acute attacks of hereditary angioedema. As a consequence, section 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6. of the SmPC are updated. The Package Leaflet is likewise updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to reflect the results of a juvenile toxicity study in SmPC section 5.3.

To update section 5.2 of the SmPC to reflect the effect of age (elderly), gender and race on pharmacokinetics of icatibant. The Package Leaflet is updated accordingly. All relevant pharmacokinetics studies have previously been assessed, as part of prior submissions.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0243/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0243/2015 was completed.

The PDCO issued an opinion on compliance for the PIP P/0243/2015.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Nithyanandan Nagercoil

Timetable	Actual dates
Submission date	30 August 2016
Start of procedure:	17 September 2016
CHMP Rapporteur Assessment Report	11 November 2016
CHMP Co-Rapporteur Assessment Report	11 November 2016
PRAC Rapporteur Assessment Report	18 November 2016
PRAC Outcome	1 December 2016
CHMP members comments	5 December 2016
Request for supplementary information (RSI)	15 December 2016
CHMP Rapporteur Assessment Report	26 April 2017
PRAC Rapporteur Assessment Report	25 April 2017
PRAC Outcome	5 May 2017
CHMP members comments	8 May 2017
Updated CHMP Rapporteur Assessment Report	12 May 2017
Request for supplementary information (RSI)	18 May 2017
CHMP Rapporteur Assessment Report	15 August 2017
PRAC Rapporteur Assessment Report	15 August 2017
PRAC Outcome	1 September 2017
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	07 September 2017
Opinion	14 September 2017

2. Scientific discussion

2.1. Introduction

Based on the completion of the first part of Study HGT-FIR-086 "A Multicenter, Open-Label, Non-Randomized Study to Assess the Pharmacokinetics, Tolerability, and Safety of a Single Subcutaneous Administration of Icatibant in Children and Adolescents with Hereditary Angioedema", the intent of this Type II variation is to update the currently approved indication for Firazyr to also include paediatric patients aged 2 years and above. In addition, the following changes were proposed to be implemented in the SmPC as well, as they are all related to the data being submitted with this application:

- Section 5.2 Pharmacokinetic properties: As part of the population PK analysis performed in relation to the proposed label for paediatric patients, it is proposed to update the wording to reflect the effect of age (elderly), gender and race on PK of icatibant. All studies utilized for this analysis are either part of this application (HGT-FIR-086) or have previously been assessed by the EMA with prior submissions.
- Section 5.3 Preclinical safety data: Addition of conclusions from the non-clinical study JE0419-0172 "Icatibant: 14 Day Subcutaneous Administration Range-Finding Toxicity Study in the Juvenile Rat". This study was submitted as a Follow-up Measure (FUM RM2 023.1) in April, 2012 in EU (eCTD 0056. Module 4.2.3.2). The results of this study did not warrant modification to the SmPC. However, in order to fulfil the intentions of the paediatric regulation (EC) 1901/2006, all results from studies conducted as part of the agreed PIP (EMEA-000408-PIP01-08-M05; EMA decision P/0243/2015) are being included in the Firazyr SmPC. The corresponding changes have also been made to the Patient Information Leaflet (PIL) where relevant.

This variation is supported by a clinical data from an interim report of an ongoing paediatric study (HTG-FIR-086) evaluated the effect of a single standard subcutaneous administration of icatibant in children and adolescents aged 2 to <18 years with a documented diagnosis of hereditary angioedema (HAE) type I or II. The study is ongoing and will examine the effect of 3 total exposures of icatibant in 10 adolescents who are currently being followed. The data now submitted includes the data for the initial administration of icatibant from 11 pre-pubertal subjects during an HAE attack and 21 pubertal/post-pubertal subjects (including 11 treated during an HAE attack and 10 treated without an attack).

In accordance with Article 37 of the Paediatric Regulation (Regulation (EC) No 1901/2006), it is considered that Firazyr is eligible for the extension of the ten-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 to twelve years, as the results from studies conducted as part of the agreed PIP (EMEA-000408- PIP01-08-M05; EMA decision P/0243/2015) will be reflected in the Firazyr SmPC ~~a~~

Hereditary angioedema (HAE) can be caused by either a quantitative (type I) or qualitative (type II) deficiency of C1 inhibitor (C1-INH). The deficiency in C1-INH results in accelerated release of bradykinin by its cleavage from high-molecular-weight kininogen by activated kallikrein. Bradykinin is the principal mediator of the increased vascular permeability characteristic of HAE.

The clinical presentation and management of HAE in paediatric patients is different from adults and also more complex. The age at onset, frequency and duration of symptoms, as well as severity of attacks all exhibit substantial interindividual variation. Although acute episodes of HAE may occur at any age, the median age at first symptomatic HAE attack is estimated to range between 4 and 11 years. Subcutaneous oedema of the extremities, face, neck, torso, and genitals is the most common, and usually the earliest, manifestation of HAE seen in children. In the GI tract, submucosal oedema may be associated with colicky abdominal pain, nausea, vomiting, and diarrhoea. In a large paediatric cohort, increased frequency and

severity of HAE symptoms were reported at between 3 and 6 years of age and at around puberty and were attributed to physiological changes which occur during these periods of development.

Though infrequent compared to cutaneous and abdominal manifestations, attacks of acute HAE involving the larynx may result in submucosal oedema of the upper airways and risk of death by asphyxiation if undiagnosed and/or untreated. In comparison to adults, asphyxia may ensue more rapidly in children because of smaller airway diameter.

Prompt control of attacks, short-term prophylaxis, "intermittent" prophylaxis, long-term prophylaxis, and emergency therapy are recommended for the management of paediatric HAE.

Treatment options for children with HAE according to current guidelines include antifibrinolytics, attenuated androgens, and plasma-derived C1-INH replacement therapy.

Current guidelines favour antifibrinolytics for long-term prophylaxis because of their safety profile relative to attenuated androgens. The preferred antifibrolytic agent, where approved for use, is tranexamic acid, though Ɛ-aminocaproic acid is sometimes also used for this purpose. C1-INH replacement therapy has been used successfully for management of acute attacks of HAE in children; however, its use in children is associated with the same drawbacks (i.e. requirement for intravenous administration) as in adults.

Icatibant is a synthetic decapeptide with a structure similar to bradykinin that acts as an antagonist of the bradykinin B2 receptor. Inhibition of bradykinin action through use of a B2 receptor antagonist is a therapeutic strategy for treatment of clinical symptoms of HAE and represents the rationale for use of icatibant in treatment of acute attacks of angioedema in HAE patients.

In adults, SC icatibant 30 mg is approved for the treatment of cutaneous, abdominal, and laryngeal attacks of acute HAE.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical data presented in this variation application have been reported to and assessed by CHMP previously in FUM RM2 023.1 (April, 2012) and in procedure EMEA/H/C/000899/II/0017/G approved on 25 October 2012. Thus the following data are included in this report for completeness.

2.2.2. Methods – analysis of data submitted

A dose range finding study was conducted in juvenile rats (JE049-0172) to identify the dose for a future juvenile rat toxicology study. In this study, rats were dosed daily subcutaneous starting on Postnatal Day 22 at doses of 0, 6.25, 12.5, and 25 mg/kg/day for 14 days.

Results

There were no icatibant-related mortalities; group mean body weight gain was slightly decreased in females in the 12.5 and 25 mg/kg/day groups, males were unaffected. Females showed a slight reduction in food consumption at 25 mg/kg/day, males were unaffected. In males only there was a very slight but dose-related increase in spleen weight when adjusted for body weight. In males and females there were slight decreases in mean thymus weight as well. The absolute changes in body weight, food consumption, and organ weights were so slight that they were not considered as dose-limiting toxicities.

Discussion

Based on these findings, 25 mg/kg/day was considered a maximally tolerated dose and a 7 week repeat dose toxicity study, including a fertility assessment in the juvenile rat was conducted (JE049-0173). *This study was submitted as a Follow-up Measure (FUM RM2 023.1) in April, 2012 in the EU.*

A 7 week GLP toxicity study was performed in juvenile rats (Crl:WI(Han), 22 day of age, 12 rats/sex/group + 20 rats/sex/group for recovery and analysis of fertility, which were dosed 0, 3, 9 or 25 mg/kg/day subcutaneously. Doses were selected based on findings in previous studies; a 13-week toxicity study and a 14 day dose range-finding study. According to the MAH toxicokinetic data showed exposure in juvenile and adult animals to be approximately equivalent. Full recovery was expected after exposure to the low dose based on findings from a previous 6 month toxicity study. (Post-natal Day 22 in rats was considered to be equivalent to a 2 year old human.) An assessment of effects on fertility was assessed during the recovery period of 4 to 6 weeks (necroscpoies of females were performed on Day 13 of gestation and males week 13 [5 animals/group] or 14 [15 animals/group]).

The following were assessed: clinical observations, dose site observations, body weight, food intake, long bone measurements, sexual maturation data, mating data, seminology, organ weights and gross pathology and microscopic pathology.

Results

No mortalities were seen. (One female receiving 9 mg/kg/day was killed on Day 42 due to not having a patent vaginal opening. This developmental anomaly was confirmed at microscopic examination as being associated with excessive epithelial folding and was not considered to be an effect of treatment.) Clinical observations such as thinning fur, hair loss and sores/lesions were made at the injection site and were seen at 9 and 25 mg/kg/day, with more frequent findings seen at 25 mg/kg/day. These signs diminished during the treatment-free period of the study. A slight dose-related decrease in body weight gain was seen in toxicity group males which was statistically significant only as a dose response from PND 22-46 ($P<0.05$) and at 25 mg/kg/day only PND 46-71 ($P<0.01$). Recovery/fertility group males were also slightly affected while female rats were less affected (recovery/fertility group females even showed a slight dose-related increase in body weight gain compared to controls). However, no statistically significant changes in mean body weight were detected. Mean food intake was generally slightly lower than controls in animals receiving 25 mg/kg/day. Mean long bone measurements showed no adverse effect of treatment (no dose response, both increases and decreases seen relative to control and no difference larger than 10% of control).

Sexual maturation data: Balano-preputial separation showed a dose-related increase in the mean day of separation at all dose levels (mean postnatal day: 51.4/52.4/54.8/54.1) which was statistically significant in recovery/fertility males at 9 and 25 mg/kg/day (both $P<0.01$) (mean postnatal day: 50.5/50.6/54.7/55.4). Vaginal opening was unaffected by treatment at any dose level tested (mean postnatal day: 34.8/35.5/34.9/35.4).

Mating data: Recovery/fertility males and untreated females: Median pre-coital time (days) 2/1/2/3 Pregnancy rate (%) 95/100/90/65 Mating index % 100/95/100/71 Fertility index (%) 95/100/90/65 Fecundity index (%):95/100/90/65. Recovery/fertility females and untreated males: Median pre-coital time (days) 2.5/3/3/3 Pregnancy rate (%) 100/100/95/100 Mating index (%) 100/100/100/74.1 Fertility index (%) 100/100/95/100 Fecundity index (%):100/100/95/100.

Caesarean implantation data: Recovery/fertility group females paired with untreated males, mean numbers of corpora lutea, the incidence of pre- and post-implantation loss and mean number of embryos per female all showed no adverse effect of treatment. Recovery/fertility group males paired with untreated females, mean numbers of corpora lutea and the incidence of post-implantation loss were

similar to controls, however the mean number of implantations per female was significantly lower than controls at 25 mg/kg/day, and this was reflected in fewer embryos per female at 25 mg/kg/day (both P<0.01). As these females were untreated, this was a male-mediated effect in males receiving 25 mg/kg/day.

Seminology: In toxicity group males, 25 mg/kg/day mean percentage motility was significantly reduced compared with controls (P<0.001), as were average path velocity, curvilinear velocity and straight line velocity (all P<0.01). Mean percent abnormal sperm was increased compared to controls at 9 and 25 mg/kg/day, significant only as a dose-response (both P<0.05). In recovery/fertility group males mean sperm count was lower than controls in all the treated-groups although not in a dose-proportional manner, and was statistically significant only at 25 mg/kg/day. All other parameters were similar to control at all dose levels, indicating at least partial functional recovery from the findings seen in the terminal kill males.

Organ weights: Mean prostate weight in the terminal kill males was lower than controls in all the treated groups, although not in a dose-proportional manner and was statistically significant only at 9 and 25 mg/kg/day (both P<0.05). Testes/epididymides showed a dose-proportional decrease which was statistically significant at 25 mg/kg/day only. Mean heart weight adjusted for body weight was reduced in all treated groups in a non dose-proportional manner and was statistically significant only at 3 mg/kg/day. Mean heart weight adjusted for body weight in terminal kill females was significantly lower in animals receiving 25 mg/kg/day only (P<0.05). Mean uterus weight showed an approximately dose-proportional decrease compared to controls although this difference did not attain statistical significance.

Gross pathology: small testis and small epididymis were recorded macroscopically in occasional animals dosed at 25 mg/kg/day. Also, fur loss, red, dark, sore and thick were recorded in injection sites of variable numbers of animals dosed at 25 mg/kg/day.

Microscopic pathology: there were effects in the testis, epididymis and injection sites associated with effects of icatibant.

In the testis, there was tubular cell vacuolation and germ cell degeneration in animals in all dose groups. Also, there were atypical residual bodies, multinucleated cells and tubular atrophy in the majority of animals dosed at 25 mg/kg/day.

In the epididymis, there was cellular debris in animals in all dose groups and oligospermia in some animals dosed at 25 mg/kg/day.

Terminal kill:

Group incidence of selected microscopic findings in the testis

Tissue and finding	Level (mg/kg/day)	1M 0	2M 3	3M 9	4M 25
Testis	No. examined:	12	12	12	12
tubular cell vacuolation	Grade -	12	10	7	0
	1	0	2	2	2
	2	0	0	2	8
	3	0	0	1	2
germ cell degeneration	Grade -	12	10	7	0
	1	0	2	3	2
	2	0	0	2	7
	3	0	0	0	3
atypical residual bodies	Grade -	12	12	11	1
	1	0	0	1	11
multinucleated cells	Grade -	12	12	12	8
	1	0	0	0	4
tubular atrophy	Grade -	12	12	11	7
	1	0	0	0	2
	2	0	0	0	2
	3	0	0	0	1
	4	0	0	0	0
	5	0	0	1	0

Group incidence of cellular debris and oligosperma in the epididymis

Tissue and finding	Level (mg/kg/day)	1M 0	2M 3	3M 9	4M 25
Epididymis	No. examined:	12	12	12	12
cellular debris	Grade -	12	8	5	0
	1	0	4	6	4
	2	0	0	1	6
	3	0	0	0	2
oligospermia	Grade -	12	12	11	6
	1	0	0	0	0
	2	0	0	0	3
	3	0	0	0	1
	4	0	0	0	2
	5	0	0	1	0

1=minimal, 2=slight, 3=moderate, 4=moderate severe, 5= severe

In the injection sites, there was an overall increase in inflammatory lesions including dermatitis/folliculitis, cellulitis, myositis/myopathy, epidermal hyperplasia, hyperkeratosis and dermal fibrosis in animals in all dose groups, compared with control animals, suggestive of minor local irritation associated with the injection of icatibant. There was evidence of complete reversal of the injection site findings seen at the terminal kill in the fertility phase animals.

