Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Icatibant (as acetate)

Proprietary Product Name: Firazyr

Sponsor: Shire Australia Pty Limited

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ACE	Angiotensin converting enzyme
ACM	Advisory Committee on Medicines
AE	Adverse event
AUC_{0-4}	Area under the plasma concentration curve from time 0 to 4 hours post-dose
AUC_{0-6}	Area under the plasma concentration curve from time 0 to 6 hours post-dose
$AUC_{0-\infty}$	Area under the plasma concentration curve from time 0 to infinity post-dose
B2	Bradykinin type 2
BLQ	Below the limit of quantification
BMI	Body mass index
C1	Complement 1
C1-INH	Complement 1 (esterase) inhibitor
C1-INH-HAE	Hereditary angioedema with complement 1 (esterase) inhibitor deficiency
CDC	Center for Disease Control and Prevention (USA)
CI	Confidence interval
CL/F	Total plasma clearance
C_{max}	Maximum plasma concentration
CMI	Consumer Medicines Information
DSMB	Data and safety monitoring board
EC_{50}	Half maximum effective concentration
ECG	Electrocardiogram
EMA	European Medicines Agency (EU)
ETA	Random effects
EU	European Union

Abbreviation	Meaning
FLACC	Faces, Legs, Activity, Cry, and Consolability (compartmental pain scale)
FPS-R	Faces Pain Scale-Revised
FSH	Follicle stimulating hormone
GI	Gastrointestinal
HAE	Hereditary angioedema
HPLC	High-performance liquid chromatography
IOS	Icatibant Outcome Survey
IV	Intravenous
Ka	Absorption rate constant
LC-MS/MS	Liquid chromatography – tandem mass spectrometry
LH	Luteinising hormone
NONMEM	Non-linear mixed effects modelling
PBRER	Periodic benefit-risk evaluation report
PI	Product Information
PK	Pharmacokinetic(s)
PopPK/PD	Population pharmacokinetic(s)/pharmacodynamic(s)
PSUR	Periodic safety update reports
PT	Preferred Term
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDP	Solvent detergent-treated plasma
SERPING1	Serpin family G member 1
SOC	System Organ Class
$t_{½}$	Elimination half-life

Abbreviation	Meaning
$t_{½}$ abs	Absorption half-life
TEAE	Treatment emergent adverse event
T_{lag}	Lag time
t_{max}	Time to peak concentration
TOSR	Time to onset of symptom relief
USA	United States of America
VAS	Visual Analog Score
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
VPCs	Visual predictive checks
V_z/F	Volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	23 July 2019
Date of entry onto ARTG:	26 July 2019
ARTG number:	160313
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved.
Active ingredient:	Icatibant (as acetate)
Product name:	Firazyr
Sponsor's name and address:	Shire Australia Pty Ltd Level 39 Grosvenor Place, 225 George Street Sydney, NSW, 2000
Dose form:	Solution for injection
Strength:	30 mg/3 mL
Container:	Prefilled syringe
Pack size:	1
Approved therapeutic use:	*Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase-inhibitor deficiency.*
Route of administration:	Subcutaneous
Dosage:	**Adults** The recommended dose of Firazyr for adults is one subcutaneous injection of 30 mg. **Adolescents and children (aged 2 to 17 years)** The recommended dose of Firazyr is based on body weight in children and adolescents (aged 2 to 17 years). For further information refer to the Product Information.

Product background

This AusPAR describes the application by Shire Australia Pty Limited (the sponsor) to register Firazyr (icatibant acetate) for the following indication:

> *Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase-inhibitor deficiency.*

Hereditary angioedema (HAE) is a rare, autosomal dominant disease caused by deficiency or dysfunction of the complement 1 (C1) esterase inhibitor (C1-INH). The condition is characterised clinically by episodic swelling of subcutaneous tissues, gut and upper respiratory tract. Recognised exacerbating factors include stress, infection, injury, dental and other surgery although often no precipitating factor can be discerned. Typically attacks last approximately 2 to 5 days before resolving spontaneously.[1]

HAE can be caused by a quantitative (type I) or qualitative (type II) deficiency of C1-INH. C1 inhibitor functions in several biochemical pathways, including inhibition of C1 complement auto-activation; inactivation of coagulation factors XIIa, XIIf, and XIa; and inhibition of activated kallikrein. The deficiency in C1-INH results in accelerated release of bradykinin by cleavage from kininogen by activated kallikrein. Bradykinin is the principal mediator of the increased vascular permeability characteristic of HAE.

Australian treatment recommendations are outlined in the Australasian Society of Clinical Immunology and Allergy Position Paper on Hereditary Angioedema (HAE) most recently updated in February 2017.[2] Current paediatric options include purified C1-INH concentrate (Berinert, Cinryze), which is available for intravenous use in the hospital setting or may be used by the patient at home after adequate training. C1-INH concentrate supply is managed by the National Blood Authority. Danazol and tranexamic acid may be used for prophylaxis. Danazol use is limited by side effects and tranexamic acid by relative lack of efficacy.

Icatibant is a potent, selective antagonist of the bradykinin type 2 receptor. In adults, subcutaneous (SC) administration of icatibant 30 mg has been shown to produce a rapid and durable response in the treatment of cutaneous, abdominal, and laryngeal attacks of acute HAE. In this submission the sponsor sought to extend the indications of icatibant to the paediatric population for the treatment of HAE.

Regulatory status

Firazyr was granted Orphan Drug designation on 12 February 2009 for 'the treatment of acute attacks of hereditary angioedema'.

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 3 September 2010 for the following indication:

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

At the time the TGA considered this application, a similar application for a paediatric indication had been approved in Argentina (23 January 2019), Brazil (23 August 2019), Colombia (8 July 2018), European Union (EU; 19 October 2017), Mexico (12 February 2019), New Zealand (29 November 2018), Russia (11 March 2019), Serbia (30 July 2018) and Switzerland (14 February 2019), and was under consideration in Canada (submitted

[1] Ugochukwu, C. et al. (2001), Hereditary Angioedema A Broad Review for Clinicians, *Arch Intern Med*, 2001; 161: 2417–2429.
[2] Katelaris, C. et al. (2017), Position Paper on Hereditary Angioedema (HAE), accessed from the Australasian Society of Clinical Immunology and Allergy website.

27 June 2018), Israel (submitted 4 June 2018) and South Korea (submitted 19 November 2018).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-02506-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	30 June 2018
First round evaluation completed	20 December 2018
Sponsor provides responses on questions raised in first round evaluation	20 February 2019
Second round evaluation completed	13 March 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 May 2019
Sponsor's pre-Advisory Committee response	21 May 2019
Advisory Committee meeting	7 June 2019
Registration decision (Outcome)	23 July 2019
Completion of administrative activities and registration on ARTG	26 July 2019
Number of working days from submission dossier acceptance to registration decision*	217

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Submission overview and risk/benefit assessment

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

Background

Background on condition being treated

HAE is a rare, autosomal dominant disease caused by deficiency or dysfunction of the C1 esterase inhibitor (C1-INH).

Clinical

HAE is characterised clinically by recurrent episodes of angioedema, without urticaria or pruritus, which most commonly affect the skin, bowel, or upper airway (leading to cutaneous, abdominal, and laryngeal symptoms, respectively). An HAE attack usually only involves one site at a time. Although the swelling is usually self-limiting, laryngeal HAE may lead to fatal asphyxiation. Untreated, an attack usually lasts between 2 to 5 days.

Pathophysiology

HAE can be caused by a quantitative (type I) or qualitative (type II) deficiency of C1-INH associated with ay one of the more than 450 serpin family G member 1 (SERPING1) gene mutations. Types I and II are collectively known as HAE with C1-INH deficiency (C1-INH-HAE). C1 inhibitor functions in several biochemical pathways, including inhibition of C1 complement auto-activation; inactivation of coagulation factors XIIa, XIIf, and XIa; and inhibition of activated kallikrein. The deficiency in C1-INH results in accelerated release of bradykinin by cleavage from kininogen by activated kallikrein. HAE attacks are associated with increased bradykinin release. Bradykinin is the principal mediator in the development of the clinical symptoms.

Additionally, HAE with normal C1-INH (previously known as type III HAE) exists, and has been associated with different gene mutations or unknown aetiology.

Epidemiology

The prevalence of HAE is estimated to be between 1 in 10,000 and 1 in 150,000 and appears equally distributed across sexes. The median age of the first symptomatic HAE attack is estimated to be between 4 to 11 years. Attacks appear to become more frequent in puberty or early adulthood. Once attacks have commenced, they will recur lifelong, but can be reduced with treatment.

Treatment of acute attacks

For acute attacks, current guidelines recommend C1-INH concentrate, ecallantide (recombinant plasma kallikrein inhibitor; not currently registered on the ARTG), or icatibant.[3] If these are not available solvent detergent-treated plasma (SDP) should be considered.

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

Australian regulatory status

Firazyr was granted Orphan Drug designation by the TGA on 12 February 2009 for the treatment of acute attacks of HAE. Firazyr was approved for registration in Australia in June 2010.

[3] Maurer, M. et al. (2018). The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*, 2018; 73: 1575-1596.