There was evidence of partial reversal of the changes seen in the testis and epididymis at the terminal kill.

In the testis, there were reduced levels of tubular cell vacuolation, germ cell degeneration and multinucleated cells, together with an absence of atypical residual bodies after recovery. The minor increase in the level of tubular atrophy in fertility animals compared with terminal kill animals was considered to be a result of progression of the degenerative changes seen during the treatment period, rather than evidence of delayed toxicity.

In the epididymis, the levels of cellular debris were reduced compared to those recorded at the terminal kill. Oligospermia was only recorded sporadically at the treatment-free kill.

After recovery:

Group incidence of selected microscopic findings in the testis

Tissue and finding	Level (mg/kg/day)	1M 0	2M 3	3M 9	4M 25
Testis	No. examined:	20	20	20	20
tubular cell vacuolation	Grade -	18	17	16	4
	1	2	2	2	7
	2	0	1	2	9
germ cell degeneration	Grade -	20	19	13	12
	1	0	0	3	8
	2	0	0	2	0
	3	0	1	2	0
multinucleated cells	Grade -	20	19	20	18
	1	0	0	0	2
	2	0	1	0	0
tubular atrophy	Grade -	20	19	16	7
	1	0	0	1	10
	2	0	0	1	2
	3	0	0	2	1
	4	0	1	0	0

Group incidence of cellular debris and oligosperma in the epididymis

Tissue and finding	Level (mg/kg/day)	1M 0	2M 3	3M 9	4M 25
Epididymis	No. examined:	20	20	20	20
cellular debris	Grade -	20	18	13	12
	1	0	1	7	8
	2	0	0	0	0
	3	0	1	0	0
oligospermia	Grade -	20	19	19	20
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	1	0
	4	0	0	0	0
	5	0	1	0	0

1=minimal, 2=slight, 3=moderate, 4=moderate severe, 5= severe

Discussion

Icatibant, at a dose level of 25 mg/kg/day (s.c.), induced an increase in the mean day of pre-putial separation, partially reversible effects on seminology parameters and impaired fertility in male juvenile rats. Increased intra-uterine pre-implantation loss, lower testes, epididymides, prostate and uterine weights were also seen.

At a dose level of 9 mg/kg/day there was an increase in the mean day of pre-putial separation, increased numbers of abnormal sperm, decreased sperm count and lowered testes/epididymides and prostate weights in male rats. At a dose level of 3.0 mg/kg/day there was reduced body weight gain in toxicity males only, as well as lower testes/epididymides weights. At all doses there were microscopic findings in the testes and epididymides which were partially reversible and at the dose sites, which were fully reversible.

The no-observed-adverse-effect-level (NOAEL) for females was 9 mg/kg/day. The reduced uterine weight seen in females at dose levels of 9 mg/kg/day are expected based on similar findings seen in a previous 13-week toxicity study in rat, where dose levels of 10 mg/kg/day or higher resulted in icatibant-related changes in the uterus of females.

Due to the microscopic findings in testes and epididymides seen at all dose levels, which were partially reversible, a no-observed-effect-level (NOEL) for males could not be established for this study. The effects seen in males are largely expected due to the known effects of icatibant and similar effects were also seen in a previous 26 week rat toxicity study at dose levels of 3 and 10 mg/kg/day. However, the effects seen in the present study at 3 and 9 mg/kg/day did not result in a functional deficit in terms of the mating performance and fertility of the male rat and an effect on fertility was only seen at 25 mg/kg/day.

Decreases in circulating reproductive hormone levels and effects on reproductive organs seen in animals are consistent with the involvement of bradykinin in the control of the hypothalamic-pituitary-gonadal axis, as well as the presence of B2 receptors in the testis.

This study was submitted as a revision to the SmPC, procedure EMEA/H/C/000899/II/0017/G, which was approved on 25 October 2012.

2.2.3. Environmental Risk Assessment

A justification for not submitting an updated ERA was provided by the MAH.

The CHMP agrees that based on the nature of icatibant, extending the use to paediatrics will not lead to an increase in environmental exposure.

2.2.4. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

The studies presented have been assessed before, and appropriate changes have been introduced in SmPC section 5.3 within previous procedures. However, in order to fulfil the intentions of the paediatric Regulation (EC) 1901/2006, all results from studies conducted as part of the agreed PIP (EMEA-000408-PIP01-08-M05; EMA decision P/0243/2015) are being included in the Firazyr SmPC. Thus, the MAH proposes to introduce a sentence from the DRF-study stating that the dose-range finding study identified 25 mg/kg/day as a maximally tolerated dose. This change is considered acceptable.

Given the limited clinical data available, in order to add reassurance in terms of patient safety, the MAH was asked to discuss how the exposures (Cmax and AUC) observed during the juvenile toxicity study, compare to the proposed and/or observed clinical exposures for paediatric patients of at least 2 years of age.

In addition, on the basis of the non-clinical and clinical data generated thus far, the MAH was asked to clarify how the metabolism of icatibant in the proposed paediatric population compares to that observed in adults (see clinical section). These questions have been addressed by the Applicant, and in the response the Applicant has shown that icatibant exhibited higher body-weight adjusted clearance, CL/F (L/h/kg), in paediatrics (ages 2-17) when compared to adults; otherwise, no differences in metabolism are expected.

Regarding the exposure, it can be concluded that administration of Firazyr to the paediatric population is supported when given once per HAE attack. However, it is noted that clinical experience with respect to the exact frequency of dosing for the paediatric population could possibly be further revised to give an accurate indication of the frequency of dosing per month in this subset of the population (as specified for adults). (See the clinical part of this report for further detail)..

Finally, the MAH was asked to note that in accordance with the guideline on the environmental risk assessment of medicinal products for human use, for type II variations which involve a new indication, the evaluation of the environmental impact should be made to establish whether there is an increase in the environmental exposure. The Applicant therefore submitted further documentation and appropriate justification for not submitting an environmental risk assessment to support the extension of use. The CHMP agrees that based on the nature of icatibant, extending the use to paediatrics will not lead to an increase in environmental exposure. In summary, the updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of icatibant.

2.2.5. Conclusion on the non-clinical aspects

The non-clinical data results are adequate to support a use in a paediatric indication.

2.3. Clinical aspects

2.3.1. Introduction

The clinical development program to support the use of icatibant as a treatment for HAE type I or II in children and adolescents consists of a single pivotal Phase 3 trial (HGT-FIR-086). NB. The study was intended to determine the pharmacokinetic profile of SC icatibant when administered to children and adolescents with HAE and to identify an optimal paediatric dosing regimen.

GCP

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

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

2.3.1. Clinical pharmacology

2.3.1.1. PK and PK/PD modelling

Study Title: Clinical study HGT-FIR-086: An open-label, nonrandomized, single-arm study to assess the pharmacokinetics, tolerability, and safety of a single sc administration of icatibant in children and adolescents with hereditary angioedema

Methods – analysis of data submitted

The study enrolled children and adolescents from 2 to less than 18 years of age, divided into 2 groups: pre-pubertal (Tanner stage I) and pubertal/post-pubertal (Tanner stages II to V). All subjects received treatment with icatibant as a single, weight-adjusted dose of 0.4 mg/kg up to a maximum of 30 mg administered in the abdominal region as an SC injection.

Blood samples for determination of plasma concentrations of icatibant, M1, and M2 in pubertal/post-pubertal subjects were collected on Day 1 at pre-treatment, and at 15 (±5) minutes, 30 (±5) minutes, 45 (±5) minutes, 1 hour (±10 minutes), 2 hours (±10 minutes), 4 (±0.5) hours, and 6 (±0.5) hours after treatment. Blood samples for determination of plasma concentrations of icatibant in pre-pubertal subjects were collected on Day 1 at pre-treatment and at 15 (±5) minutes, 30 (±5) minutes, 2 hours (±10) minutes, 4 (±0.5) hours, and 6 (±0.5) hours after treatment.

Non-compartmental analysis was used to calculate exposure metrics (eg. Cmax, AUC) and summary statistics were used to display these results.

Population pharmacokinetic analysis

The PK information obtained in the trial was also included in a Population PK analysis together with data from 6 adult studies.

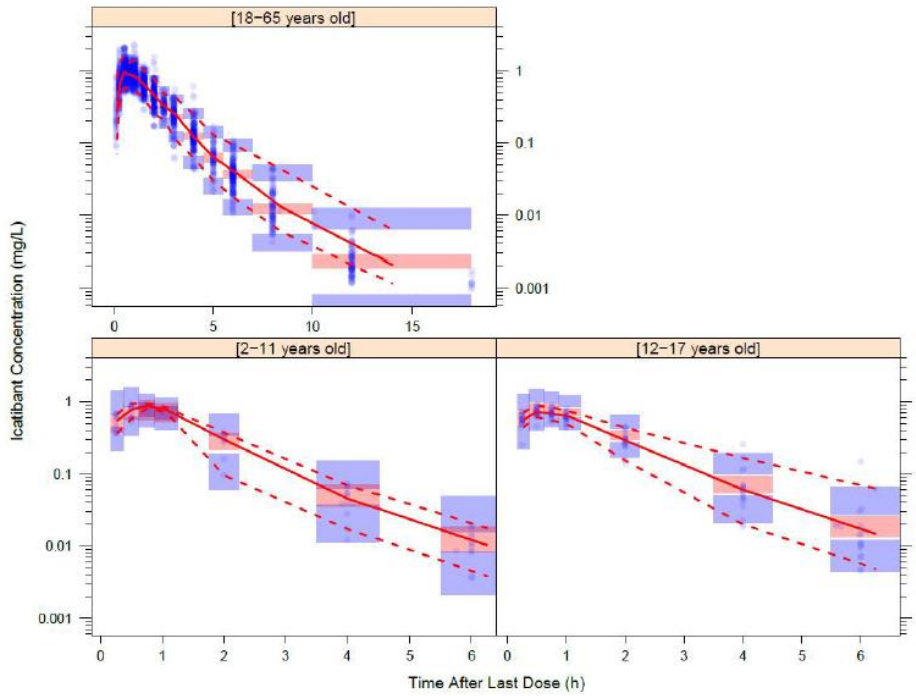
The objectives of the analysis were as follows:

- To characterize icatibant PK in this population
    - By performing a population PK analysis to fit concentration-time profiles of icatibant in children and adolescents with HAE.

- By characterizing the source of variability in icatibant PK parameters in children and adolescents with HAE.
- By deriving individual post hoc PK parameters of icatibant (e.g., area under the concentration-time curve over the dosing interval (AUC0-6), maximum plasma concentration (Cmax), terminal half-life (t1/2), as well as the apparent clearance (CL/F), and apparent central volume of distribution (Vc/F).

- To compare icatibant exposure in children and adolescents to those in adults.
- To assess the relationship between the time of onset of symptom relief (TOSR) and various exposure metrics of icatibant (Cmax, AUC0-2, AUC0-4 and AUC0-6, T1/2 and Tmax) in children and adolescents.

A previously developed PopPK model was used as a starting point for the modelling. The relationships between covariates and PK parameters were explored graphically. Covariate analysis was performed using a "full model" approach to identify sources of variability in PK parameters of icatibant. The performance of the "full population PK model of icatibant" was evaluated with a bootstrap re-sampling strategy. Based on the estimates of the population PK model, concentration-time profiles of icatibant were simulated (~1000 replicates). Non-significant covariates were to be removed from the model. The quality-of-fit of the population PK models was evaluated using standard graphical representations of goodness-of-fit and the performance of the final population PK model of icatibant was evaluated with several methods including diagnostic plots and visual predictive check (see below).



Legend: The red solid and dashed lines represent median and 2.5-97.5th percentiles of the observed data. Shaded areas represent the 95% prediction intervals of the medians (red) and 2.5-97.5th percentiles (blue) obtained from simulations.

Study HGT-FIR-086

Population PK modeling

PopPK modeling of icatibant was performed based on PK data collected from four Phase I studies in healthy subjects (HGT-FIR-061, HGT-FIR-065, JE049-1102, JE049-1103), a Phase IIa study in adult

subjects with HAE (JE049-2101), and a Phase III study (HGT-FIR-086) in children and adolescents with HAE. A table describing the studies in short is provided below.

Table 1 Description of Studies Included in the Population Pharmacokinetic Modeling of Icatibant

Study	Dose	Study Objective	Duration of Treatment
JE049-1102 (Module 5.3.1.1)	SC injection of 0.05 mg/kg (40 mg/mL), 0.2 mg/kg (40 mg/mL), 0.2 mg/kg (20 mg/mL), 0.4 mg/kg (20 mg/mL) and SC injection or IV infusion 0.4 mg/kg (10 mg/mL)	Absolute bioavailability of icatibant after SC injection compared to IV infusion	Single dose
JE049-1103 (Module 5.3.3.3)	30 mg SC 3 doses day 1, single dose days 8 and 15	PK, safety (including QT/QTc), in young and elderly male and female subjects	5 doses over 15 days
HGT-FIR-065 (Module 5.3.3.3)	30 mg icatibant(3 10-mg 3-mL injections) 3 doses at 6-h intervals	PK of icatibant and metabolites M1 and M2	Approximately 24 days
HGT-FIR-061 (Module 5.3.5.1)	icatibant or placebo 4 treatment periods; placebo SC or icatibant 30 mg SC single dose, icatibant 90 mg SC 3 injections, moxifloxacin 400 mg PO	Effect of single SC dose of icatibant on QT/QTc prolongation	4 cycles of treatment 43 days total
JE049-2101 (Module 5.3.5.2)	IV icatibant: 0.4 mg/kg 2 h or 30 min infusion, 0.8 mg/kg (30-min infusion) , 1 IV dose SC icatibant, 30 mg and 45 mg 1 SC dose	Efficacy, safety and tolerability, PK, PD	5 days (IV and SC groups)
HGT-FIR-086 (Module 5.3.5.2)	0.4 mg/kg icatibant 1 SC dose	PK, safety (including reproductive hormones), efficacy	90 days

Source: Refer to Module 5.2 Icatibant EU Type II Peds Tabular Listing of All Studies
IV=intravenous; SC=subcutaneous

The population PK dataset included concentration-time data of icatibant in 31 children and adolescents with HAE and 141 adults (healthy subjects and patients with HAE) below 65 years of age.

A total number of 2172 concentrations were included in the PK analysis. Of the 523 BLQ samples, 166 were observed prior to icatibant dosing and 228 BLQ samples were observed 18-h after administration.

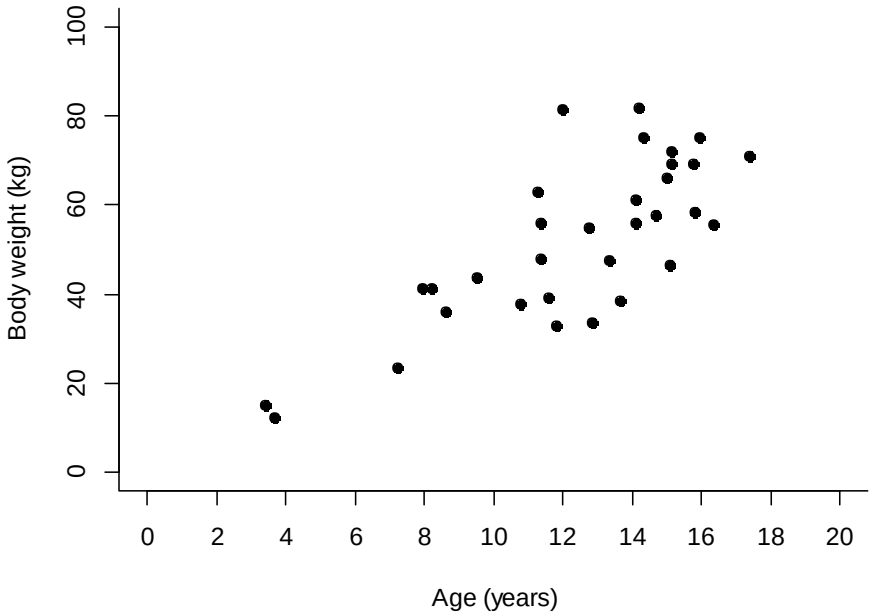
Results - Descriptive PK from Study HGT-FIR-086.

The pharmacokinetic analysis included all subjects in the safety population who received study drug and provided evaluable plasma drug concentrations.

A total of 32 subjects had pharmacokinetic blood samples taken. Among those subjects, 2 subjects were excluded from pharmacokinetic analysis for icatibant, M1, and M2.

Among the 30 subjects who provided evaluable plasma concentrations, 13 were female and 17 were male. The mean age was 7.9 ± 2.72 years for the pre-pubertal subjects, 14.3 ± 1.62 for the pubertal/post-pubertal subjects. The distribution of age and body weight is shown in the figure below.

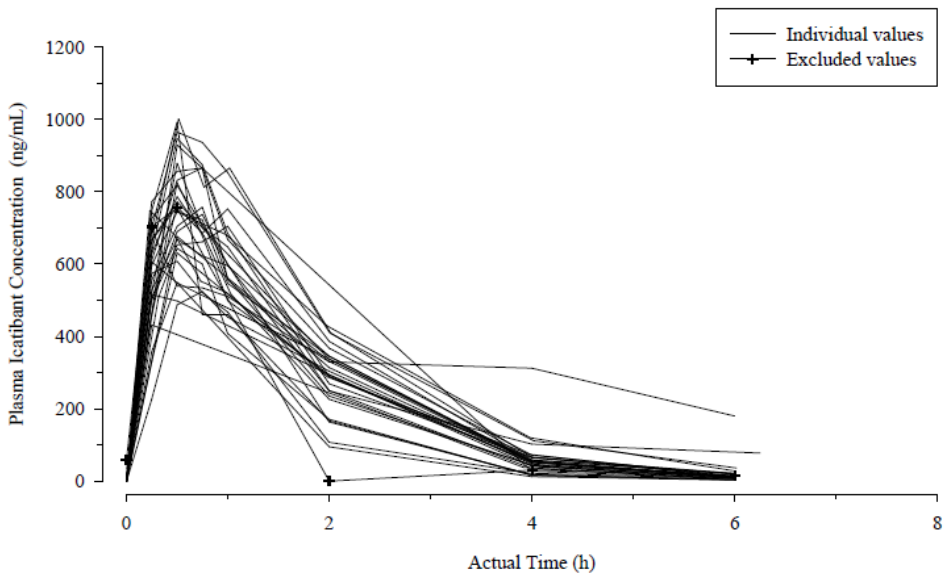
Figure 1 Distribution of age and body weight Study HGT FIR 086



Single-dose treatment with icatibant was given based on body weight (0.4 mg/kg) SC up to a maximal dose of 30 mg. The mean ± SD total SC dose of icatibant received were 14.0 ± 5.97 and 23.8 ± 5.15 mg for pre-pubertal subjects and pubertal/post-pubertal subjects, respectively. The minimum total dose received was 4.9 mg by a 3-year-old male subject weighing 12.3 kg, and the maximum total dose was 30 mg of icatibant in 4 subjects whose body weight ≥75 kg.

The individual plasma concentration-time profiles for icatibant are shown in the figure below.

Figure 2 Individual Plasma Icatibant Concentrations vs. Time Following Subcutaneous Administration Icatibant – All subjects - Linear Scale



Icatibant was rapidly absorbed in pediatric HAE subjects with a tmax of approximately 0.5 hours. Following administration of a single 0.4 mg/kg dose of icatibant, Cmax values of 659, 805, and 761 ng/mL were observed for the pre-pubertal with an HAE attack, pubertal/post-pubertal with an HAE attack, and pubertal/post-pubertal without an HAE attack, respectively.

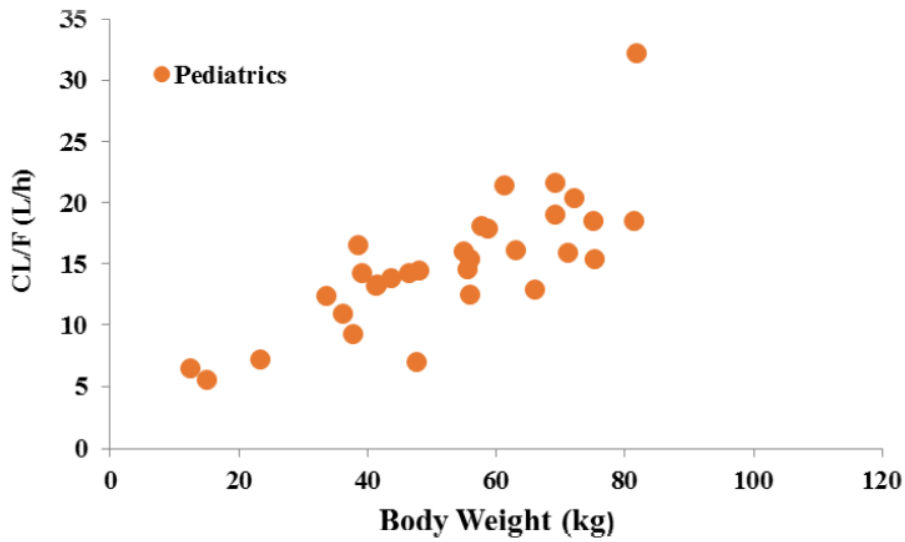
The mean AUC0-t was 1289, 1573, and 1398 h•ng/mL, for the pre-pubertal with an HAE attack, pubertal/post-pubertal with an HAE attack, and pubertal/post-pubertal without an HAE attack, respectively. The mean plasma clearance was 10.8, 13.1, and 19.3 L/hr, and the mean body weight normalized plasma clearance was 0.334, 0.256 and 0.285 L/hr/kg for the pre-pubertal with an HAE attack, pubertal/post-pubertal with an HAE attack, and pubertal/post-pubertal without an HAE attack, respectively.

Based on these data, the paediatric subjects in this study appear to have exhibited lower systemic exposure to icatibant compared to adult HAE subjects receiving the marketed dose of 30 mg SC during an attack (previous Study JE049-2101). In JE049-2101, the Cmax was 815 ng/mL and the AUC was 1568 h.ng/mL. However, the average dose of icatibant received in the current study was lower than in the 30 mg dose prescribed for adults.

The estimated exposure to the 2 metabolites is lower than to icatibant, as evaluated by AUC0-4, AUC0-t, and Cmax. Compared to icatibant, M1 and M2 were slowly formed (tmax ~2.0 hours post SC dose for pre-pubertal subjects with an attack, pubertal/post-pubertal subjects with an attack, and pubertal/post-pubertal subjects without an attack). The molar metabolite-to-parent exposure (AUC0-t) ratios were 1.09, 0.808, and 0.699 for M1 and 0.744, 0.618, and 0.562 for M2 for pre-pubertal subjects with an attack, pubertal/post-pubertal subjects with an attack, and pubertal/post-pubertal subjects without an attack, respectively.

The relation between icatibant model derived plasma clearance and body weight is shown in the figure below.

Figure 3 Relationship between CL/F (L/h) and Body Weight (Pediatric Population)



Population Pharmacokinetic Modeling

A 2-compartment model with first-order absorption and lag-time resulted in an adequate quality-of-fit. The population PK model included the effect of body weight on CL/F and apparent central volume distribution (Vc/F; traditional allometric function). The population PK models were evaluated/qualified

based on standard model diagnostics and by looking at pertinent graphical representations of goodness-of-fit. Typical population PK parameters of icatibant derived with the base model and representations of goodness-of-fit of the structural model were presented in the report titled "Population PK Modeling and Exposure-response Analysis of Icatibant in Children and Adolescents with Hereditary Angioedema".

Table 2 Typical Population PK Parameters of Icatibant Following SC Administration – Final Population PK Model

Population Pharmacokinetic Parameter	Typical Values	Between Subject Variability (%)	Shrinkage
Ka (h^{-1})	**3.27**	35.3	19.1
Tlag (h)	**0.0426**	55.6	34.2
CL/F (L/h)	**15.4** $(Weight/70)^{0.516}$ x (1 + (-0.0107*(Age-25))) x 0.882 if Female x 0.911 if HAE attack (within 12-h of dosing)	22.7	2.0
Vc/F (L)	**20.4** $(Weight/70)^{0.671}$ x 0.855 if Female x 1.11 if Non-White	26.9	5.8
CLp/F (L/h) Weight	**0.398** $(Weight/70)^{0.516}$	107.8	19.2
Vp/F (L) Weight	**1.75** $(Weight/70)^{0.671}$	53.9	23.5
Error Model Proportional (%)	 **13.0**	NA	NA

CL/F = apparent total clearance; CLp/F = apparent inter-compartmental clearance; HAE = hereditary angioedema;

Ka = absorption rate constant; NA = not applicable; PK = pharmacokinetic; SC = subcutaneous; Tlag = Lag time; Vc/F = apparent volume of distribution in plasma; Vp/F = apparent peripheral volume of distribution.

The CHMP noted that to compare with the PopPK model, a non-compartmental analysis of the observed PK data from study HGT-FIR-086 was performed. Individual values of clearance were calculated as the ratio of nominal dose (0.4 mg/kg capped at 30 mg which corresponds to a body weight of 75 kg) and AUC(0-Inf). A linear model (method lm in R) was fitted to individual values of clearance vs body weight centred to 70 kg. Both variables were log-transformed before calculation of regression coefficients. The slope of the regression line was estimated to 0.78 with a 95% confidence interval of 0.56 to 1.0. No definitive conclusion is made, however it should be noted that the point estimate differ compared to the Population PK model where the exponent of the clearance vs bodyweight relation was estimated to 0.516.

In general, exposure to icatibant in paediatric subjects with HAE, as evaluated by Cmax and AUC, is lower than in adults (predominantly healthy, non-HAE subjects) due to the weight-adjusted doses received compared to a single nominal dose in adults regardless of weight. The CL/F of icatibant is related to body weight with lower clearance values noted for lower body weights in this paediatric population. Thus, at the same total dose administered, paediatric subjects with lower body weights would demonstrate higher exposure to icatibant compared to subjects with higher body weights.

Proposed paediatric dosing regimen

Children and adolescents enrolled in Study HGT-FIR-086 received a single 0.4 mg/kg icatibant SC administration up to 30 mg (4.9 - 30 mg). Healthy volunteers received a single 30 mg icatibant SC dose with the exception of subjects from Study JE049-1102 who received a single 0.4 mg/kg icatibant SC dose (26 – 37 mg). Adult patients with HAE were treated with icatibant after an HAE attack either at 30 mg or 45 mg. Of note, the recommended dose for adults is 30 mg.

Based on the PK findings the MAH initially suggested a fixed dosing regimen in children. This was different from the regimen (0.4 mg/kg caped at 30 mg) that was studied. The proposed dose levels and weight bands are shown in the table below.

Body Weight	Dose
>10 kg to ≤25 kg	10 mg
>25 kg to ≤50 kg	20 mg
>50 kg	30 mg

Table 3 below presents the predicted exposure for the proposed paediatric 10 mg, 20 mg, and 30 mg doses based on dosing band and comparatively,

Table 4 presents post-hoc PK parameters and PK parameters estimated by NCA from the adult 30 mg, 45 mg, and 90 mg groups.

The Applicant's response included a discussion about dosing regimen and a proposal to use the studied regimen (0.4 mg/kg) instead of the initially proposed three weight band regimen. This was seen to result in a lower exposure in children compared to adults which was also concluded from the assessment of pharmacokinetics in the first round. Instead, for example an extension to 5 weight bands was suggested as an alternative to better mimic the adult exposure in children. The Applicant discussed this proposal in the response to the request for supplementary information in the second round.