Current indication:

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

Overseas regulatory status

Use in adults

Icatibant was approved for the symptomatic treatment of acute attacks of HAE in adults with C1-INH deficiency in the EU in July 2008. Currently, Firazyr is approved in more than 40 countries worldwide including the United States of America (USA) and Canada.

Paediatric use

Firazyr was approved in the EU (October 2017) and Switzerland (October 2018) for children aged 2 years and older with the dosage schedule as proposed in this submission.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier included:

- The clinical study report of pivotal Study HGT-FIR-086 assessing pharmacokinetics, tolerability, safety, efficacy in 11 pre-pubertal and 21 post-pubertal paediatric participants.
- Report SHIR-RAS-003: Population pharmacokinetic modelling and exposure response analysis based on adult and paediatric data, submitted in support of dose recommendations for paediatric patients.

Study HGT-FIR-086

Study HGT-FIR-086 was the sole paediatric clinical study in this submission, used to assess efficacy, safety, and pharmacology.

Design

Study HGT-FIR-086 was a Phase III, multicentre (27 sites), open label, non-randomised, single arm study to assess the pharmacokinetics, tolerability, safety and efficacy of a single subcutaneous administration of icatibant in 32 children and adolescents with HAE aged 2 to 17 years (only 22 assessed for efficacy).

There were only 2 subjects in the 2 to < 6 age group with a minimum age of 3.42 years and minimum weight of 12.3 kg. 10 subjects were in the 6 to < 12 age group and 19 subjects were in the 12 to 17 years age group.

At the time of submission the study was still ongoing to also assess efficacy and safety of icatibant after repeated exposures. However, the current submission was only concerned with the first part of the study, namely the assessment after a single exposure.

Subjects had to be aged 2 to < 18 years and had a documented diagnosis of HAE type I or type II, initially permitted to be based on medical history. Confirmation of the diagnosis was required based on immunogenic and/or functional C1-INH deficiency. Subjects with a diagnosis of angioedema other than HAE were excluded.

The primary objectives (relevant to this submission) were related to a single SC dose of icatibant and investigated efficacy, safety, pharmacokinetics (PK), tolerability, and the effect on reproductive hormone levels.

Treatments

Treatment was a single 0.4 mg/kg dose of icatibant up to a maximum of 30 mg SC in the abdominal region administered at the hospital/study centre under controlled conditions.

Efficacy information obtained from Phase III clinical studies in adults demonstrate that a single SC 30 mg dose of icatibant (0.4 mg/kg for a 75 kg adult) provides a sufficient magnitude and duration of effect to clinically manage the majority of acute attacks in adult HAE participants across a wide range of demographics.

Use of the following concomitant medications was allowed:

- Chronically administered medications on stable doses for ≥ 1 month (except treatments of HAE);
- Prophylactic therapies for HAE (for example, anti-fibrinolytics or C1-INH) other than attenuated androgens.

Prohibited concomitant medications were:

- Therapies known to attenuate an acute HAE attack unless required as rescue medications (except for chronically administered fibrinolysis inhibitors);
- Angiotensin converting enzyme (ACE) inhibitors;
- Androgens or attenuated androgens;
- Hormonal contraceptives.

Repeat administration of icatibant for treatment of a single attack was not allowed. Rescue therapies included agents such as C1-INH inhibitor concentrates or fresh frozen plasma, epinephrine and intravenous fluids. Medications to ameliorate the symptoms such as pain and nausea were allowable.

Participants were, divided into 2 groups determined prior to treatment:

- Pre-pubertal (Tanner stage I [4]), planned n = 10; and
- Pubertal/post-pubertal (Tanner stages II to V), planned n = 20: 10 to be treated for acute HAE attacks, 10 to be treated in the absence of HAE episodes.

Except for PK determinations, all primary and secondary endpoints were to be measured after each icatibant administration.

Statistics

The efficacy population included participants treated with icatibant for an HAE attack. The safety population included participants treated with icatibant on at least one occasion.

For efficacy, the median time and the 95% confidence interval were calculated for time to onset of symptom relief (TOSR), time to minimal symptoms and the time to first use of rescue medication using the Kaplan-Meier methodology. For individual

[4] Tanner staging (or sexual maturing rating) is a scale of physical development during puberty, ranging from I-V, with V being the most physically mature.

investigator-reported symptom scores, a shift table from Baseline was presented for each post-treatment time point.

No hypothesis testing or adjustments for multiple endpoints were planned. No statistical comparison analysis between pre- and post-pubertal groups, or between paediatric and adult groups were planned. No subgroup or sensitivity analyses were planned.

For safety and PK purposes, summary statistical methods were used.

Pharmacology

Only one study assessed the pharmacology pertaining to this submission, namely Study HGT-FIR-086 (methods described above).

Pharmacokinetics (PK)

Study HGT-FIR-086

The PK profile was assessed after a single SC injection in pre-pubertal children with an acute attack of HAE and pubertal/post-pubertal children with or without an acute HAE attack.

Individual PK variables for icatibant and major (inactive) metabolites designated M1 and M2, were measured using a validated high-performance liquid chromatography (HPLC) tandem mass spectrometry (LC-MS/MS) method.

Blood samples were collected pre-treatment, at 15 (± 5) min, 30 (± 5) min, 2 hours (± 10 min), 4 (± 0.5) hours, and 6 (± 0.5) hours after treatment. For pubertal/post-pubertal subjects, additional blood samples were collected at 45 (± 5) min and 1 hour (± 10 min) after treatment.

Pharmacokinetic parameters (estimated using non-compartmental methods) were:

- Pharmacokinetic parameter estimated were time to peak concentration (t_{max});
- Maximum plasma concentration (C_{max}) and minimum plasma concentration (C_{min});
- Total plasma clearance (CL/F);
- Area under the plasma concentration-time curve (AUC) from time zero to:
  - 4 hours post-dose (AUC_{0-4}),
  - 6 hours post-dose (last) (AUC_{0-6}),
  - Infinity ($AUC_{0-\infty}$);
- Volume of distribution (V_z/F) (at steady state); and
- Elimination half-life ($t_{1/2}$).

Results

32 subjects provided PK samples. One pre-pubertal subject was excluded due to an insufficient sample. One (aged 11.4 years) had a pre-dose C_{max} > 5% (59.1 ng/mL).

For 31 subjects, the PK parameters were estimated, but only 30 were included in the PK summary: 13 were female and 17 were male. The mean age was 7.9 ± 2.72 years (pre-pubertal) or 14.3 ± 1.62 (pubertal/post-pubertal).

The mean ± SD total SC dose of icatibant received were 14.0 ± 5.97 (pre-pubertal) and 23.8 ± 5.15 mg (pubertal/post-pubertal). The minimum total dose received was 4.9 mg for a 3 year old male weighing 12.3 kg; the maximum total dose was 30 mg of icatibant for 4 participants weighing ≥ 75 kg.

Icatibant demonstrated a monophasic plasma concentration time profile across the paediatric HAE population.

Estimated PK parameters

Icatibant was rapidly absorbed. t_{max} was approximately 0.5 hours post SC dose for all participants. M1 and M2 t_{max} was approximately 2.0 hours for all participants.

An overview of estimated PK parameters of icatibant (and its metabolites M1 and M2) is shown in Table 2. Graphical representations are shown in Figures 1 to 4.

Table 2: Study HGT-FIR-086 Estimated PK parameters of icatibant and its metabolites M1 and M2

Time	Prepubertal (N=10)[a]		Pubertal/Postpubertal With Acute Attack (N=11)		Pubertal/Postpubertal Without Acute Attack (N=10)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Icatibant						
AUC_{0-t} (h•ng/mL)	9	1241 (319)	11	1448 (304)	10	1335 (211)
AUC_{0-t} (h•ng/mL)	9	1289 (325)	11	1573 (372)	10	1398 (225)
AUC_{0-inf} (h•ng/mL)	6	1243 (244)	11	1710 (569)	10	1416 (229)
C_{max} (ng/mL)	9	659 (158)	11	805 (125)	10	761 (133)
t_{max} (h)	9	0.42 (0.13)	11	0.55 (0.19)	10	0.57 (0.17)
$t_{1/2}$ (h)	6	0.80 (0.04)	11	1.34 (0.96)	10	0.90 (0.10)
CL/F (mL/min)	6	10.8 (4.63)	11	13.1 (3.42)	10	19.3 (4.84)
CL/F/Weight (L/h/kg)	6	0.33 (0.08)	11	0.26 (0.08)	10	0.29 (0.05)
V_z/F (L)	6	12.5 (5.28)	11	23.5 (13.9)	10	25.4 (8.87)
V_z/F/Weight (L/kg)	6	0.39 (0.11)	11	0.44 (0.18)	10	0.37 (0.09)
M1						
AUC_{0-t} (h•ng/mL)	9	446 (175)	11	665 (94)	10	708 (80)
AUC_{0-t} (h•ng/mL)	9	605 (249)	11	896 (180)	10	922 (91)
AUC_{0-inf} (h•ng/mL)	0	NC	3	1052 (493)	2	1323 (NC)
C_{max} (ng/mL)	9	158 (62.4)	11	218 (28.2)	10	237 (26.9)
t_{max} (h)	9	2.05 (0.86)	11	1.70 (0.51)	10	1.80 (0.42)
$t_{1/2}$ (h)	0	NC	3	2.18 (0.79)	2	2.91 (NC)
Icatibant to M1 AUC_{0-t} ratio	9	1.09 (0.46)	11	0.81 (0.13)	10	0.70 (0.12)
M2						
AUC_{0-t} (h•ng/mL)	9	592 (204)	11	828 (186)	10	828 (105)
AUC_{0-t} (h•ng/mL)	9	816 (274)	11	1128 (283)	10	1089 (135)
AUC_{0-inf} (h•ng/mL)	0	NC	2	883 (NC)	2	1417 (NC)
C_{max} (ng/mL)	9	213 (76.9)	11	281 (64.1)	10	276 (33.5)
t_{max} (h)	9	2.27 (1.08)	11	2.18 (1.33)	10	1.80 (0.42)
$t_{1/2}$ (h)	0	NC	2	1.89 (NC)	2	2.84 (NC)
Icatibant to M2 AUC_{0-t} ratio	9	0.74 (0.27)	11	0.62 (0.07)	10	0.56 (0.05)

NC=not calculated

[a] Subject was excluded from the calculation of descriptive statistics.

Figure 1: Study HGT-FIR-086 Mean icatibant concentration-time graph (linear and semi-logarithmic scales)

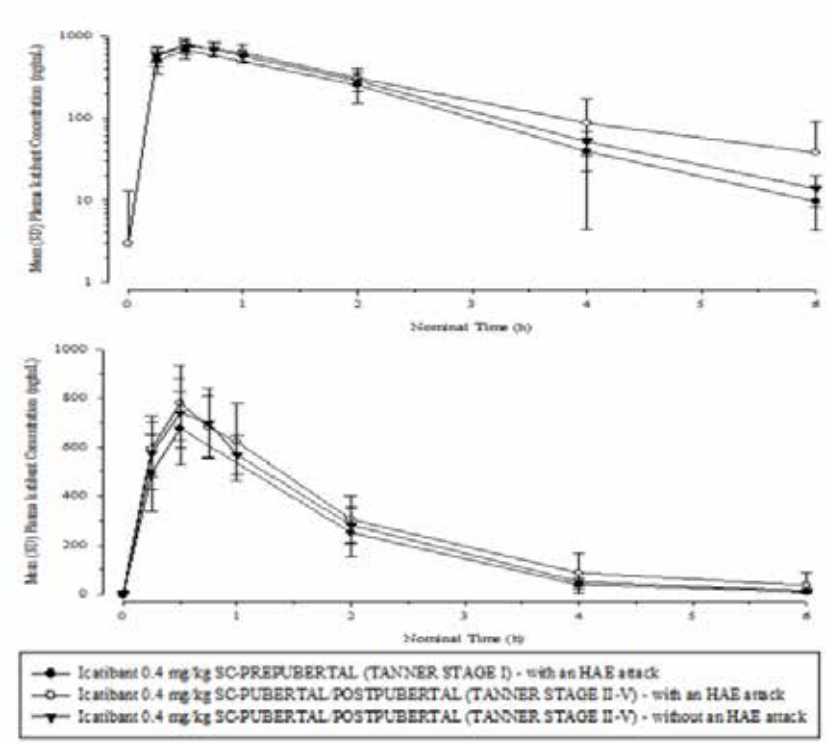


Figure 2: Study HGT-FIR-086 Individual icatibant concentration-time graph: (linear and semi-logarithmic scales)

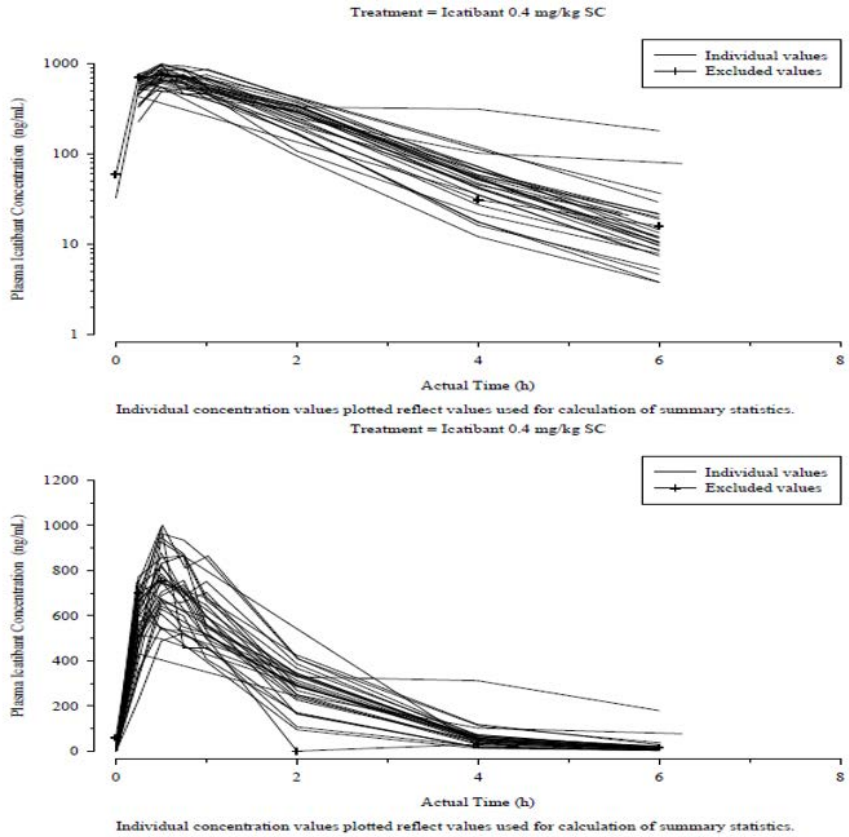


Figure 3: Study HGT-FIR-086 Mean M1 concentration-time graph (linear and semi-logarithmic scales)

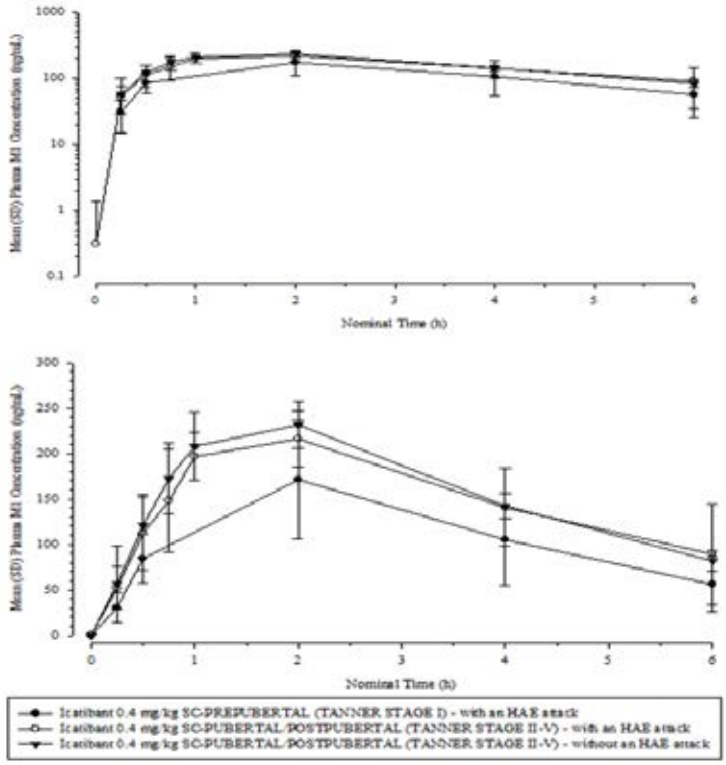
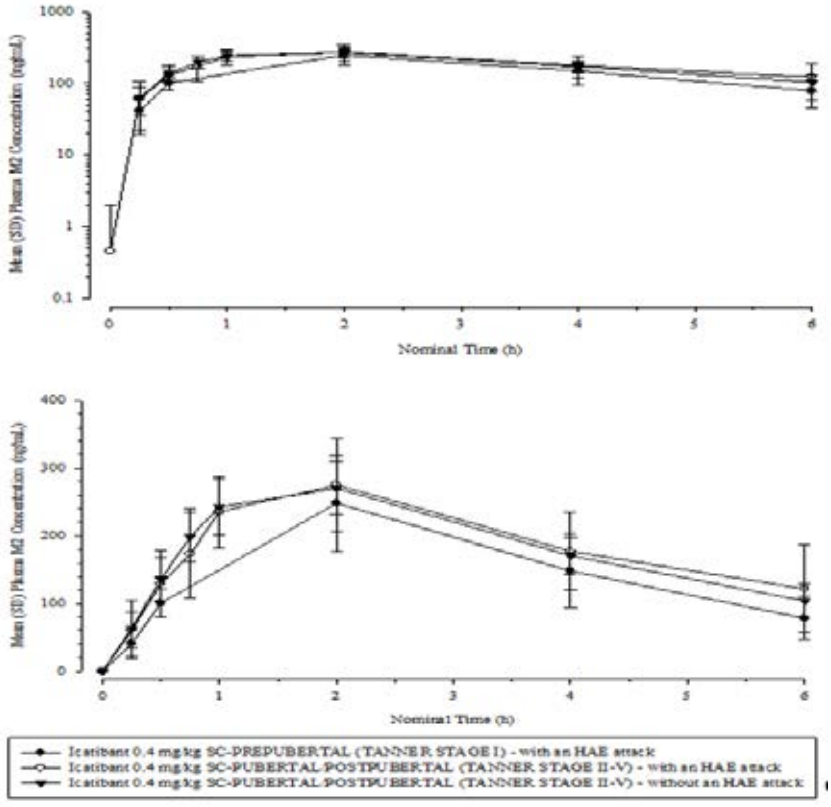


Figure 4: Study HGT-FIR-086 Mean M2 concentration-time graph (linear and semi-logarithmic scales)



Population PK/PD analysis

One population pharmacokinetic/pharmacodynamic (PopPK/PD) analysis was conducted, namely PopPK/PD analysis SHIR-RAS-003.