Table 3 Predicted Pharmacokinetic Parameters of Icatibant in Pediatrics (Study HGT-FIR-086)

Nominal Dose	Weight Group	Mean (SD, CV%) Median [Min-Max]									
		Weight (kg)	Cmax (ng/mL)	Tmax (h)	$T_{1/2}$ (h)	AUC_{0-6} (ng.h/mL)	AUC_{0-24} (ng.h/mL)	CL/F (L/h)	Vc/F (L)	CL/F (L/h/kg)	Vc/F (L/kg)
10 mg	> 10-≤25 kg (n=3)	16.8 (5.75, 34.2%) 14.9 [12.3-23.3]	1157 (192, 16.6%) 1232 [939-1301]	0.433 (0.0577, 13.3%) 0.400 [0.400-0.500]	2.05 (0.417, 20.4%) 2.00 [1.66-2.49]	1544 (204, 13.2%) 1518 [1354-1761]	1564 (202, 12.9%) 1535 [1378-1779]	6.47 (0.821, 12.7%) 6.52 [5.63-7.27]	5.23 (0.805, 15.4%) 4.86 [4.66-6.15]	0.407 (0.112, 27.6%) 0.378 [0.312-0.530]	0.324 (0.0665, 20.5%) 0.313 [0.264-0.395]
20 mg	>25-≤50 kg (n=11)	41.2 (4.83, 11.7%) 41.2 [33.4-48.0]	852 (170, 19.9%) 797 [663-1223]	0.573 (0.101, 17.6%) 0.600 [0.400-0.700]	4.05 (5.21, 128.7%) 2.73 [1.61-19.6]	1581 (337, 21.3%) 1454 [1194-2269]	1658 (462, 27.9%) 1496 [1207-2816]	12.7 (2.69, 21.1%) 13.4 [7.09-16.6]	15.0 (4.17, 27.8%) 14.4 [10.4-25.3]	0.313 (0.0725, 23.1%) 0.320 [0.149-0.432]	0.362 (0.0755, 20.8%) 0.337 [0.280-0.531]
30 mg	>50 kg (n=17)	66.0 (9.10, 13.8%) 66.0 [54.9-81.6]	894 (183, 20.4%) 875 [646-1294]	0.582 (0.0951, 16.3%) 0.600 [0.400-0.800]	3.25 (1.44, 44.3%) 3.09 [1.41-8.05]	1696 (342, 20.2%) 1646 [918-2359]	1740 (356, 20.5%) 1674 [932-2400]	18.1 (4.52, 25.0%) 17.9 [12.5-32.2]	21.9 (4.87, 22.2%) 21.2 [13.8-35.6]	0.274 (0.0525, 19.2%) 0.276 [0.197-0.395]	0.332 (0.0556, 16.8%) 0.328 [0.246-0.473]

Table 4 Descriptive Statistics of Post-hoc Pharmacokinetic Parameters of Icatibant in Adults (30 mg, 45 mg, and 90 mg)

Actual Dose	Mean (SD, CV%) Median [Min-Max]									
	Weight (kg)	Cmax (ng/mL)	Tmax (h)	$T_{1/2}$[c] (h)	AUC_{0-6}[a] (ng.h/mL)	AUC_{0-24}[b,c] (ng.h/mL)	CL/F[c] (L/h)	Vc/F[c,d] (L)	CL/F (L/h/kg)	Vc/F (L/kg)
30 mg (N=120)	71.6 (11.8, 16.4%) 69.6 [46.6-102]	994 (294, 29.5%) 956 [524-2115]	0.659 (0.143, 21.8%) 0.600 [0.300-1.10]	3.42 (0.992, 29.0%) 3.33 [1.62-6.56]	2082 (506, 24.3%) 2018 [1126-3311]	2162 (529, 24.5%) 2089 [1137-3486]	14.7 (3.62, 24.6%) 14.4 [8.60-26.4]	21.1 (6.35, 30.0%) 19.9 [9.22-42.1]	0.206 (0.0396, 19.2%) 0.205 [0.0999-0.323]	0.294 (0.0657, 22.4%) 0.293 [0.153-0.493]
45 mg[e] (N=4)	82.9 (11.7, 14.1%) 80.0 [73.0-98.5]	2136 (348, 16.3%) 2222 [1680-2421]	0.775 (0.0957, 12.4%) 0.750 [0.700-0.900]	4.12 (0.800, 19.4%) 4.07 [3.34-4.99]	5473 (1020, 18.6%) 5565 [4155-6608]	5893 (1223, 20.8%) 6005 [4297-7264]	7.91 (1.82, 23.0%) 7.49 [6.18-10.5]	14.2 (1.40, 9.9%) 14.3 [12.8-15.5]	0.0948 (0.0106, 11.1%) 0.0952 [0.0825-0.106]	0.172 (0.0101, 5.8%) 0.176 [0.157-0.180]
90 mg[f] (N=72)	70.9 (11.2, 15.8%) 69.2 [46.6-98.4]	2719 (666, 24.5%) 2660 [1360-4600]	0.778 (0.2329, 29.9%) 0.751 [0.485-1.565]	2.00 (0.566, 28.2%) 1.84 [1.20-4.26]	6734 (1221, 18.1%) 6663 [4572 -10524]	6736 (1230, 18.3%) 6640 [4575-10529]	13.81 (2.54, 18.4%) 13.55 [8.55-19.67]	31.4 (7.45, 23.7%) 30.1 [17.6-58.7]	NC	NC

Source: Refer to Module 5.3.3.5, "Simulation Predicted Icatibant Exposure in Children and Adolescents with Hereditary Angioedema", Table 2 and Table 9

AUC_{0-6} = area under the concentration-time curve from 0 to 6 hours post icatibant SC dosing; AUC_{0-24} = area under the concentration-time curve from 0 to 24 hours post icatibant SC dosing
Cmax = maximum plasma concentration; CL/F = apparent systemic clearance; Max = maximum; Min = minimum; PK = pharmacokinetic; $T_{1/2}$ = terminal half-life; Tmax = time to maximum plasma concentration; Vc/F = apparent central volume of distribution.

[a] AUC_{0-t} reported for the 90 mg dose (study HGT-FIR-061).

[b] $AUC_{0-\infty}$ reported for the 90 mg dose (study HGT-FIR-061).

[c] N=71 (Study HGT-FIR-061).

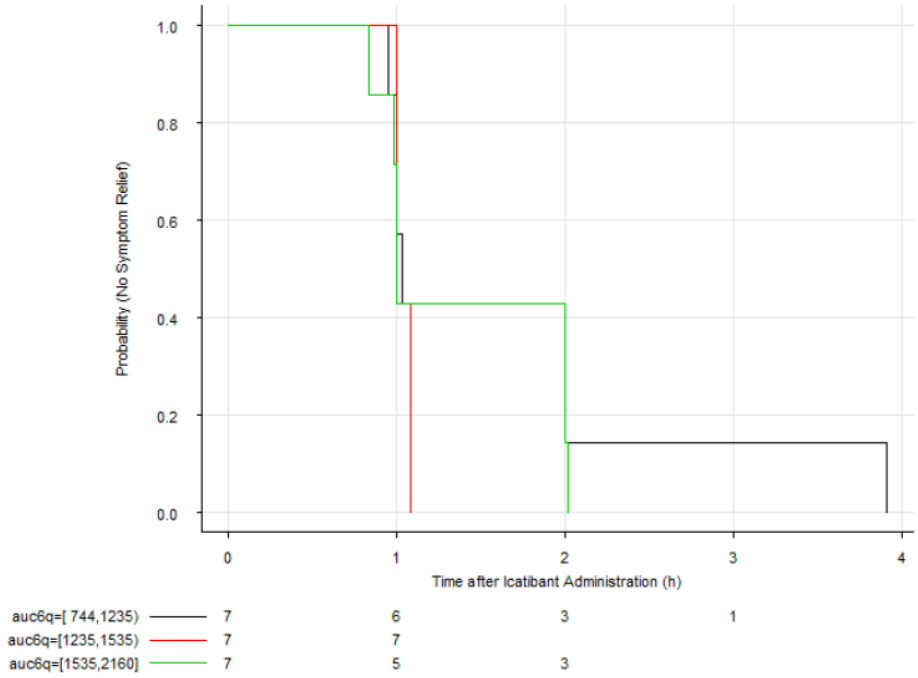
The proposed dosing weight bands are based on the actual exposure observed in study HGT--FIR-086, the simulated exposure (using nonparametric simulation based on actual observed concentrations and nominal doses), and higher exposures seen in studies following higher dose SC administrations in adult HAE subjects (30 mg, N=120; 45 mg, N=4; and 90 mg, N=72).

According to the population PK model the lightest subject (age=3.7 years; weight=12.3 kg) who received 4.9 mg icatibant in study HGT-FIR-086 had a Cmax and AUC0-6 of 604 ng/mL and 744 ng.h/mL, respectively. Assuming a 10 mg SC dose was given to this subject, model predicted Cmax and AUC0-6 would be 1232 ng/mL and 1518 ng.h/mL, respectively.

Exposure-response analysis of time to onset of relief of symptoms

One of the secondary endpoint of Protocol HGT-FIR-086 was the time to onset of relief of symptoms (TOSR). TOSR was measured in a total of 21 patients administered SC icatibant dose within 12 hours following an HAE attack. The mean TOSR was very short (1.38 h) and all subjects displayed resolution of symptoms within 4 h after icatibant administration. While patients with exposure values in the lower tertiles displayed the slowest onset of symptom relief, the rapid onset of response did not allow a discrimination of exposure-response between the 2nd and 3rd tertiles of exposure (see below).

Figure 4 Probability of No Symptom Relief as a Function of AUC0-6 Tertiles in Study HGT-FIR-086 (PD Population)



The CHMP noted that the analysis indicates that symptom relief is rapid in children. Possibly, there is an indication of slower onset in subjects with lower exposure. However, the data is very limited to draw definite conclusions.

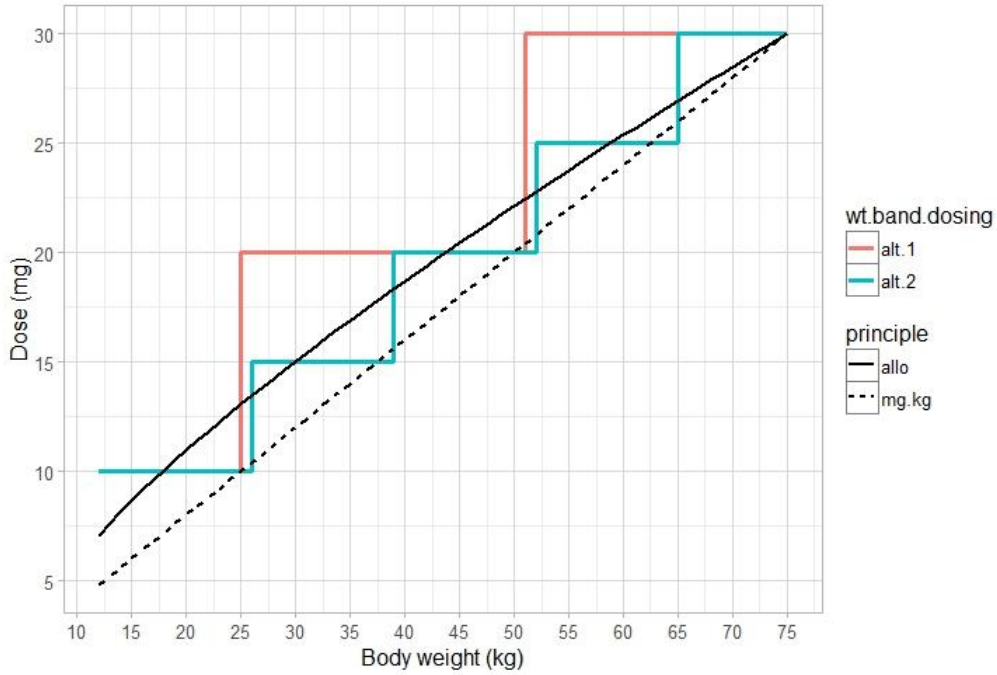
The applicant submitted documentation to amend information in section 5.2 of the SmPC to reflect the effect of age (elderly), gender and race on pharmacokinetics of icatibant. The data have been reviewed and the amendment is acceptable.

2.3.2. Discussion on Clinical Pharmacology

The pharmacokinetics of icatibant in children was investigated in a study including 31 subjects. Only two subjects were below 6 years of age. There were no subjects below 3 years of age. Approximately 80% of the subjects were > 10 years and had a body weight > 30 kg. The information about PK in the age range from 2 to 6 years of age is very limited and there is uncertainty in the expected exposure in this group of children. However, the available PK data show that icatibant clearance and distribution is related to body size. This supports body weight based dosing including in the younger children population. Of note, the studied 0.4 mg/kg dose results in slightly lower exposure compared to the adult dose of 30 mg which is also confirmed by modelling.

It should be noted that the efficacy and safety in children treated with the 0.4 mg/kg dose was adequate. Nevertheless, the dosing regimen in children should provide an exposure that matches the adult exposure unless it can be clearly justified that the exposure-response in children is different. The MAH initially proposed a simplified dosing regimen with three weight bands. This regimen was considered too coarse as it would lead to unnecessary over exposure in some children. In the response to the first list of questions from the CHMP, the MAH proposed that dosing should be identical to the one applied in the pivotal paediatric study. The clinical feasibility of such a very detailed dosing regimen in an acute stressful clinical setting could potentially be questioned. Further, as noted above the studied dose led to slight under exposure. As an alternative option, a dose regimen with five weight bands could reduce the risk of over exposure (see figure below). The corresponding dosing table is slightly simplified compared to the figure for ease of use.

Figure 5 Proposed dose (mg) vs body weight (kg) for different dosing regimens



The dashed black line ("mg.kg") denotes the studied dosing regimen (0.4 mg/kg). The solid black curve denotes the dosing regimen supported by PK analysis including modelling ("allo" referring to allometric scaling). The blue staircase shape ("alt.2") with 5 steps is the dosing regimen suggested by the CHMP. The red staircase shape ("alt.1") with 3 steps is the dosing regimen initially proposed by the MAH. NB the staircase shapes coincide at certain body weights.

Corresponding dosing table with 5 weight bands

Body weight	Injection volume
12 kg to 25 kg:	1.0 mL

26 kg to 40 kg: 1.5 mL

41 kg to 50 kg: 2.0 mL

51 kg to 65 kg: 2.5 mL

65 kg or more: 3.0 mL

In the response to the request from the CHMP for supplementary information (second round), the MAH discussed the potential advantages, drawbacks and feasibility of the suggested regimen based on 5 weight bands. This discussion was considered satisfactory and the proposed dosing regimen was agreed. The corresponding information has been introduced in sections 4.2 and 5.2 of the SmPC.

2.4. Clinical Efficacy

Title of study : HTG-FIR-086 multicenter, open-label, non-randomized, single-arm study to evaluate the Pharmacokinetics, tolerability,safety, and efficacy on reproductive hormones, of a single subcutaneous (SC) administration of icatibant in approximately 30 pediatric subjects with Hereditary Angioedema (HAE) during an initial acute attack

Methods – analysis of data submitted- sample size

The paediatric study (HTG-FIR-086) evaluated the effect of a single standard subcutaneous (SC) administration of icatibant in children and adolescents aged 2 to <18 years with a documented diagnosis of HAE type I or II. The study is ongoing and will examine the effect of 3 total exposures of icatibant in 10 adolescents who are currently being followed for this purpose. The data from the initial administration phase of the study is submitted for support of this variation. This includes complete data for the initial administration of icatibant from 11 pre-pubertal subjects during an HAE attack and 21 pubertal/post pubertal subjects (including 11 treated during an HAE attack and 10 treated without an attack). The study is an open-label, nonrandomized, single-arm study to evaluate the pharmacokinetics, tolerability, and safety, including effects on reproductive hormones of icatibant in pediatric subjects.

Study participants

Patients included had to have a documented diagnosis of HAE type I or II. Diagnosis may have been made on the basis of historical data: family history, characteristic attack manifestations, recurrent attacks, historical C1-INH deficiency, and exclusion of other forms of angioedema. Inclusion was permitted initially based on medical history only if a clear diagnosis had been made based on all of the preceding criteria. However, the diagnosis must have been confirmed prior to treatment by documented immunogenic and/or functional C1-INH deficiency (C1-INH protein level below the lower limit of normal and/or functional level <50% of normal) as performed by the sponsor's central laboratory.

Treatments

Subjects received treatment with a single standard SC administration of icatibant on Day 1 and were monitored closely in the hospital/study center for at least 6-8 hours after treatment. Subjects underwent PK and safety assessments; efficacy assessments were performed if treatment occurred during an acute HAE attack. All subjects had serum reproductive hormone measurements.