PopPK/PD analysis SHIR-RAS-003

Study data

PopPK/PD analysis SHIR-RAS-003 (based on data from Studies JE049-1102, JE04-1103, HGT-FIR-061, HGT-FIR-065, JE049-2101, and HGT-FIR-086). Only Study HGT-FIR-086 involved paediatric patients with HAE.

Table 3: PopPK/PD analysis SHIR-RAS-003 study data

Healthy Adult Subjects (Phase I studies)	Adult Patients with HAE (Phase IIa)	Pediatric Patients with HAE (Phase III)
JE049-1102 (n = 24) JE049-1103 (n = 12) HGT-FIR-061 (n = 76) HGT-FIR-065 (n = 21)	JE049-2101 (n = 8)	HGT-FIR-086 (n=31)

HAE = hereditary angioedema; n = number of subjects.

The dataset included results of 31 children and adolescents and 141 adults < 65 years of age. The median age (range) was 25.0 years (3.42 to 54.0 years). The median body weight (range) was 69.5 kg (12.3 to 102 kg). The proportions of female and male participants were 41.3% and 58.7%, respectively. Eighteen percent of participants were less than 18 years old of age. The majority were White, 132 (76.7%); 36 (20.9%) were Black or African American and 4 (2.3%) were 'Other'.

In total, 2172 concentrations were included in the PK analysis. Of the 523 below the limit of quantification (BLQ) samples, 166 were observed prior to icatibant dosing and 228 BLQ samples were observed 18 h after administration (Table 4).

Table 4: Analysis SHIR-RAS-003 Number of plasma concentration samples

Study	Number of Samples (%)	
	Measurable Concentrations	BLQ (Excluded)
HGT-FIR-061	989 (81.5)	225 (18.5)
HGT-FIR-065	483 (95.8)	21 (4.2)
JE049-1102	226 (64.0)	127 (36.0)
JE049-1103	243 (68.8)	110 (31.2)
JE049-2101	40 (85.1)	7 (14.9)
HGT-FIR-086	191 (85.3)	33 (14.7)
Total	**2172 (80.6)**	**523 (19.4)**

BLQ = Below the limit of quantification

Objectives

The objectives were to:

- Characterise icatibant PK in children and adolescents with HAE:
  - By performing a population PK analysis to fit concentration-time profiles of icatibant;
  - By characterising the source of variability in icatibant PK parameters; and
  - By deriving individual *post hoc* PK parameters of icatibant: AUC_{0-6}, C_{max}, $t_{1/2}$, CL/F, and apparent central volume of distribution (Vc/F).
- Compare icatibant exposure in children and adolescents to those in adults.

- Assess the relationship between the time of onset of symptom relief (TOSR) and various exposure metrics of icatibant (C_{max}, AUC_{0-2}, AUC_{0-4} and AUC_{0-6}, $t_{1/2}$ and t_{max}) in children and adolescents.
- Include simulations to support fixed-based dosing of icatibant in children and adolescents with HAE.

Modelling and assumptions

The model used was based on an existing model. The starting point was an existing 2 compartment model with first order absorption and lag-time (T_{lag}) and allometric components accounting for differences in body weight. Modelling was performed using a non-linear mixed effect approach with non-linear mixed effects modelling (NONMEM) 7.3 and PsN 4.2.0.

Issues were raised by the European Medicines Agency (EMA), or example visual predictive checks (VPCs), BLQ omission, simulations (sensitivity analyses) to compare PK under various scenarios (with and without age effect, linear CL and weight effect, fixing allometric exponents). However, none of these resulted in identifying model misspecifications and the sponsor's original model was retained.

The relationships between covariates and PK parameters were explored graphically to identify covariates and extrinsic factors likely to affect the PK. Other covariates were tested in the model based on trends from the scatter matrix plots and boxplots. A summary of covariates tested is in Table 5.

Table 5: Analysis SHIR-RAS-003 Effects included in the final population PK model

Covariates	PK Parameter
Weight	CL/F, Vc/F, Vp/F, CLp/F
Age	CL/F
Sex	CL/F and Vc/F
Race	Vc/F
Occurrence of an HAE attack within 12 hours prior dosing	CL/F

CL/F = apparent clearance; CLp/F = apparent inter-compartmental clearance; HAE = hereditary angioedema; PK = pharmacokinetic; Vc/F = apparent volume of distribution in plasma; Vp/F = apparent peripheral volume of distribution.

Covariate analysis was performed using a full population PK model approach to identify sources of variability in PK parameters of icatibant. The performance of the model was evaluated with a bootstrap re-sampling strategy. Based on the estimates of the population PK model, concentration-time profiles of icatibant were simulated (approximately 1000 replicates). Non-significant covariates were removed from the model. The final population PK model was evaluated using diagnostic plots and visual predictive check.

Concentration time profiles for 31 patients in Study HGT-FIR-086 were simulated using the final population PK model and the actual dosing history in the study. PK and exposure parameters (AUC_{0-2}, AUC_{0-4}, AUC_{0-6}, $t_{½}$, C_{max}, and t_{max}) of icatibant for these patients were estimated, and exploratory analyses were performed to assess the relationship between TOSR and the above exposure parameters.

Model predicted AUC_{0-6} and C_{max} of icatibant derived for the 5 weight based dosing regimen proposed for registration were compared to those derived for the fixed based dosing regimen (0.4 mg/kg, capped at 30 mg).

Results: fit

A 2 compartment model with first-order absorption and T_{lag} resulted in an adequate quality of fit. The population predicted concentrations were generally clustered around the identity line.

Results: PK comparison based in differences in dosing and HAE attack status

In summary, 0.4 mg/kg SC dosing resulted in lower exposures compared to adults, namely 46% and 39% lower mean AUC_{0-24}, and 34% and 34% lower C_{max}, in children (2 to

< 12 years) and adolescents (12 to 17 years), respectively (compared to adults with weight less than 75 kg). t_{max} remained similar at 0.6 hours for all age groups.

Plasma concentration-time profiles of icatibant in participants treated within 12 hours after an HAE attack were similar to those without an HAE attack prior to dosing.

Results: PK parameters and covariates

Statistically significant (not necessarily clinically relevant) effects included into the final population PK model of icatibant are summarised in Table 6.

The absorption of icatibant in the systemic circulation was rapid (absorption rate constant (K_a) = 3.27/h), corresponding to an absorption half-life (t½ abs) of ~ 12.7 min. Based on these parameters, complete absorption would be expected within ~ 1 hour of dosing (5 absorption half-lives).

The typical CL/F was 15.4 L/h. The typical apparent central volume of distribution (Vc/F) and apparent peripheral volume of distribution (Vp/F) were 20.4 L and 1.75 L, respectively.

There appeared to be no relevant trend between the random effects (ETA) values of:

- Vc/F and HAE attack within 12 hours of dosing; and
- CL/F and race.

The following values refer to typical circumstances/participants:

- Weight: CL/F of icatibant in a 40 kg child and a 60 kg adolescent were expected to be, respectively, 25% and 7% lower than that observed in a 70 kg participant.
- Sex: CL/F was approximately 12% lower in females compared to males. Vc/F was approximately 15% lower in females compared to males.
- HAE attack status: CL/F was approximately 9% lower in patients with a HAE attack within 12 h prior (compared to healthy volunteers and HAE patients without an acute attack).
- Race: Vc/F was approximately 11% higher in non-White subjects (Black/African American and others) compare to White subjects.
- Clinical relevance: The above effects of age, sex, and HAE attacks within 12 h of dosing on the CL/F were not deemed clinically relevant. The above effects of sex and race on the Vc/F were not deemed clinically relevant.

Table 6: Analysis SHIR-RAS-003 Typical population PK parameters of icatibant SC based on the final model

Parameters	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** x $(Weight/70)^{0.516}$ 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** x $(Weight/70)^{0.671}$ x 0.855 if Female x 1.11 if Non-White	26.9	5.8
CLp/F (L/h)	**0.398** $(Weight/70)^{0.516}$	107.8	19.2
Vp/F (L)	**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.

Results: paediatric PK parameter comparison to adults

PK and exposure parameters of icatibant by age group are summarised in Table 7.

Table 7: Analysis SHIR-RAS-003 Descriptive statistics of PK parameters of icatibant by weight and age

Weight Group	Age Group	Mean (SD, CV%) Median [Min-Max]								
		Actual Total Dose (mg)	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)
< 75 kg	2- <12 years (n=12)	15.2 (6.04, 39.7%) 16.0 [4.90-25.2]	737 (134, 18.1%) 727 [547-962]	0.575 (0.106, 18.4%) 0.600 [0.400-0.700]	2.61(0.667, 25.5%) 2.71 [1.66-4.18]	1271 (265, 20.8%) 1249 [744-1753]	1294 (272, 21.0%) 1268 [752-1784]	11.5 (3.50, 30.5%) 12.9 [5.63-16.2]	12.3 (4.80, 39.1%) 13.6 [4.66-19.6]	0.324 (0.0791, 24.4%) 0.316 [0.224-0.530]	0.329 (0.0644, 19.6%) 0.323 [0.246-0.473]
	12-17 years (n=15)	22.8 (4.71, 20.6%) 23.0 [13.4-28.8]	734 (98.5, 13.4%) 747 [516-916]	0.560 (0.106, 18.8%) 0.600 [0.400-0.800]	3.97 (4.40, 111%) 3.09 [1.61-19.6]	1404 (330, 23.5%) 1342 [916-2160]	1465 (431, 29.4%) 1367 [926-2681]	16.3 (3.82, 23.5%) 16.1 [7.09-21.6]	20.0 (4.47, 22.3%) 20.2 [10.4-26.2]	0.291 (0.0690, 23.7%) 0.293 [0.149-0.432]	0.353 (0.0584, 16.6%) 0.342 [0.298-0.531]
	18-65 years (n=99)	30.0 (1.81, 6.0%) 30.0 [26.0-45.0]	1116 (325, 29.1%) 1030 [582-2421]	0.662 (0.143, 21.5%) 0.600 [0.400-1.10]	3.40 (0.928, 27.3%) 3.35 [1.62-6.16]	2319 (605, 26.1%) 2237 [1361-5764]	2407 (645, 26.8%) 2310 [1417-6146]	13.1 (2.90, 22.0%) 13.0 [7.32-21.2]	18.4 (4.89, 26.5%) 17.8 [9.22-34.9]	0.204 (0.0415, 20.3%) 0.205 [0.100-0.318]	0.286 (0.0682, 23.9%) 0.283 [0.153-0.493]
≥ 75 kg	12-17 years (n=4)	30.0 (0.0, 0.0%) 30.0 [30.0-30.0]	756 (113, 15.3%) 746 [657-875]	0.550 (0.100, 18.2%) 0.600 [0.400-0.600]	3.77 (2.98, 79.1%) 2.80 [1.41-8.05]	1462 (375, 25.6%) 1578 [918-1774]	1527 (425, 27.8%) 1618 [932-1939]	21.2 (7.30, 35.4%) 18.6 [15.5-32.2]	26.5 (6.56, 24.8%) 24.5 [21.2-35.6]	0.269 (0.0857, 31.9%) 0.238 [0.206-0.395]	0.339 (0.0925, 27.2%) 0.305 [0.274-0.473]
	18-65 years (n=61)	31.5 (3.51, 11.2%) 30.0 [30.0-45.0]	988 (399, 40.4%) 838 [524-2394]	0.667 (0.140, 21.0%) 0.700 [0.300-1.00]	3.45 (1.05, 30.3%) 3.31 [1.85-6.56]	2188 (993, 45.4%) 1804 [1126-6608]	2301 (1092, 47.4%) 1909 [1137-7264]	15.4 (4.38, 28.5%) 15.7 [6.18-26.4]	23.0 (6.96, 30.2%) 22.9 [9.76-42.1]	0.184 (0.0511, 27.8%) 0.191 [0.0825-0.323]	0.274 (0.0750, 27.3%) 0.269 [0.117-0.467]

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 C_{max} = maximum plasma concentration; CL/F = apparent systemic clearance; Max = maximum; Min = minimum; PK = pharmacokinetic; $T_{1/2}$ = terminal half-life; T_{max} = time to maximum plasma concentration; Vc/F = apparent central volume of distribution.

Mean CL/F in children (2 to < 12 years), adolescents (12 to 17 years) and adults < 75 kg (18 to 65 years) were 11.5 L/h, 16.3 L/h, and 13.1 L/h, respectively.

Following an SC administration of 0.4 mg/kg (capped at 30 mg), mean AUC_{0-24} in children and adolescents with HAE were 1294 and 1465 ng.h/mL, respectively. These values were 46% and 39% lower than the mean AUC_{0-24} in adults of less than 75 kg.

Mean C_{max} in children (2 to < 12 years) and adolescents (12 to 17 years) with HAE were similar (737 and 734 ng/mL, respectively), but approximately 34% lower than those derived in adults (who received 30 to 45 mg SC) less than 75 kg (1116 ng/mL). Median

time to peak icatibant concentration (T_{max}) was observed at 0.6 hour post dose in children, adolescents and adults less than 75 kg.

Pharmacodynamics

Exploratory exposure response analyses did not identify any differences in onset of symptom relief with the reduced exposures (compared to typical adult exposure). Exposure response relationships were not observed for the probability of no symptom relief given the rapid onset across the groups. Based on these findings, 0.4 mg/kg was identified as appropriate dose in paediatrics.

In Study HGT-FIR-086, the mean TOSR was 1.38 h and all participants showed resolution of symptoms within 4 h of administration (Table 8). These results suggest that the lower exposure of icatibant in children and adolescent is not clinically relevant.

Table 8: Study HGT-FIR-086 Descriptive statistics of TOSR (PK population)

N	Mean (h) (CV%)	Median (h) (Range)
21	1.38 (52.6)	1.00 (0.83 – 3.92)

Patients with AUC_{0-6} values in the lower tertiles (744 to 1235 ng.h/mL) displayed the slowest onset of symptom relief. The rapid onset of response did not allow a discrimination of exposure response between the second and third tertiles. Similar results were observed for AUC_{0-2} and C_{max}. No exposure response relationship was observed for t_{max}, and $t_{½}$.

Simulations to model different dose regimens

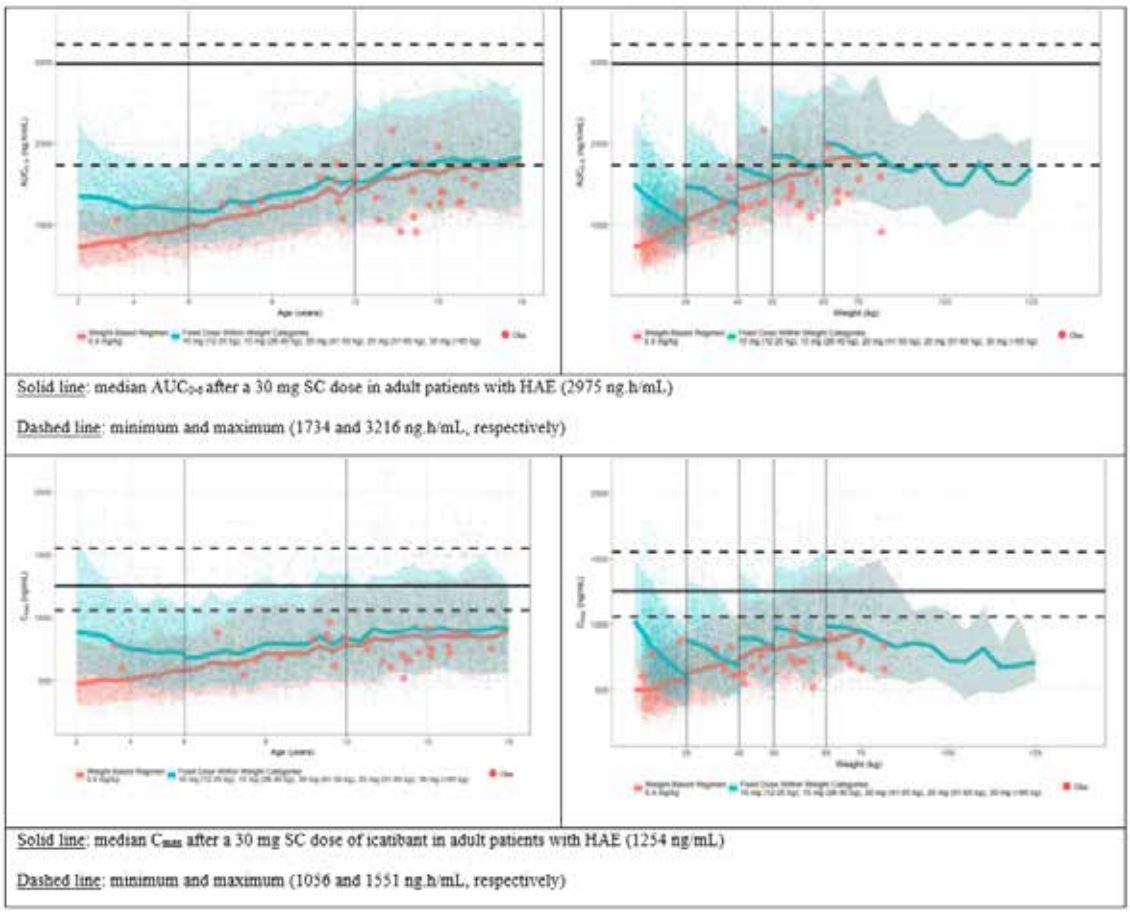
A total of 6000 virtual paediatric patients were simulated (Monte Carlo) using a generalised additive modelling for location, scale, and shape approach on age normative data for male and females based on the growth charts at Center for Disease Control and Prevention (CDC) in the following groups: 2 to 5, 6 to 11 and 12 to 17 years of age.