A subject was discharged after completion of assessments at 6 hours post-treatment, if deemed medically stable in the investigator's clinical judgment, and, if applicable, the subject's HAE symptoms

had resolved (the subject's investigator-rated symptom score was 0, denoting the absence of symptoms). If HAE symptoms had not completely resolved at 6 hours (ie, the investigator-rated symptom score was >0), the subject remained in the hospital/study center for at least 8 hours after icatibant administration for further evaluation.

Telephone follow-up occurred at both 24 and 48 hours after treatment.

Subjects returned to the hospital/study center for scheduled assessments on Day 8 and for a follow-up visit on Day 90. The investigator scheduled a telephone contact approximately 6 months after Day 1.

Outcomes / endpoints

Investigator Symptom Score

The primary efficacy endpoint was time to onset of symptom relief measured using the investigator-reported symptom score

The investigator used a symptom score to assess the severity of symptoms of acute cutaneous, abdominal, and laryngeal attacks of HAE using the following 5-point scale:

0=none; absence of symptoms
1=mild (no to mild interference with daily activities)
2=moderate (moderate interference with daily activities)
3=severe (severe interference with daily activities)
4=very severe (very severe interference with daily activities)

Symptom scores were recorded on Day 1 at pretreatment and at predetermined time points after treatment.

For attacks classified as cutaneous and/or abdominal, investigator-rated symptom scores were collected for 8 symptoms: abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, and skin swelling.

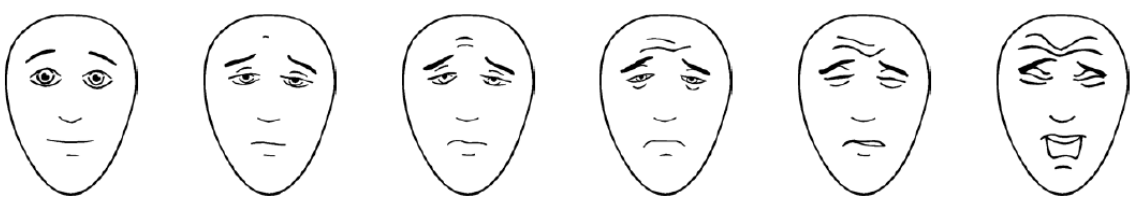
For attacks classified as laryngeal, investigator-assessed symptom scores were collected for 13 symptoms: abdominal tenderness, nausea, vomiting, diarrhea, skin pain, erythema, skin irritation, skin swelling, dysphagia, voice change, breathing difficulties, stridor, and asphyxia.

The investigator assessed symptom scores at pretreatment; at 1, 2, 4, 6 hours post-treatment; and at 8 hours post-treatment for subjects who did not have complete resolution of HAE symptoms at 6 hours.

Subject Self-assessment of Pain

Subjects who were at least 4 years of age self-assessed HAE-related pain using the Faces Pain Scale-Revised (FPS-R).

Point to the face that shows how much you hurt



Investigator Assessment of Pain

Subjects who were below 4 years of age underwent investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the Faces, Legs, Activity, Cry, and Consolability (FLACC) compartmental pain scale. The FLACC scale is a behaviour pain assessment scale for use in non-verbal patients.

FLACC SCALE (FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY)			
	0	**1**	**2**
FACE	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
LEGS	**0** Normal position Or relaxed	**1** Uneasy, Restless, Tense	**2** Kicking, Or Legs drawn up
ACTIVITY	**0** Lying quietly Normal position Moves easily	**1** Squirming Shifting back/forth Tense	**2** Arched Rigid Or Jerking
CRY	**0** No Cry (Awake or Asleep)	**1** Moans or Whimpers Occasional Complaint	**2** Crying Steadily Screams or Sobs Frequent Complaints
CONSOLABILITY	**0** Content Relaxed	**1** Reassured by occasional touching, hugging, or 'talking to.' Distractible	**2** Difficult to console or comfort.

Other Analyses

Time to first use of rescue medication: The number and percentage of subjects who received rescue medications before the onset of symptom relief were summarized.

Investigator recorded time to initial symptom relief: The investigator was asked to record the date and time when overall subject improvement was first noted. The time to initial symptom relief was defined as the duration of time in hours from study drug administration until the time when overall subject improvement was first noted.

The CHMP noted that the open label non-randomised design is acceptable taking the objectives and the characteristics of the disease into account. The methodology for efficacy evaluation can be considered appropriate and expected to provide a basis for comparison with the efficacy and safety documentation in adults that supported the approval of Firazyr.

Based on the experience in adults relief of symptoms can be accepted as an indicator for reduction of oedema and if efficacy is demonstrated in cutaneous and abdominal HAE attacks similar effects can be expected in HAE attacks with laryngeal localisation.

Statistical Methods

The study sample size was not based on a formal sample size calculation. The study was planned to enroll a sufficient number of children and adolescents to ensure study completion of 30 evaluable subjects. The

study population was planned to consist of at least 10 pre-pubertal and 20 pubertal/post-pubertal subjects from 2 to less than 18 years of age. This sample size was believed to provide basic information concerning the PK, tolerability and safety, and efficacy of icatibant in children and adolescents with HAE.

The following analysis populations were defined:

- The Efficacy Population consists of those subjects who were treated with icatibant for their first and any additional attacks during the study.
- The Safety Population consists of those subjects who were treated with icatibant at least once during the study (irrespective of the presence of an HAE attack).

All efficacy analyses were performed on the Efficacy Population. Safety and tolerability analyses were based on the Safety Population.

No hypothesis testing was planned in the study and adjustment for multiple testing was considered not necessary. Study data were presented for descriptive purpose, using summary statistics and subject listings. Time-to-event efficacy variables were presented using Kaplan-Meier estimates of the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CI) for the median, as well as percentage of censored observations.

The primary efficacy endpoint was time to onset of symptom relief (TOSR) measured using the investigator-reported symptom score. Eight symptoms were assessed for abdominal and cutaneous attacks, and 13 symptoms were assessed for laryngeal attacks. Time to onset of symptom relief was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there was at least a 20% improvement in the composite (or average) post-treatment symptom score with no worsening of any single component score. An alternative efficacy endpoint was the time to minimum symptoms measured using the investigator-reported symptom score. It was defined as the earliest time post-treatment when all symptoms were either mild or absent.

Subjects who were at least 4 years of age performed self-assessment of pain using FPS-R. Time to onset of symptom relief was defined as the duration of time in hours from the time of study drug administration to the earliest time at which the post-treatment score improved by at least 1 level.

For subjects who were younger than 4 years of age, the investigator assessed HAE-related pain (cutaneous, abdominal, and laryngeal) using FLACC. Time to onset of symptom relief was calculated from the time of study drug administration to the earliest time at which at least a 20% improvement was seen in the total post-treatment pain score.

Interim analysis, that was performed and reported in the submitted CSR, covers only subjects' single (initial) treated attack in the study. An independent DSMB was established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study, according to the DSMB Charter and a separate DSMB SAP. Because no formal hypothesis testing was planned, multiplicity concerns regarding repeated analyses were not an issue.

Handling of missing data in efficacy assessments were described in the SAP. Individual missing pretreatment scores were planned to be assigned a value of zero (or "absent" in case of investigator-rated symptom scores). This imputation method assumes that an investigator did not rate symptoms that were not present at pretreatment. Individual missing post-treatment scores were to be assigned the last non-missing value using last observation carried forward (LOCF). If the baseline observation was the last non-missing value it was to be carried forward as well. This imputation method assumes that if an investigator did not rate a symptom at a particular assessment, then there was no change from the previous assessment.

Safety data were presented by summary statistics of physical examination, vital signs, ECGs, clinical laboratory evaluations, and immunogenicity, recording of concomitant medications, and monitoring of adverse events (AEs). Treatment-emergent adverse events (TEAEs) were summarized by system organ class (SOC) and preferred term (PT) by pubertal status stratification level. The number and percentage of subjects experiencing a TEAE, as well as total number of TEAEs, were summarized. Treatment-emergent AEs by SOC and PT also were summarized by severity and by relationship to treatment.

Local tolerability included symptoms at the injection site and was assessed separately from general reports of adverse events. Local tolerability was summarized according to the type and severity of the injection site reaction. The change from baseline in the secretion of reproductive hormones was summarized descriptively.

There were neither subgroup nor sensitivity analyses planned in the study.

Changes in the Planned Analyses

Changes from Protocol: It was defined in the protocol that the AEs would be categorized using MedDRA, Version 8.1. It was updated in the SAP that the MedDRA, Version 16.0 would be used.

Changes from Statistical Analysis Plan: The DSMB noted that for several subjects, clinical pubertal status determination is not consistent with the reproductive hormone levels at baseline. Following DSMB's recommendations, reproductive hormone tables and listings using the pubertal status based on hormonal data at baseline were added.

Results

Baseline characteristics

Subject Disposition by Pubertal Status

Parameter	Prepubertal	Pubertal/ Postpubertal	Overall
Safety Population, N	**11**	**21**	**32**
Completed assessments up to Day 8, n (%)	11 (100.0)	21 (100.0)	32 (100.0)
Completed study, n (%)	8 (72.7)	0	8 (25.0)
Prematurely withdrawn from study, n (%)	0	3 (14.3)	3 (9.4)
Ongoing, n (%)	3 (27.3)	18 (85.7)	21 (65.6)
Main reason for premature withdrawal, n (%)			
Withdrawal of consent	0	2 (9.5)	2 (6.3)
Other	0	1 (4.8)	1 (3.1)
Efficacy Population, N	**11**	**11**	**22**
Completed assessments up to Day 8, n (%)	11 (100.0)	11 (100.0)	22 (100.0)
Completed study, n (%)	8 (72.7)	0	8 (36.4)
Prematurely withdrawn from study, n (%)	0	1 (9.1)	1 (4.5)
Ongoing, n (%)	3 (27.3)	10 (90.9)	13 (59.1)
Main reason for premature withdrawal, n (%)			
Withdrawal of consent	0	1 (9.1)	1 (4.5)

Demographics and Pre-treatment Characteristics

Characteristics	Prepubertal (N=11)	Pubertal/Postpubertal (N=21)	Overall (N=32)
Age at screening (years)			
Mean (SD)	7.5 (3.14)	13.1 (1.58)	11.2 (3.49)
Min, max	2.0, 11.0	10.0, 15.0	2.0, 15.0
Age at treatment (years)			
Mean (SD)	8.6 (2.97)	14.3 (1.66)	12.3 (3.48)
Min, max	3.4, 11.8	10.8, 17.4	3.4, 17.4
Age group at treatment, n (%)			
<6 years	2 (18.2)	0	2 (6.3)
6-11 years	5 (45.5)	1 (4.8)	6 (18.8)
>11 years	4 (36.4)	20 (95.2)	24 (75.0)
Sex, n (%)			
Male	6 (54.5)	13 (61.9)	19 (59.4)
Female	5 (45.5)	8 (38.1)	13 (40.6)
Race			
White	11 (100.0)	20 (95.2)	31 (96.9)
Other	0	1 (4.8)	1 (3.1)

Thirteen patients were enrolled in Europe, 10 in US and 7 in Israel, Australia and Colombia contributed with one patient each.

In the efficacy population (patients treated during an HAE attack) 2 patients were below the age of 6, 6 were 6-11 years old and 14 >11 years.

The most common concomitant medications (>10% of subjects overall) were tranexamic acid (27.3%) and complement C1 esterase inhibitor (13.6%).

The CHMP noted that the youngest patient at treatment was 3 years old and that only 2 patients were below the age of 6. It is understood that symptoms occur more rarely in infants but nevertheless the experience in young children is limited. However, given the rarity of the disease the data, although limited, are considered acceptable to extrapolate to a population from 2 years onwards.

The majority of patients were recruited outside Europe. However, the clinical characteristics and effects of treatment is not expected to differ with respect to ethnic origin in patients with confirmed C1-INH deficiency.

Efficacy results

Sixteen subjects were experiencing a cutaneous attack: 8 pre-pubertal subjects and 8 pubertal/post-pubertal subjects; 5 were experiencing an abdominal attack: 3 pre-pubertal subjects and 2 pubertal/post-pubertal subjects, and 1 subject (pubertal/post-pubertal) experienced a cutaneous and abdominal attack. Overall, the mean time (SD) from attack onset to study drug administration was 6.1) hours (range 1.8 to 17.0).

The CHMP noted that no patient treated for an attack of laryngeal oedema was included. However, the experience from adults indicates that doses being effective for an attack with cutaneous or abdominal symptoms are also effective in oedema with a laryngeal localisation. Extrapolation to the paediatric population could also be envisaged.

Investigator Symptom score: Time to onset of symptom relief

Time to symptom relief was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there was at least a 20% improvement in the composite (or

average) post-treatment symptom score with no worsening of any single component score. All 22 (100%) subjects experienced symptom relief. At 1 hour post-treatment, 50% of subjects had experienced symptom relief, and at 2 hours post-treatment 90% of subjects had experienced symptom relief.

Time to Onset of Symptom Relief

Parameter	Prepubertal (N=11)	Pubertal/Postpubertal (N=11)	Overall (N=22)
Number of subjects available for analysis	11	11	22
Number of subjects with symptom relief	11	11	22
Percentage of subjects with symptom relief	100.0	100.0	100.0
Number of censored subjects[a]	0	0	0
Kaplan-Meier estimates			
Median time to onset of symptom relief (hours)	1.0	1.0	1.0
95% CI for the median time (hours)	1.0, 2.0	1.0, 2.0	1.0, 1.1
Q1 for time to onset of symptom relief (hours)	1.0	1.0	1.0
Q3 for time to onset of symptom relief (hours)	2.0	2.0	2.0

Investigator Symptom score: Time to minimum symptoms

Time to minimum symptoms was defined as the duration of time in hours from study drug administration to the earliest time post-treatment when all symptoms were either mild or absent. One subject with all mild or absent symptoms at pretreatment was excluded from this analysis. All 21 (100.0%) subjects included in the analysis achieved minimum symptoms. Overall, the median time to minimal symptom was 1.1 hours (95% CI: 1.0, 2.0). At 1 hour post-treatment, approximately 50% of subjects had minimal symptoms, and at 2 hours post-treatment approximately 80% of subjects had minimal symptoms. The time to minimal symptoms for both pubertal status groups was similar to the analysis of the overall population.

Subject Self-assessment of Pain: Time to onset of symptom relief for FPS-R scores

The median time to onset of pain relief was 1.0 hours (95% CI: 0.8, 1.0). At 1 hour post-treatment, approximately 80% of subjects had experienced pain relief, and at 2 hours post-treatment approximately 95% of subjects had experienced pain relief. Time to pain relief as assessed by FPS-R for both pubertal status groups was similar to the analysis of the overall population.

Subject Self-assessment of Pain: Time to minimum symptoms for FPS-R scores

Time to minimum symptoms for FPS-R was defined as the duration of time in hours from the time of study drug administration to the earliest time at which the post-treatment score improved to 0 (or no pain). Three subjects with pretreatment values of 0 were excluded from the analysis. A total of 16 (subjects included in the analysis achieved minimum symptoms. One subject who did not achieve minimum symptoms for FPS-R by 19 hours post-treatment was censored. Overall, median time to minimal symptom as assessed by the FPS-R was 3.4 hours (95% CI: 1.8, 5.3). At 2 hours post-treatment, approximately 40% of subjects had minimal symptoms, and at 6.5 hours post-treatment approximately 80% of subjects had minimal symptoms. Time to minimal symptoms for both pubertal status groups was similar to the analysis of the overall population. At 2 hours post-treatment, approximately 40% of subjects had minimal symptoms, and at 6.5 hours post-treatment approximately 80% of subjects had minimal symptoms.

Investigator assessment of pain, FLACC scores

There were 2 subjects under age 4 years in this study who were eligible for FLACC assessments. One subject, who had a pretreatment FLACC score of 0, was excluded from the time-to-event analyses. The

time to onset of pain relief as well as time to minimum symptoms was 1.0 hours for the subject with FLACC data.

Time to First Use of Rescue Medication

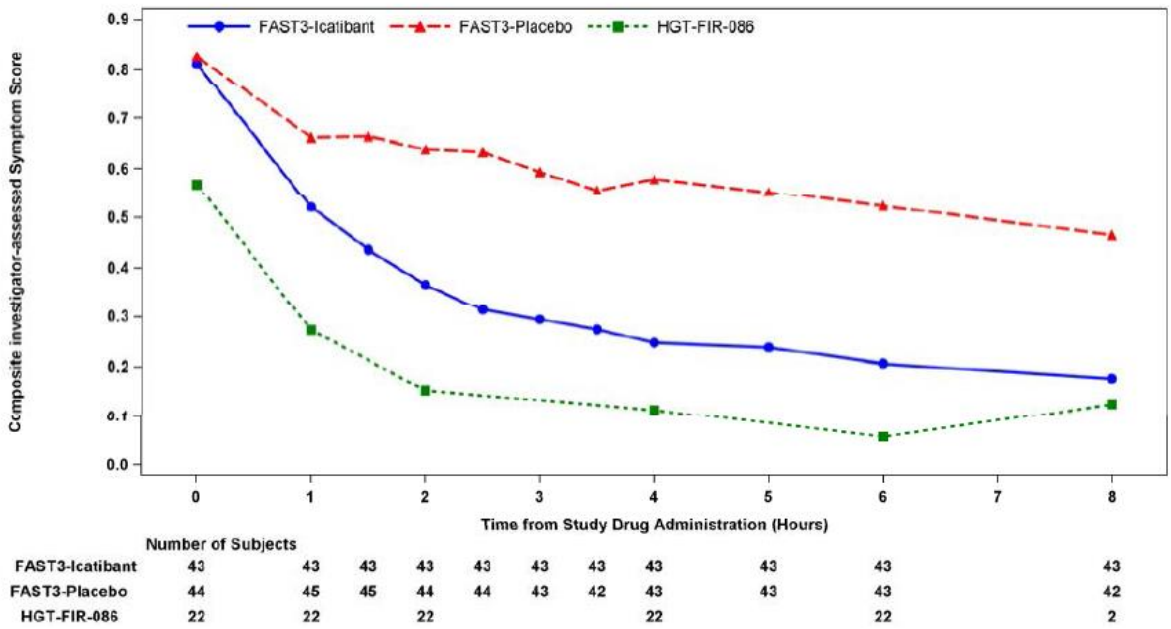
No subjects in the efficacy population received rescue medications before the onset of symptom relief for the icatibant treated HAE attack

Investigator recorded time to initial symptom relief

Median time to initial symptom relief was 1.0 hours (95% CI: 0.8, 1.1). At 1 hour post-treatment, approximately 70% of subjects had experienced initial symptom relief, and at 2 hours post-treatment approximately 95% of subjects had experienced initial symptom relief. Time to initial symptom relief for both pubertal status groups was similar to the analysis of the overall population.

Comparison of results across studies

The composite investigator-assessed symptom score in paediatric subjects with HAE attacks (HGT-FIR-086), and adult subjects with non-laryngeal HAE attacks (HGT-FIR-054) were plotted by study time point in the figure below. In HGT-FIR-054 only subjects with moderate to very severe non-laryngeal attacks were included in the analysis, while in study HGT-FIR-086 attacks at any severity were included, including mild, and no laryngeal attack was treated during the study. Thus, at pretreatment, for the pediatric study population, the mean (SD) composite investigator-assessed symptom score was 0.57 which was milder when compared to the ITT population for the icatibant group of 0.81 and 0.83 for the placebo group. By 1 hour post-treatment, the mean (SD) change from pretreatment on composite investigator-assessed symptom score was -0.30 (0.34) for the paediatric population, and -0.29 (0.36) for the icatibant treated adult population, emphasizing similar response pattern in these two groups, regardless of attack severity. There was a similar change from pretreatment for composite investigator-assessed symptom score in both the paediatric population and the icatibant treated adult population at all other time points post-treatment. Mean Composite Investigator-Assessed Symptom Score over Time HGT-FIR-054 (FAST3): Non-Laryngeal ITT Population vs HGT-FIR-086: Efficacy Population



Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 5 - Summary of Efficacy for trial HTG-FIR-086

Title: A Multicenter, Open-Label, Non-Randomized Study to Assess the Pharmacokinetics, Tolerability, and Safety of a Single Subcutaneous Administration of Icatibant in Children and Adolescents with Hereditary Angioedema			
Study identifier	HGT-FIR-086		
Design	This was an open-label, nonrandomized, single-arm study to evaluate the pharmacokinetics, tolerability, and safety, including effects on reproductive hormones, of a single SC administration of icatibant in paediatric subjects with HAE. This study evaluated the effect of an initial administration of icatibant in children and adolescents with hereditary angioedema (HAE). It also examined the effect of repeated exposures of icatibant in adolescents. The statistical analysis of data from the initial administration phase of the study is the focus of this clinical study report.		
	Duration of main phase:		At minimum, the duration of a subject's active participation in the study consisted of single-day dosing with 90-day follow-up
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Descriptive		
Treatments groups	Prepubertal		11 patients included and treated
	Pubertal/Postpubertal		21 patients included, 11 patients treated
Endpoints and definitions	Primary endpoint	Time to onset of symptom relief	Time to onset of symptom relief was measured using the investigator-reported symptom score for subjects 2-18 years of age. For subjects 4 years of age and older: subject self-assessment of HAE related pain using the Faces Pain Scale-Revised (FPS-R).
	Other endpoint	Time to first use of rescue medication	The number and percentage of subjects who received rescue medications before the onset of symptom relief were summarized.
	Other endpoint	Investigator recorded time to initial symptom relief	The investigator was asked to record the date and time when overall subject improvement was first noted. The time to initial symptom relief was defined as the duration of time in hours from study drug administration until the time when overall subject improvement was first noted.
Data cut-off:	04 November 2015		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	All patients included in the trial, that have received a single SC dose of icatibant (11 prepubertal and 11 pubertal/postpubertal children and adolescents)			
Descriptive statistics and estimate variability	Treatment group	Prepubertal	Pubertal/Postpubertal	Overall
	Number of subject	11	11	22

	Median time to onset of symptom relief, investigator symptom score (hours)	1.0	1.0	1.0
	95% CI (hours)	1.0, 2.0	1.0, 2.0	1.0, 1.1
	Median time to onset of symptom relief, FPS-R (hours)	0.9 (n=9)	1.0	1.0 (n=20)
	95% CI (hours)	0.8, 1.0	0.6, 1.0	0.8, 1.0
	Rescue medication use	0	0	0
	Median time to onset of initial symptom relief, investigator recorded time (hours)	1.0	1.0	1.0
	95% CI (hours)	0.8, 1.3	0.6, 1.0	0.8, 1.1

Effect estimate per comparison	Primary endpoint	Comparison groups	not applicable
		not applicable	not applicable
		not applicable	not applicable
		P-value	not applicable
Notes	Since this was a single arm study, no comparative data are available		

2.4.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The CHMP noted that the study was non-randomized, open-label, thus, prone to several sources of bias. There were no formal hypothesis testing and all statistical analyses were performed for descriptive purpose.

Efficacy analysis was to be performed on efficacy population, which was defined as those subjects who were treated with icatibant for their first and any additional attacks. However, the analysis of several efficacy endpoints excluded subjects who were treated but had mild or no symptoms at pretreatment, although there were no pre-specified attack severity criteria required for the treatment as initially planned. In the SAP Rev. 3, presumably revised after a data review, it was stated that subjects with all investigator symptom scores as mild or absent at pretreatment, and subjects with FPS-R or FLACC value of zero at pretreatment, would be excluded from the efficacy analyses. Missing pretreatment values, according to this SAP, were to be imputed by 'absent' (investigator-rated symptom scores) or zero value, which also led to exclusion from the analysis. The outcome for the excluded subjects was not presented in the CSR. This is not in accordance with the ITT approach. Available efficacy data for the subjects who were excluded from the analysis has been presented with the requests for further information.

Study HGT-FIR-086 was generally designed and conducted along the lines agreed by PDCO as part of the initial PIP and its subsequent modifications. Twenty two children 3.4 to 17.4 years old with a HAE diagnosis received Firazyr for an acute HAE attack. Most episodes were cutaneous and moderate in severity but there were also some more severe cases. There were no laryngeal attacks.

Firazyr was administered within 1.8 to 17 hours after the attack (mean around 6 hours) and resulted in relatively fast symptom relief in the majority of patients. In approximately 50% of the subjects onset of symptom relief, as evaluated by the investigator, occurred in an hour after Firazyr administration, with almost all patients showing symptom relief within the first 2 hours. All endpoints, either based on investigator's evaluation or self-assessment, were consistent in showing a positive and relatively rapid effect of Firazyr treatment on HAE symptoms in the majority of patients. The results were also similar for pre-pubertal and pubertal/post-pubertal subjects.

HGT-FIR-086 is an open label study and considering the lack of control, the small number of patients and the absence of disease specific tools to evaluate symptoms, robust conclusions on the efficacy of Firazyr in this setting have limitations. However, as previously acknowledged by PDCO, because of the rarity of the condition a large randomised controlled study in children would not be feasible. In fact the initially larger number of patients planned to be included in the efficacy part of the trial had to be revised because of difficulties with recruitment. Nevertheless, despite the unpredictable nature of the condition and the general difficulties in conducting such a study in children, a sufficient amount of data was collected indicating that Firazyr therapy can have a beneficial effect on symptoms following an acute HAE attack, with a general pattern similar to than seen in the adult studies. Overall the clinical package despite its limitations above mentioned is acceptable.

Assessment of paediatric data on clinical efficacy

In study HGT-FIR-086 children received a weight adjusted dose of 0.4mg/kg, ranging from 4.9 mg to 30 mg (maximum dose). However, the MAH initially proposed a different regime with three doses based on weight bands: 10 mg (1.0 Ml) for children >10 kg to ⩽25 kg; 20 mg (2.0 mL) for >25 kg to ⩽50 kg; 30 mg (3.0 mL) for >50 kg. Such a dosing would result in overdosing (compared to the 0.4mg/Kg dose used in HGT-FIR-086) in the majority of children. At the most extreme, patients close to the lower bound of each of the suggested weight bands will receive almost double the dose compared to those tested in the pivotal trial. As discussed in the section Clinical Pharmacology, a dosing regimen based on 5 weight bands was eventually considered appropriate for providing exposures close to the adult target exposure.

In the same context, the MAH also suggests, in the updated SmPC and PIL, that Firazyr may be administered by a caregiver "after training in subcutaneous injection technique by a healthcare professional". In general, there are advantages if a caregiver is able to administer the drug, if necessary.

The MAH notes that although icatibant was administered by healthcare professionals in HGT-FIR-086, caregiver administration is permitted in the ongoing part of the study assessing. They also support that immediate access to treatment may result in faster relief of pain and swelling, and experience from self-administration in adults suggests that this can be a safe and efficacious practice. The arguments are acknowledged and the findings of the ongoing part of the study will help confirming the usefulness but also potential problems with administration by a caregiver. The Applicant has on the CHMP request further justified the possibility to allow administration of a caregiver .This proposal can therefore be accepted and it is considered that appropriate information has been included in the product information.

2.4.2. Conclusions on the clinical efficacy

In conclusion, despite the limitations the HGT-FIR-086 results suggest that, as in adults, Firazyr can be an efficacious treatment option for acute HAE attacks in children from the age of 2 years.

2.5. Clinical safety

Patient exposure

Overall, 32 (100.0%) subjects received an initial dose of the study drug in HGT-FIR-086. At the time of the analyses included in this SCS, 1 pubertal/post-pubertal subject had also been treated with icatibant for a second HAE attack.

Adverse events

There were a total of 32 TEAEs in 9 (28%) subjects. The pre-pubertal group experienced fewer TEAEs than the pubertal/post-pubertal group: 9 TEAEs in 2 (18%) pre-pubertal subjects.

Table 6: Summary of Treatment-emergent Adverse Events

	Prepubertal (N=11)		Pubertal/Postpubertal (N=21)		Overall (N=32)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Subjects who experienced at least 1 AE	2 (18.2)	9	7 (33.3)	23	9 (28.1)	32
Subjects who experienced at least 1 drug-related AE	0	0	1 (4.8)	2	1 (3.1)	2
Subjects who experienced at least 1 severe AE	0	0	0	0	0	0
Subjects who experienced at least 1 SAE	0	0	0	0	0	0
Subjects who experienced at least 1 ISR that was deemed an SAE	0	0	0	0	0	0
Subjects who discontinued due to an AE	0	0	0	0	0	0
Subjects who died due to an AE	0	0	0	0	0	0

The most frequent TEAEs were gastrointestinal (GI) disorders with 9 events in 3 (9.4%) subjects. Headache, experienced by 2 subjects, was the only TEAE experienced by more than 1 subject.