Individual AUC_{0-6} and C_{max} values were derived according to weight-based regimen (0.4 mg/kg) and a fixed dose regimen (within weight categories) and summarised by age groups. Median (fifth and ninety fifth percentiles) values of AUC_{0-6} and C_{max} are shown in Table 9.

Table 9: Study HGT-FIR-086 Descriptive statistics of AUC_{0-6} and C_{max} of icatibant in paediatric patients according to weight-based and fixed-dose regimens

Parameters	Age Group	Median [5th and 95th Percentiles]	
		Weight-Based Regimen (0.4 mg/kg)	Fixed-Dose within Weight Categories [10 mg (12-25 kg), 15 mg (26-40 kg), 20 mg (41-50 kg), 25 mg (51-65 kg), 30 mg (>65 kg)]
AUC_{0-6} (ng.h/mL)	2 to 5 years	853 [550, 1262]	1251 [819, 1882]
	6 to 11 years	1198 [753, 1878]	1362 [858, 2152]
	12 to 17 years	1643 [1074, 2449]	1745 [1111, 2589]
	2 to 17 years	1193 [645, 2158]	1432 [884, 2332]
C_{max} (ng/mL)	2 to 5 years	529 [331, 826]	777 [470, 1271]
	6 to 11 years	690 [417, 1098]	771 [472, 1252]
	12 to 17 years	839 [539, 1297]	892 [562, 1388]
	2 to 17 years	679 [384, 1164]	812 [490, 1320]

Figure 5: Study HGT-FIR-086 Simulated AUC_{0-6} and C_{max} versus age (weight based and fixed dose regimens) and versus weight



Model derived AUC_{0-6} and values with the weight-based regimen were compared to those derived with the fixed-dose regimen (within weight categories) for each age group (as shown in Figure 5):

- In the weight based regimen (compared to the fixed dose regimen within weight categories), the median AUC_{0-6} was:
  - 32% lower in the 2 to 5 year group;
  - 12% lower in the 6 to 11 year group; and
  - 6% lower in the 12 to 17 year group.
- In the weight based regimen (compared to the fixed dose regimen within weight categories), the median C_{max} was:
  - 32% lower in the 2 to 5 year group;
  - 11% lower in the 5 to 11 year group; and
  - 6% lower in the 12 to 17 year group.

Dosing considerations: clinical trials

In the paediatric Study HGT-FIR-086, all subjects received a single SC icatibant dose of 0.4 mg/kg per attack (up to a maximum dose of 30 mg).

The 0.4 mg/kg dose was derived from PK/PD modelling of data from Phase I PK studies in healthy male adult volunteers (Study JE049-1001). The results supported a minimum effective dose of 0.4 mg/kg to treat acute attacks of HAE. 0.4 mg/kg corresponds to a dose of 30 mg of icatibant in a 75 kg subject.

A subsequent Phase II dose ranging proof of concept efficacy study in adults (Study JE049-2101) investigated icatibant doses of 0.4 to 0.8 mg/kg intravenous (IV) and 30 to 45 mg SC, but indicated that 45 mg SC showed no improvement in efficacy over 30 mg SC.

The Phase III program confirmed that a single SC 30 mg dose of icatibant provided sufficient magnitude and duration of effect to clinically manage the majority of acute attacks in adult HAE subjects across a wide range of demographics. This is the currently approved adult dose for icatibant.

Based on the above, 0.4 mg/kg SC icatibant was chosen for the paediatric study.

Dosing considerations: extrapolating to clinical practice

To simplify the dosing for medical practitioners in an emergency setting (and to reduce the potential for medication errors, in particular in the paediatric setting), the sponsor originally proposed dosing with three weight bands (see Table 10) based on the based on:

- The actual exposure observed in Study HGT-FIR-086;
- Simulated exposure based on three weight bands;
- Higher exposures seen in studies following higher SC dose administrations (45 and 90 mg) in adult subjects with HAE; and
- The overall safety and efficacy profile of icatibant.

Table 10: Three weight band dosing regimen

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

This regimen was believed to result in unnecessary overexposure in some children with concerns about the very limited PK information in subjects aged 2 to 6 years and uncertainty in the expected exposure.

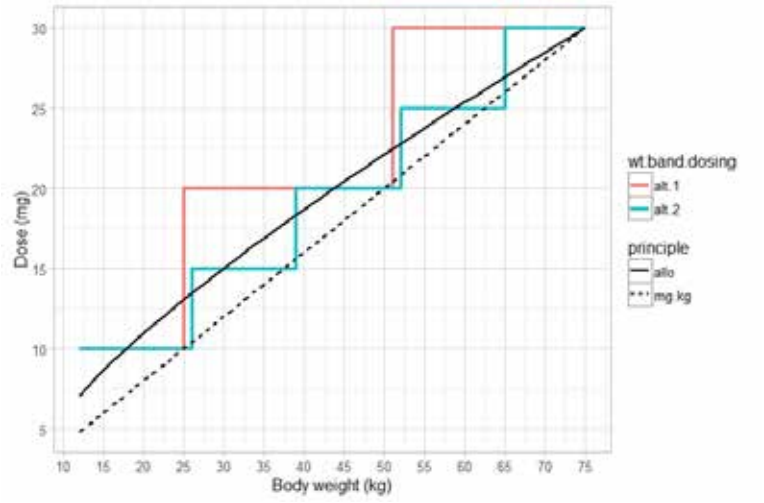
Given those concerns, the sponsor investigated simulated AUCs versus weight/age for different regimens (weight based 0.4 mg/kg; three band dosing; five band dosing). Exposures were found to be lower than those observed in adults.

The population PK/PD modelling showed that body weight was the most significant covariate explaining the variability in CL/F.

Table 11: Comparison of C_{max} and AUC_{0-6} comparing the three dosing regimens under consideration

	Weight based dosing 0.4 mg/kg (median)			Three weight bands (mean)			Five weight bands (mean)					Adult
	2 to 5 yrs (approx. 12-18kg)	6-11 yrs (19-37kg)	12-17 yrs (40-55kg)	>10 to ≤25kg	>25 to ≤50kg	>50kg	<12 to 25kg	26 to 40kg	41 to 50kg	51 to 65kg	>65kg	
Cmax (ng/mL)	529	690	839	1157	852	894	747	775	867	924	907	994
AUC0.6 (ng.h/mL)	853	1198	1643	1154	1581	1696	1211	1370	1617	1783	1836	2082

Figure 6: Graphical representation of the three dosing regimens



The dashed black line ('mg.kg') denotes the 0.4 mg/kg dosing regimen. 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') illustrates five weight band dosing. The red staircase shape ('alt.1') illustrates three weight band dosing.

Given that the paediatric extrapolation exercise was to match the adult exposure, the EMA proposed to use the five weight band dosing regimen rather than the 0.4 mg/kg or the three band regimen. This was adopted by the sponsor.

Table 12: Five weight band dosing regimen

Regimens	Body Weight	Injection Volume	Dose
Weight-Based	12 to 25 kg	1.0 mL	10 mg
	26 to 40 kg	1.5 mL	15 mg
	41 to 50 kg	2.0 mL	20 mg
	51 to 65 kg	2.5 mL	25 mg
	>65 kg	3.0 mL	30 mg

PopPK working group discussion (March 2019)

The PopPK working group was asked to comment on:

- The confidence of the model for estimating exposures in 2 to 6 years age group;
- Concerns in relation to the sponsor's modelling approach (given the complex interplay between weight, age and CL) (including the sponsor's response to TGA questions);
- Any other relevant matters.

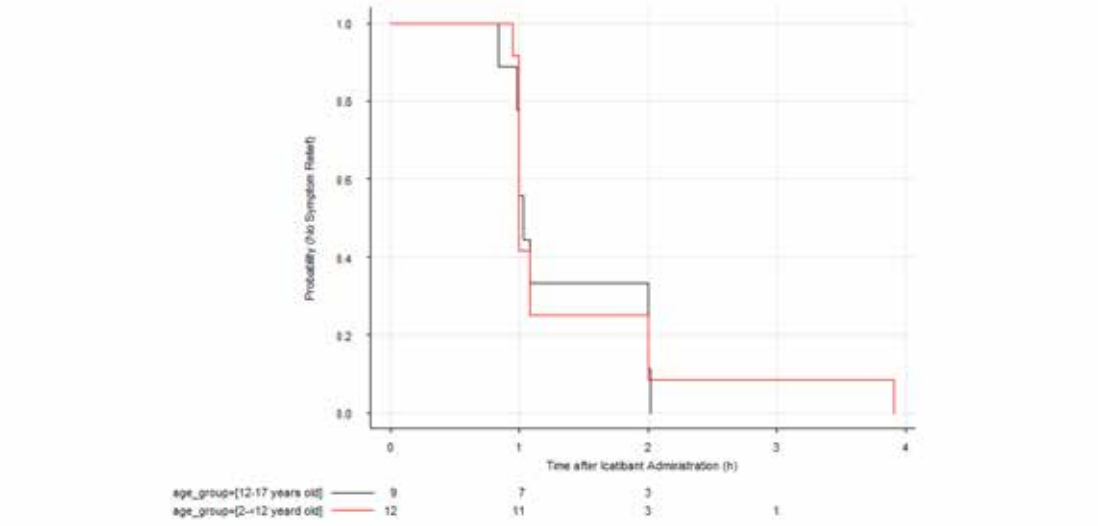
Outcomes of the PopPK working group discussion (March 2019):

- The model was not ideal and the working group was not entirely convinced with regard to model predictability and applicability. The model was data driven, that is, not mechanistic or based entirely on allometry. This may limit the application of the model. However, distribution of the simulated exposures capture the observed concentrations (Figure 5) and exploratory exposure response Kaplan-Meier plots were similar between age groups 2 to < 12 and 12 to 17 years.
- The group noted that the youngest patient in Study HGT-FIR-086 was 3.42 years old.
- In majority of the paediatric subjects (especially < 12 years age), the simulated AUC_{0-6} and C_{max} were not in the range of adult AUC_{0-6} and C_{max} (Figure 5).
- The probability of no symptom relief endpoint in Kaplan-Meier plots did not differ between age groups 2 to <12 and 12 to 17 years (Figure 7). This could be in part

explained by half maximum effective concentration (EC_{50}), which was very low compared to the observed concentrations in Study HGT-FIR-086. The working group did not identify any concerns in the response to TGA questions provided by the sponsor.

- Conclusion: Considering the entirety of the pharmacometric data, the working group agreed with the sponsor's conclusions in relation to PopPK and exposure response analysis and advocated for a risk management approach (for example, use of a registry, et cetera).

Figure 7: Study HGT-FIR-086 Probability of no symptom relief as a function of age groups (PD population)



Note: The number in lower part of the graph represents then number of subjects in the respective age group who did not have symptom relief at each specific time after icatibant dosing. At 4 hours, all subjects had symptom relief thus the probability = 0%

Efficacy

Only one study assessed the efficacy pertaining to this submission, namely Study HGT-FIR-086 (methods described above).

Study HGT-FIR-086

Efficacy variables and analysis

The efficacy endpoints (only for subjects treated with icatibant during an HAE attack) were:

- TOSR and time to minimal symptoms, as measured by a composite of investigator and subject reported outcomes:
  - For subjects aged 2 to < 18 years: investigator assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks by an investigator rated symptom score:
    - 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).

  - For subjects aged ≥ 4 years: subject self-assessment of HAE related pain using the Faces Pain Scale-Revised (FPS-R).
  - For subjects aged < 4 years: investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using a validated pain scale (Faces, Legs, Activity, Cry, and Consolability (FLACC)).
- Incidence of rescue medication use.
- Proportion of subjects with worsened intensity of clinical HAE symptoms between 2 and 4 hours after treatment with icatibant.

TOSR was defined as the duration in hours from study drug administration to the earliest time at which there was at least a 20% improvement in the composite, post treatment symptom score with no worsening of any single component score.

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.

For cutaneous and/or abdominal attacks, investigator assessed symptom scores were collected for 8 symptoms: abdominal tenderness, nausea, vomiting, diarrhoea, skin pain, erythema, skin irritation, and skin swelling.

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

Demographic characteristics

Pre-pubertal participants

The mean age was 7.5 years at screening and 8.6 years at study drug administration. There were 2 children < 6 years old (3.4 years and 3.7 years); 5 participants were between 6 and 11 years old, and 4 were aged > 11 years. All were white, 54.5% were male. Most were enrolled in the USA (4) or Israel (3). The mean weight was 36.0 kg, and the mean weight percentile was 67.5; the mean height was 132.1 cm, the mean height percentile was 61.4; the mean body mass index (BMI) was 19.5 kg/m^2, and the mean BMI percentile was 65.5.

Pubertal/post-pubertal participants

The mean age was 13.1 years at screening and 14.3 years at study drug administration. The majority were > 11 years old (95.2%), male (61.9%), and white (95.2%). Most participants were enrolled in the US (6), Israel (4), Austria (3), or Hungary (3). The mean weight was 60.2 kg, and the mean weight percentile was 69.5; the mean height was 163.2 cm, the mean height percentile was 53.4; the mean BMI was 22.4 kg/m^2, and the mean BMI percentile was 70.4.

Overall, a family history of HAE was reported by 90.6%. The mean time since diagnosis was 5.8 years, and the time since the last attack was 13.8 months. The most frequent type of previous attack was cutaneous (40.6%) or abdominal (31.3%).

Overall, 16 (72.7%) participants experienced a cutaneous attack (8 pre-pubertal, 8 pubertal/post-pubertal). 5 (22.7%) experienced an abdominal attack (3 pre-pubertal, 2 pubertal/post-pubertal). One (4.5%) pubertal/post-pubertal patient experienced a cutaneous and abdominal attack.

For pre-pubertal patients, the most common concomitant medications were complement C1 esterase inhibitor (21.9%), tranexamic acid (18.8%), and ibuprofen (12.5%). For pubertal/post-pubertal patients the most common concomitant medications were tranexamic acid (27.3%) and complement C1 esterase inhibitor (13.6%). One

pubertal/post-pubertal participant used rescue medication (C1-INH) when an HAE attack occurred approximately 6 hours following icatibant administration without an HAE attack.

Efficacy results

Investigator-rated symptom score: Time to onset of symptom relief (TOSR)

TOSR results for both pubertal status groups were similar. At 1 hour post-treatment, approximately 50% of participants recorded symptom relief; at 2 hours post-treatment approximately 90% of participants had experienced symptom relief (see Table 13 and Figure 8, below).

Table 13: Study HGT-FIR-086 TOSR results (efficacy population)

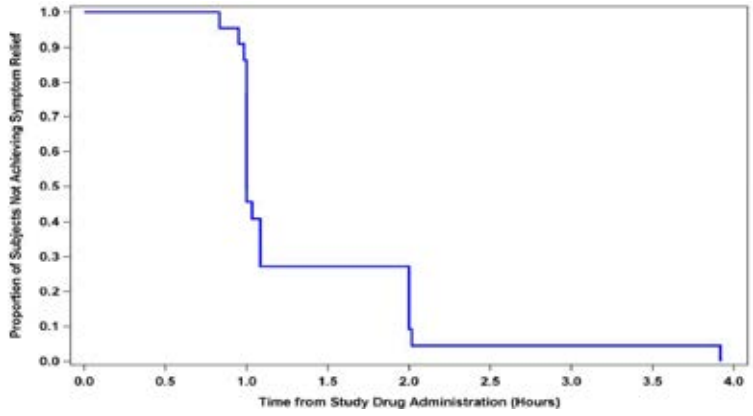
Parameter	Prepubertal (N=11)	Pubertal/ Postpubertal (N=11)	Overall (N=22)
Number of subjects available for analysis	11	11	22
Number of subjects with symptom relief	11	11	22
Percentage of subjects with symptom relief	100.0	100.0	100.0
Number of censored subjects[a]	0	0	0
Kaplan-Meier estimates			
Median 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

Note: Time to onset of symptom relief is defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there is at least a 20% improvement in the composite (or average) posttreatment symptom score with no worsening of any single component score.
CI=confidence interval
[a] Subjects who did not achieve symptom relief within the observation period were censored at the last observation time.

Investigator-rated symptom score: Time to minimum symptoms

One participant with mild or absent symptoms at pre-treatment was excluded from the analysis of time to minimum symptoms. All 21 other participants achieved minimum symptoms with overall median time to minimal symptom 1.1 hours (95% confidence interval (CI): 1.0, 2.0). The median time to minimal symptoms was similar for the pre-pubertal participants (median: 1.9 hours; 95% CI: 1.0, 2.0) and the pubertal/post-pubertal participants (median: 1.0 hour; 95% CI: 1.0, 2.0).

Figure 8: Study HGT-FIR-086 Kaplan-Meier plot of TOSR results (efficacy population)



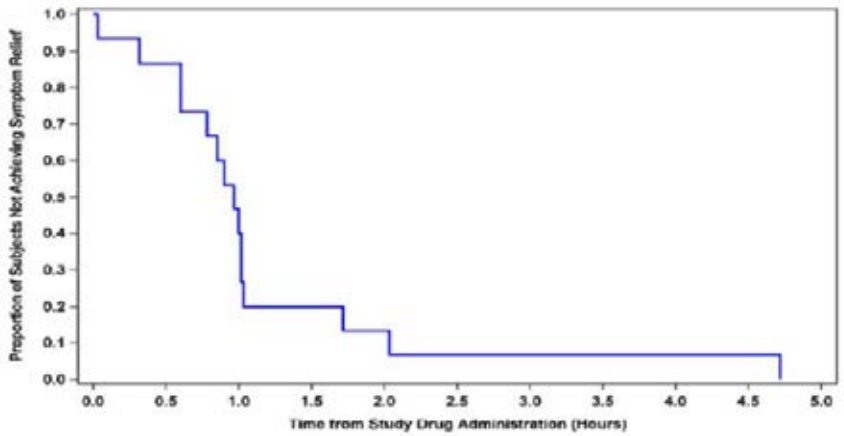
Note: Time to onset of symptom relief was defined as the duration of time in hours from study drug administration to the earliest time post-treatment at which there was at least a 20% improvement in the composite (or average) post-treatment symptom score with no worsening of any single component score.