Table 7: Treatment-emergent Adverse Events by System Organ Class and Preferred Term

System Organ Class/ Preferred Term	Prepubertal (N=11)		Pubertal/Postpubertal (N=21)		Overall (N=32)	
	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n
Any adverse event	2 (18.2)	9	7 (33.3)	23	9 (28.1)	32
Congenital, Familial, and Genetic Disorders	0	0	1 (4.8)	1	1 (3.1)	1
Hereditary angioedema	0	0	1 (4.8)	1	1 (3.1)	1
Eye Disorders	0	0	1 (4.8)	5	1 (3.1)	5
Conjunctivitis allergic	0	0	1 (4.8)	5	1 (3.1)	5
Gastrointestinal Disorders	0	0	3 (14.3)	9	3 (9.4)	9
Diarrhea	0	0	1 (4.8)	2	1 (3.1)	2
Vomiting	0	0	1 (4.8)	2	1 (3.1)	2
Abdominal pain	0	0	1 (4.8)	1	1 (3.1)	1
Abdominal pain upper	0	0	1 (4.8)	1	1 (3.1)	1
Dry mouth	0	0	1 (4.8)	1	1 (3.1)	1
Odynophagia	0	0	1 (4.8)	1	1 (3.1)	1
Toothache	0	0	1 (4.8)	1	1 (3.1)	1
General Disorders and Administrative Site Conditions	0	0	2 (9.5)	2	2 (6.3)	2
Asthenia	0	0	1 (4.8)	1	1 (3.1)	1
Fatigue	0	0	1 (4.8)	1	1 (3.1)	1
Infections and Infestations	1 (9.1)	1	1 (4.8)	1	2 (6.3)	2
Nasopharyngitis	0	0	1 (4.8)	1	1 (3.1)	1
Upper respiratory tract infection	1 (9.1)	1	0	0	1 (3.1)	1

Musculoskeletal and Connective Tissue Disorders	1 (9.1)	1	1 (4.8)	1	2 (6.3)	2
Arthralgia	1 (9.1)	1	0	0	1 (3.1)	1
Back pain	0	0	1 (4.8)	1	1 (3.1)	1
Nervous System Disorders	1 (9.1)	2	2 (9.5)	2	3 (9.4)	4
Headache	1 (9.1)	2	1 (4.8)	1	2 (6.3)	3
Dizziness	0	0	1 (4.8)	1	1 (3.1)	1
Respiratory, Thoracic, and Mediastinal Disorders	1 (9.1)	2	1 (4.8)	1	2 (6.3)	3
Bronchospasm	1 (9.1)	2	0	0	1 (3.1)	2
Painful respiration	0	0	1 (4.8)	1	1 (3.1)	1

Based on the closest relationship to study drug of a particular TEAE, 8 (25.0%) subjects experienced TEAEs that were assessed by the investigator to be not related and 1 (3.1%) experienced 2 TEAEs that were assessed by the investigator as possibly related (a mild attack of dry mouth and a mild attack of fatigue, both of which resolved).

Based on the most severe occurrence of a particular TEAE, 7 (21.9%) subjects experienced a mild TEAE and 2 (6.3%) subjects experienced a moderate TEAE. No subjects experienced a severe TEAE. At the time of the analysis included in this SCS, 1 pubertal/post-pubertal subject had been treated with icatibant for a second HAE attack. No AEs were reported by this subject following the subsequent icatibant treatment.

Injection site reactions were experienced by 29 (90.6%) subjects. The most frequently noted injection site reactions were erythema (27 subjects) and swelling (22 subjects). The majority of injection site reactions were mild or moderate in intensity. Two subjects experienced injection site reactions that were assessed as severe, both resolved at 6 hours postdose.

Laboratory findings

No clinically significant changes in laboratory values were observed during the treatment period for either treatment group. No clinically meaningful changes in vital signs were noted.

Anti-icatibant antibodies were measured in samples drawn at prospectively defined time points. No subjects were antibody-positive at baseline, Day 8 post-treatment, or Day 90 post-treatment.

The CHMP noted that the systemic adverse event was of mild or moderate severity and the pattern appears benign. The majority of events were judged as not related to study drug.

Adverse events judged as related to study drug were injection site reactions most of which had resolved at 6 hours. The safety characteristics appear consistent with what has been observed in adults.

Other significant events

Reproductive hormones

In addition to its roles in vasodilation, vascular permeability, and smooth muscle contraction, bradykinin has been implicated to play a role in control of the hypothalamic-pituitary-gonadal hormonal system. In nonclinical studies performed in rat and dog, high repeated doses of icatibant have been associated with effects on sexual organs and sexual maturation.

A Phase 1, double-blind, randomized, placebo-controlled study (HGT-FIR-062) evaluated the effect of repeated administration of SC icatibant 30 mg on reproductive parameters (serum reproductive hormone levels in males and premenopausal females, and seminal fluid analysis in males) in healthy adults prior to investigational use in the paediatric population. Subjects were randomized to receive icatibant or placebo as a single SC injection at 6-hour intervals 3 times daily on Days 1, 4, and 7 of the treatment week (a total of 9 doses/week) with an 8-week follow-up phase. A total of 39 healthy adult subjects (23 males and 16 females) with normal reproductive hormone levels were enrolled and randomized to treatment with either

icatibant or placebo. Twenty subjects were treated with icatibant and 19 received placebo. Repeated doses of icatibant had no clinically concerning effect on basal or stimulated levels of circulating reproductive hormones or on other fertility parameters in healthy male and female adult subjects in this study. Specifically, no clinically significant changes from baseline in basal and GnRH-stimulated concentrations of reproductive hormones (testosterone, dehydroepiandrosterone [DHEA], dehydroepiandrosterone-sulfate [DHEA-S], sex hormone binding globulin [SHBG], FSH, LH, and inhibin-B in males and oestradiol, progesterone, prolactin, DHEA, DHEA-S, SHBG, FSH, and LH in females) were observed in subjects exposed to icatibant. Additionally, there were no significant effects of icatibant on the concentration of luteal phase progesterone, an indicator of ovulation status and luteal function, or on menstrual cycle length in females, and there were no significant effects of icatibant on semen parameters in males.

In the paediatric study (HTG-FIR-086) other than progesterone levels in pre-pubertal subjects, the majority of subjects were categorized as normal at all time points. Three (60.0%) pre-pubertal subjects had low progesterone levels at pre-treatment, 6 hours post-treatment, and Day 8 post-treatment. At Day 90, 2 (40.0%) pre-pubertal subjects continued to have low levels of progesterone.

Table 8: Reproductive Hormone Assessments (Females)

Time	Prepubertal (N=5)			Pubertal/Postpubertal (N=8)			Overall (N=13)		
	n	Actual Value	Change from Predose	n	Actual Value	Change from Predose	n	Actual Value	Change from Predose
Estradiol (pg/mL)									
Pretreatment	5	7.79 (10.49)		8	57.61 (53.49)		13	38.45 (48.39)	
6 hours post-treatment	5	8.82 (11.74)	1.02 (1.75)	8	54.13 (51.84)	0.76 (27.78)	13	36.70 (46.26)	0.86 (21.24)
Day 8 post-treatment	5	10.40 (13.79)	2.61 (4.35)	8	34.54 (26.32)	-18.83 (44.54)	13	25.26 (24.84)	-10.59 (35.80)
Day 90 post-treatment	3	27.24 (23.83)	14.81 (13.81)	7	59.10 (34.64)	-0.80 (49.72)	10	49.54 (34.11)	3.88 (41.80)
FSH (mIU/mL)									
Pretreatment	5	4.09 (3.44)		8	3.88 (1.65)		13	3.96 (2.35)	
6 hours post-treatment	5	3.86 (3.57)	-0.23 (0.63)	6	4.02 (2.36)	0.85 (2.53)	11	3.94 (2.81)	0.36 (1.92)
Day 8 post-treatment	5	3.56 (3.34)	-0.53 (0.57)	8	4.02 (2.16)	0.68 (1.63)	13	3.84 (2.55)	0.22 (1.43)
Day 90 post-treatment	4	4.30 (2.90)	-0.63 (1.32)	7	3.90 (2.00)	0.39 (2.84)	11	4.05 (2.23)	0.02 (2.37)
LH (mIU/mL)									
Pretreatment	5	2.23 (3.25)		8	3.94 (2.69)		13	3.28 (2.91)	
6 hours post-treatment	5	1.80 (2.43)	-0.44 (1.16)	7	3.39 (3.27)	-0.07 (4.10)	12	2.72 (2.94)	-0.22 (3.11)
Day 8 post-treatment	5	1.17 (1.86)	-1.06 (2.60)	8	4.88 (3.94)	1.45 (3.81)	13	3.45 (3.70)	0.49 (3.52)
Day 90 post-treatment	4	2.06 (2.91)	-0.72 (3.17)	7	4.87 (3.16)	0.96 (2.40)	11	3.85 (3.25)	0.35 (2.69)
Progesterone (ng/mL)									
Pretreatment	5	0.21 (0.22)		8	3.18 (5.22)		13	2.03 (4.26)	
6 hours post-treatment	5	0.19 (0.25)	-0.02 (0.07)	8	3.03 (5.05)	-0.22 (0.58)	13	1.94 (4.12)	-0.15 (0.46)
Day 8 post-treatment	5	0.34 (0.49)	0.13 (0.27)	8	1.14 (1.40)	-2.12 (3.91)	13	0.83 (1.18)	-1.25 (3.20)
Day 90 post-treatment	4	0.24 (0.20)	0 (0.07)	7	2.46 (2.92)	-1.25 (4.06)	11	1.65 (2.53)	-0.80 (3.21)

No clinically significant changes in reproductive hormones in males were observed.

Table 9: Reproductive Hormone Assessments (Males):

Time	Prepubertal (N=6)			Pubertal/ Postpubertal (N=13)			Overall (N=19)		
	n	Actual Value	Change from Predose	n	Actual Value	Change from Predose	n	Actual Value	Change from Predose
FSH (mIU/mL)									
Pretreatment	6	1.33 (0.93)		11	3.72 (2.26)		17	2.88 (2.20)	
6 hours post-treatment	5	1.10 (0.78)	-0.16 (0.26)	13	3.51 (2.38)	0.02 (0.83)	18	2.84 (2.32)	-0.03 (0.69)
Day 8 post-treatment	6	1.38 (1.14)	0.05 (0.49)	13	3.51 (2.31)	0.06 (0.61)	19	2.84 (2.22)	0.05 (0.55)
Day 90 post-treatment	5	1.45 (1.23)	0.20 (0.40)	12	3.76 (2.83)	0.33 (1.22)	17	3.08 (2.66)	0.28 (1.00)
LH (mIU/mL)									
Pretreatment	6	0.30 (0.27)		11	2.98 (2.60)		17	2.03 (2.45)	
6 hours post-treatment	5	0.26 (0.24)	-0.08 (0.10)	13	2.85 (2.00)	-0.12 (2.28)	18	2.12 (2.07)	-0.11 (1.87)
Day 8 post-treatment	6	0.61 (0.77)	0.31 (0.54)	13	3.27 (2.81)	0.28 (1.26)	19	2.43 (2.65)	0.29 (1.04)
Day 90 post-treatment	5	0.86 (1.37)	0.56 (1.10)	12	3.00 (1.89)	-0.07 (1.23)	17	2.37 (1.98)	0.14 (1.18)
Testosterone (ng/dL)									
Pretreatment	6	11.96 (12.84)		11	317.66 (271.82)		17	209.76 (262.50)	
6 hours post-treatment	5	6.24 (6.42)	-1.58 (2.53)	13	218.44 (199.49)	-94.08 (187.37)	18	159.50 (194.08)	-65.18 (159.27)
Day 8 post-treatment	6	31.62 (44.46)	19.65 (45.47)	13	290.59 (234.34)	2.98 (155.86)	19	208.81 (229.03)	8.86 (126.08)
Day 90 post-treatment	5	23.10 (37.42)	15.28 (28.75)	12	280.84 (194.73)	-19.33 (183.90)	17	205.04 (202.67)	-7.79 (149.21)

The CHMP noted a rather pronounced inter- and intra-individual variability of the levels of reproductive hormones without a distinct pattern in relation to study drug administration was observed. Nevertheless, there seems to be a slight trend for a reduction of oestradiol, progesterone and testosterone levels at different time points. Taking the expected infrequent need for administration of icatibant in the majority of patients, where usually a single dose is sufficient for treatment of an attack, no long-term consequences of the modest transient fluctuations are to be expected. For patients with frequent attacks in need of treatment the situation may be different. The MAH has appropriately addressed these concerns and further clarifications in the RMP is provided.

Post marketing experience

Postmarketing safety data are consistent with the safety profile observed in clinical trials of icatibant. Injection site reactions were the most commonly reported events.

Cumulatively, 23 cases of icatibant use in children and adolescents (aged <18 years) were received from postmarketing surveillance. The majority of events reported concerned injection site reactions.

In addition to routine pharmacovigilance and data collection from post-marketing sources, the company has implemented a FIRAZYR patient registry. This voluntary registry (known as the Icatibant Outcome Survey [IOS]) is a long-term, international, multicenter, prospective, observational study open to all patients receiving FIRAZYR (icatibant injection) treatment.

As of April 2016, the IOS database included 5 patients who received icatibant for an HAE type I or II attack when <18 years of age. Details follow for each patient who received icatibant when younger than 18 years of age.

One patient was treated 4 times for 3 severe laryngeal attacks. The first attack occurring around 17years of age required treatment with 2 doses of icatibant, with 8 hours between doses; resolution of symptoms occurred 2 hours following the second dose. The 2 other angioedema attacks occurred in a short timeframe and time to resolution was ~3 days for each of these attacks. All doses of icatibant were administered at a hospital emergency department by a healthcare provider. No AEs were reported.

Another patient was treated for 2 abdominal attacks: 1 severe around the age of 17 with resolution of symptoms at ~22 hours and 1 very severe after two months with resolution of symptoms at ~6.5 hours. Icatibant was self-administered once in the hospital for the first attack and self-administered once at

home for the second attack. No AEs were reported. This patient received concomitant/rescue medication (antifibrinolytics) for each attack.

Another patient was treated for a moderate skin attack around the age of 16 with resolution of symptoms at ~4 hours. Icatibant was administered once in the hospital by a healthcare provider. No AEs were reported. This patient received concomitant/rescue medication (C1 inhibitor [C1-INH] concentrate).

One patient was treated for 10 severe abdominal attacks around the age of 16 and 17. Each attack was treated with 1 dose of icatibant; resolution of symptoms for each attack occurred in <24 hours. Icatibant was administered in an outpatient setting by a healthcare provider for the first 2 attacks and administered at home by a caregiver for the remaining 8 attacks. No AEs were reported.

One patient was treated for 4 abdominal attacks: 2 with moderate intensity around the age of 16, and 2 with severe intensity after about one year. Each attack was treated with 1 dose of icatibant; resolution of symptoms for each attack occurred in <24 hours, with the exception of the moderate attack around 16 years of age for which resolution status is unknown. Icatibant was administered at home by a caregiver for the first attack and at home by a healthcare provider for the remaining 3 attacks. No AEs were reported.

2.5.1. Discussion on clinical safety

Study HGT-FIR-086 provided safety data from 32 children who received a single dose of Firazyr (22 during an acute HAE attack).

Consistently with the adult studies, a high number of injection site reactions were reported that affected the majority of patients. No other important safety issues were identified. Firazyr's immunogenic potential appears low and there was no clear indication of significant laboratory or ECG abnormalities. Also the results of reproductive hormones measurements do not suggest a clinically significant effect.

In general, in Study HGT-FIR-086 there were no unexpected findings and no serious events, indicating a general safety profile similar to that in adults. Still the high frequency of injections site reaction is of concern. Although the reactions were for the most part mild-moderate and resolved within hours this is an important issue than needs to be further considered in the light of the currently proposed posology in children.

Several possible mechanisms were previously suggested to explain the injection site reactions with Firazyr seen in the adult studies but the rather large injection volume of 3 ml was also implicated. In Study HGT-FIR-086 children received doses from 4.9 mg to 30 mg (0.49ml – 3ml) based on a 0.4mg/Kg posology. As noted in the previous sections of this report with the currently recommended posology and use of fixed doses based on weight bands, the majority of children will receive higher doses than those administered in the pivotal trial. It is clear that the possibility of more serious injection site reactions due to the larger volume cannot be excluded and this is particularly relevant to younger children. It should be noted here that the "Guideline on pharmaceutical development of medicines for paediatric use" (EMA/CHMP/QWP/805880/2012 Rev. 2) states that normally subcutaneous injection volumes should not exceed 1 ml (with even lower volumes advised for infants).

In conclusion, in Study HGT-FIR-086 the administration of Firazyr in children raised no major safety concerns and the overall safety profile appears similar to adults.

Some patients experienced frequent HAE attacks (e.g. weekly). It cannot be excluded that very frequent administration of icatibant in such patients would be associated with long-term safety problems such as more permanent effects on reproductive hormones or immunogenic complications, affecting efficacy or safety.

Clinicians prescribing icatibant off-label for use in subjects <18 years of age have been encouraged to enroll those patients into the ongoing IOS Patient Registry study. As of 29 February 2016, the IOS database included 21 children aged <18 years of age (range 3.5-17.9 years). According to the study protocol, effects on sexual maturation in pubertal adolescents will be measured using Tanner staging and, if available, sexual hormone level measurements will be recorded before, during, and after puberty.

The MAH has clarified that the ongoing IOS register study will continue to monitor effects on sexual maturation in pubertal adolescents, although, the enrolment in the study is voluntarily. Moreover, the ongoing study HGT-FIR-086 evaluates the effect on reproductive hormone levels in pubertal/ post-pubertal children after repeated exposures. Both study IOS and HGT-FIR-086 are included in the Pharmacovigilance plan of the RMP for icatibant. The 'effect on reproductive hormone levels in pubertal/ post-pubertal children' has been included as an important potential risk in the RMP, addressed by the studies IOS and HGT-FIR-086.

Monitoring of medication error (e.g. appropriate schedule, correct technique) include administrations by health care professional, by caregiver and self-administration. Administration mode (caregiver/self-administration/HCP administration) should be specified when presenting data on medication errors in future PSURs. The Applicant has stated in the response to the CHMP request that the effectiveness and safety of caregiver administration will continue to be monitored in study HGT-FIR-086 and study IOS alongside routinely PhV activities. The studies HGT-FIR-086 and IOS registry have been included as additional PhV activities for the safety concern 'Medication error'.

2.5.2. Conclusions on clinical safety

Overall the safety data are acceptable and updated information was included in the RMP. Additionally the SmPC has been updated appropriately to reflect safety in the paediatric population.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 6.2 with the following content:

Safety concerns

Table 10: Summary of Safety Concerns	
Important identified risks	Injection site reactions
Important potential risks	Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism Partial bradykinin agonism (excluding injection site reactions) Antigenicity manifesting as drug hypersensitivity and lack of efficacy Lack of efficacy Medication errors

Table 10: Summary of Safety Concerns	
	Effect on reproductive hormone levels in pubertal/ post-pubertal children
Missing information	Use in pregnant and lactating women Use in children below 2 years of age

Pharmacovigilance plan

Table 11: Ongoing and planned Additional PhV Studies/Activities in the Pharmacovigilance Plan				
Study/Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status**	**Date for Submission of Interim or Final Reports**
Icatibant Outcome Survey (IOS) (Category 3)	The objectives of the IOS are to monitor the safety of icatibant during long-term use by patients, with a focus on the frequency of cardiac ischaemic events, generalised reactions that might be indicative of B2 receptor agonism (eg, hypotension, mucosal swelling, bronchoconstriction, and aggravation of pain), use in children and adolescents (particularly effects on sexual maturation in pubertal adolescents), monitoring the safety and response to treatment in patients with laryngeal oedema, and hypersensitivity reactions.	Deterioration of cardiac function under ischaemic conditions; Partial bradykinin agonism (excluding injection site reactions) Antigenicity manifesting as drug hypersensitivity and lack of efficacy; Lack of efficacy Use during pregnancy and lactation Effect on reproductive hormone levels in pubertal/ post-pubertal children Medication errors To continue to monitor use in children and adolescents	Ongoing	Interim findings reported in PSURs
Clinical study HGT-FIR-086: An open-label, nonrandomized, single-arm study to assess the pharmacokinetics, tolerability, and safety of a single sc administration of icatibant in children and adolescents with hereditary angioedema (Category 3)	Primary objective: To investigate the PK, tolerability, and safety of a single sc dose of icatibant in children and adolescents with HAE during an acute HAE attack Secondary objectives: To evaluate the efficacy of a single sc dose of icatibant in children and adolescents with HAE. To evaluate levels of reproductive hormones after a single sc dose of icatibant in children and adolescents with HAE.	To continue to monitor use in children and adolescents Effect on reproductive hormone levels in pubertal/ post-pubertal children Medication errors	Ongoing	Final study report: Q1 2018

Risk minimisation measures

Table 12: Summary of Risk Minimisation Measures		
Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Injection site reactions	Injection site reactions described in Section 4.8 of the SmPC	None
Deterioration of cardiac ischaemia due to antagonism of beneficial bradykinin effects	Ischaemic heart disease addressed in Section 4.4 of the SmPC	None
Partial bradykinin agonism (excluding injection site reactions)	None	None
Antigenicity manifesting as drug hypersensitivity and lack of efficacy	Instructions in case of lack of efficacy described in Section 4.2 of the SmPC Immunogenicity described in Section 4.8 of the SmPC	None
Lack of efficacy	Instructions in case of lack of efficacy described in Section 4.2 of the SmPC Laryngeal attacks addressed in Section 4.4 of the SmPC	None
Medication errors	Indication is described in Section 4.1 of the SmPC. Further instructions for correct administration are provided in Section 4.2 of the SmPC	None
Use during pregnancy and lactation	Pregnancy and breast-feeding are addressed in Section 4.6 of the SmPC	None
Effect on reproductive hormone levels in pubertal/ post-pubertal children	Effects on fertility are described in section 4.6 of the SmPC.	None
Use in children below 2 years of age	Use in children less than 2 years old is addressed in sections 4.1 and 4.2 of the SmPC.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6. of the SmPC have been updated. Particularly, a new dosage has been added for the paediatric population to the product information. The possibility of caregiver/self-administration has also been introduced. The Package Leaflet has been updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity

-to reflect the results of a juvenile toxicity study in SmPC section 5.3,

-to update section 5.2 of the SmPC to reflect the effect of age (elderly), gender and race on pharmacokinetics of icatibant.

The Package Leaflet is updated accordingly. All relevant pharmacokinetics studies have previously been assessed, as part of prior submissions.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). Minor changes have been introduced in the annex II.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The clinical presentation and management of hereditary angioedema in paediatric patients is different from adults and also more complex. The age at onset, frequency and duration of symptoms, as well as severity of attacks all exhibit substantial interindividual variation. Although acute episodes of HAE may occur at any age, the median age at first symptomatic HAE attack is estimated to range between 4 and 11 years. Subcutaneous oedema of the extremities, face, neck, torso, and genitals is the most common, and usually the earliest, manifestation of HAE seen in children. In the GI tract, submucosal oedema may be associated with colicky abdominal pain, nausea, vomiting, and diarrhoea. In a large paediatric cohort, increased frequency and severity of HAE symptoms were reported at between 3 and 6 years of age and at around puberty and were attributed to physiological changes which occur during these periods of development.

Though infrequent compared to cutaneous and abdominal manifestations, attacks of acute HAE involving the larynx may result in submucosal oedema of the upper airways and risk of death by asphyxiation if undiagnosed and/or untreated. In comparison to adults, asphyxia may ensue more rapidly in children because of smaller airway diameter.

3.1.1. Available therapies and unmet medical need

Treatment options for children with HAE according to current guidelines include antifibrinolytics, attenuated androgens, and plasma-derived C1-INH replacement therapy.

This variation is supported by a clinical data from an interim report of an ongoing paediatric study (HTG-FIR-086) evaluated the effect of a single standard subcutaneous administration of icatibant in children and adolescents aged 2 to <18 years with a documented diagnosis of hereditary angioedema (HAE) type I or II. The study is ongoing and will examine the effect of 3 total exposures of icatibant in 10 adolescents who are currently being followed. The data now submitted includes the data for the initial administration of icatibant from 11 pre-pubertal subjects during an HAE attack and 21 pubertal/post-pubertal subjects (including 11 treated during an HAE attack and 10 treated without an attack).

3.1.2. Main clinical studies

The open-label, non-randomized, single-armed study design is acceptable taking the rarity of the condition into account. A design including an active comparator (plasma-derived or recombinant C1 esterase inhibitor (C1 INH)) would theoretically be an alternative. However, such a design would be challenging from a pragmatic perspective and would probably not provide additional useful information. It can be foreseen that it would be difficult to establish a meaningful non-inferiority margin. It can furthermore be assumed that the pathogenic mechanisms behind the typical symptoms in patients with low C1 INH is similar in children and adults which to some extent allows extrapolation of the experience in adults to children.

The support from the characterisation of pharmacokinetics is important for establishing appropriate dose recommendations in children of different age. In this rare disorder only very limited efficacy and safety data from clinical studies in children can be expected, but considering the pharmacodynamic action of the drug and the well-known pathogenic mechanism behind the symptoms in this condition, efficacy and safety data from adults can be judged as relevant also for the children. Thus with reasonably well justified dosing recommendations for children based on available PK data and modelling together with a bridge from the clinical experience in adults, the limitations of paediatric clinical data can be accepted. The data presented in this application are acceptable to extrapolate to patients from the age of 2 years.

It should be noted that the efficacy and safety in children treated with the 0.4 mg/kg dose was adequate. Nevertheless, the clinical feasibility of such a very detailed dosing regimen in an acute stressful clinical setting could potentially be questioned. Further, the studied dose led to slight under exposure. As an alternative option, a dose regimen with five weight bands was considered appropriate and justified in the clinical setting. The study is ongoing and will provide further safety data on the recruited patients and in accordance with the compliance on the paediatric investigation plan.

3.2. Favourable effects

The observed time to relief of symptoms associated with attacks of angioedema supports the conclusion that administration of icatibant provides a similar symptomatic benefit during an HAE attack in children as in adults. At 1 hour post-treatment, 50% of subjects had experienced symptom relief, and at 2 hours post-treatment 90% of subjects had experienced symptom relief. An untreated HAE attack is reported in the literature to have a duration of 3-5 days.

3.3. Uncertainties and limitations about favourable effects

There is very limited experience of repeated treatment in children. One single injection seems to provide satisfactory relief of symptoms during an attack in most patients. The frequency of HAE attacks vary considerably between individuals and there is no or very limited experience from repeated treatment in children. This is reflected in the PI. The experience in the smaller children is very limited, due to rareness of the condition but also due to the fact that the first clinical symptoms often occur at somewhat higher age. Thus, dosing recommendations must in part rest on pharmacokinetic modelling in addition to the clinical study results.

3.4. Unfavourable effects

The adverse events in the paediatric studies were dominated by local reactions at injection site such as swelling and erythema. No serious systemic reactions were reported. Icatibant antibodies were followed prospectively and no antibody formation was reported. The fluctuations in reproductive hormones after a single injection are not judged to be of concern.

3.5. Uncertainties and limitations about unfavourable effects

The experience from treatment in children is still limited and very few patients have had repeated injections. Preclinical data seems to indicate that long-term administration of icatibant may affect reproductive hormone levels. The Applicant has appropriately discussed these concerns and treated patients will be followed up in the post marketing setting as detailed in the RMP.

The immunogenic potential of icatibant appears to be low, which is supported from the experience in

adults where the experience from repeated treatment is rapidly growing.

Very few small children under the age of 6 were included in the paediatric study and the inclusion of the very young children is heavily dependent on accurate estimations of exposure and extrapolation from the efficacy and safety characteristics observed in older children and adults.

3.6. Effects

Table

Table 13 - Effects Table for Firazyr in the treatment of HAE in children and adolescents (data cut-off: 04 November 2015).

	Short Description	Unit	Firazyr	Uncertainties/ Strength of evidence	References
Favourable Effects					
Time to relief	Median time to onset of symptom relief, investigator symptom score	hours (95% CI)	1.0 (1.0, 1.1)	Open-label, single armed study 22 subjects treated	An untreated HAE attack is reported in the literature to have a duration of 3-5 days.
Relief at 1 hour	Proportion of subjects who had experienced symptom relief 1 hour post-treatment	%	50	As above	
Relief at 2 hours	Proportion of subjects who had experienced symptom relief 2 hours post-treatment	%	90	As above	
Unfavourable Effects					
Local reactions	Swelling and erythema	n (%)	29 (90.6)	Mild or moderate, resolved within hours	Only one subject received more than one injection

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

An HAE attack can be life threating when localised to larynx. In such situations it is utterly important that the situation is brought under control. Symptomatic relief provided by blockage of the bradykinin receptor can reliably be judged to represent regression of swelling. Furthermore, efficacy documented in cutaneous or abdominal attacks can be extrapolated to attacks of laryngeal oedema considering the pathogenic similarity and the experience in adults. Icatibant represents a different mechanism of action as compared to plasma derived (Berinert, Cinryze) or recombinant C1 INH (Rhuconest) and can be of considerable value in e.g. hypersensivity against C1 INH products. That the drug is administered subcutaneously is also an important advantage facilitating rapid treatment in e.g. the home setting.

3.7.2. Balance of benefits and risks

Despite its limitation of the clinical efficacy data (design, limited number of children), the CHMP considered that the data are sufficient to support the use in children from the age of 2 years onwards.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The benefit-risk balance of Firazyr is positive in children above 2years of age.

4. Rcommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency, for the use of Firazyr for symptomatic treatment of acute attacks of hereditary angioedema; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The possibility of caregiver/self-administration has also been introduced. In addition, the Marketing authorisation holder (MAH) took the opportunity to reflect the results of a juvenile toxicity study in SmPC section 5.3.

Update section 5.2 of the SmPC to update the effect of age (elderly), gender and race on the pharmacokinetics of icatibant. The Package Leaflet is updated accordingly.

Furthermore, the PI is brought in line with the latest QRD template version 10.

The group of variations leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (version 6.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0243/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include adolescents and children aged 2 years and older, with C1-esterase-inhibitor deficiency, for the use of Firazyr for symptomatic treatment of acute attacks of hereditary angioedema; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. The possibility of caregiver/self-administration has also been introduced. In addition, the Marketing authorisation holder (MAH) took the opportunity to reflect the results of a juvenile toxicity study in SmPC section 5.3.

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Summary

Please refer to the Scientific Discussion Firazyr EMEA/H/C/000899/II/0034/G.