FPS-R (patient-assessed)

All but 2 participants aged > 4 years had self-reported symptom relief results according the FPS-R assessments (see also Figure 4 and Table 14 below):

- Overall, median time to onset of pain relief was 1.0 hour (95% CI: 0.8, 1.0). Median time to onset of pain relief appeared similar for pre-pubertal (median: 0.9 hours; 95% CI: 0.8, 1.0) and pubertal/post-pubertal (median: 1.0 hours; 95% CI: 0.6, 1.0) patients.
- Overall, median time to minimal pain was 3.4 hours (95% CI: 1.8, 5.3). Median time to minimal symptoms appeared similar for pre-pubertal (median: 2.4 hours; 95% CI: 1.9, 5.3) and pubertal/post-pubertal (median: 3.8 hours; 95% CI: 1.0, 6.8) patients.

Figure 9: HGT-FIR-086 Kaplan-Meier Plot of TOSR for FPS-R scores (efficacy population with FPS-R data)



Note: Onset of symptom relief for FPS-R was defined as at least 1 level of improvement in the posttreatment score compared to the pretreatment score. Subjects with pretreatment value of 0 were excluded from this analysis. Subjects who did not achieve symptom relief within the observation period were censored at the last observation time.

Table 14: Study HGT-FIR-086 Overview and line listing of efficacy results (efficacy population)

Subject ID	Sex/ Age/Race/ Attack #	Type of Attack	TOSR (hour)	TMS (hour)	FPS-R Onset (hour)	MFPSR (hour)	FLACC Onset (hour)	MFLACC (hour)	TISR (hour)
Pre-pubertal (Tanner Stage I)									
	M/11.8/W/1	ABDOMINAL	1.0	1.0	1.7	6.2			0.3
	M/ 8.2/W/1	CUTANEOUS	1.0	2.0	+	+			2.0
	F/ 9.5/W/1	CUTANEOUS	1.1	5.9	+	+			1.1
	M/11.6/W/1	ABDOMINAL	3.9	1.9	1.0	1.9			0.6
	M/11.4/W/1	CUTANEOUS	1.0	1.0	0.3	2.8			1.0
	F/11.3/W/1	CUTANEOUS	2.0	2.0	+	+			1.3
	F/ 3.4/W/1	CUTANEOUS	2.0	2.0			1.0	1.0	1.5
	M/ 3.7/W/1	CUTANEOUS	1.0	1.0			+	+	0.8
	F/ 7.2/W/1	CUTANEOUS	1.1	2.1	0.8	5.3			1.3
	F/ 7.9/W/1	CUTANEOUS	1.0	1.9	0.9	1.8			0.9
	M/ 8.6/W/1	ABDOMINAL	1.0	1.0	1.0	2.0			1.0
Pubertal/Post-pubertal (Tanner Stage II-V)									
	M/15.1/W/1	CUTANEOUS	1.0	1.0	1.0	1.0			0.6
	F/10.8/W/1	CUTANEOUS	1.0	1.0	0.0	0.0			1.0
	F/11.4/O/1	CUTANEOUS AND ABDOMINAL	1.0	x	4.7	4.7			1.0
	F/11.6/O/2	LARYNGEAL	4.0	x		3.0			4.0
	F/15.8/W/1	CUTANEOUS	1.0	1.0	#	3.8			0.7
	F/17.4/W/1	CUTANEOUS	1.0	1.0	#	4.4			1.0
	F/15.0/W/1	CUTANEOUS	2.0	2.0	1.0	1.0			0.6
	F/14.1/W/1	ABDOMINAL	1.1	1.1	0.6	1.4			0.3
	M/13.3/W/1	CUTANEOUS	0.8	0.8	0.9	3.4			0.8
	M/12.8/W/1	CUTANEOUS	2.0	4.0	0.6	19.6			1.5
	M/13.6/W/1	ABDOMINAL	1.0	1.0	1.0	6.8			1.0
	M/14.3/W/1	CUTANEOUS	2.0	6.2	2.0	44.0*			2.3

M = Male, F = Female, W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other, NA = Not applicable, TOSR = Time to Onset of Symptom Relief, TMS = Time to Minumum Symptom, FPS-R Onset = Time to Onset of Symptom Relief for FPS-R, MFPSR = Minimum Symptom Relief for FPS-R Scores FLACC Onset = Time to Onset of Symptom Relief for FLACC, MFLACC = Time to Minimum Symptom Relief for FLACC ScoresTISR = Time to Initial Symptom Relief. * = Subject was censored at that time point. # = Excluded because of pre-treatment value missing. + = Excluded becansue of pre-treatment value of zero. x = Excluded because of all Pre-treatment symptoms are either mild or absent.

FLACC (investigator-rated)

Two patients under 4 years were eligible for FLACC assessments. One patient who had a pre-treatment FLACC score of 0 was excluded from the time to event analyses.

- TOSR: 1.0 hour for the subject available for analysis.
- Time to minimum pain: 1.0 hour for the subject available for analysis.

Table 14, shown above, gives an overview and line listing of all results related to (TOSR) and time to minimal symptoms. Two participants < 4 years were assessed by the investigator as having pain relief.

Time to first use of rescue treatment

No participant in the efficacy population was administered rescue medication within 48 hours of icatibant administration.

Repeated treatment

One 11 year old, female, pubertal/post-pubertal patient had icatibant treatment for a second HAE attack. She received the second administration of icatibant 3 hours and 40 minutes following the onset of a laryngeal HAE attack. TOSR and the time to initial symptom relief were 4 hours. Time to onset of pain relief was also 4 hours. No rescue medication was needed.

Comparison of the paediatric efficacy results to adult efficacy results from previous studies

Due to the small sample size, subgroup analyses of stratified groups (for example, by age) were not conducted. The sponsor has provided a comparison to an adult population

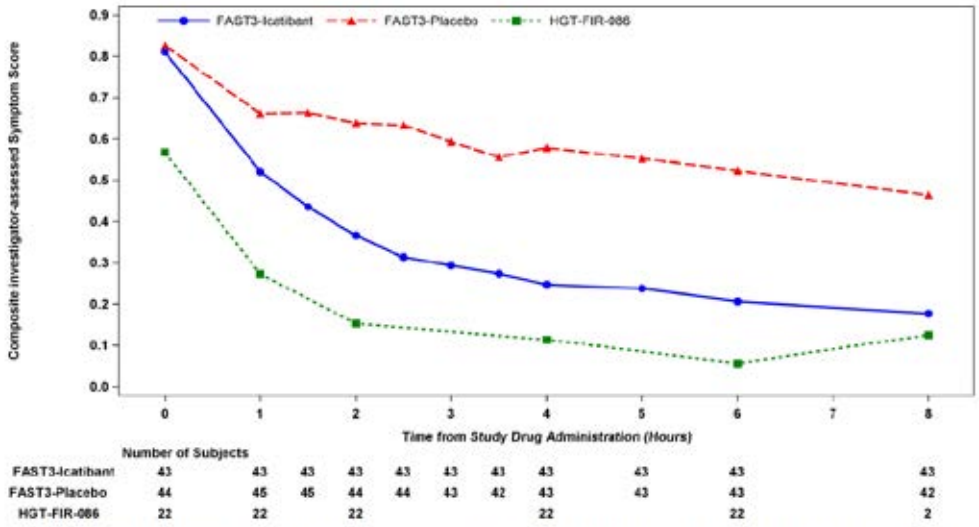
treated with Firazyr in Study HGT-FIR-054 (FAST3) (not part of the current dossier or application).

Study HGT-FIR-054 was a randomised, placebo controlled, double blind, parallel group study of adult patients with cutaneous, abdominal, or laryngeal HAE attacks. Patients received either icatibant 30 mg (0.4 mg/kg) or placebo by SC injection. The primary endpoint assessment was through a 3 item composite Visual Analog Score (VAS), comprised of averaged assessments of skin swelling, skin pain, and abdominal pain.

The median times for response (50% reduction from the pre-treatment composite 3 item VAS score) were 2.0 hours (95% CI: 1.5, 3.0) and 19.8 hours (95% CI: 6.1, 26.3) for icatibant (n = 43) and placebo (n = 45), respectively ($p < 0.001$) (cutaneous or abdominal HAE only).

Figure 10 provides a graphical representation of the comparison of the repose in paediatric patients in Study HGT-FIR-086, and the adult icatibant and adult placebo groups in Study HGT-FIR-054 (FAST3).

Figure 10: Study HGT-FIR-086 (efficacy population) versus HGT-FIR-054 (FAST3) (non-laryngeal intention to treat population) mean composite investigator-assessed symptom score over time



Note: Composite investigator-assessed symptoms score is calculated by taking an average of the 8 (cutaneous or abdominal attack) system assessment components

Safety

Only one study assessed the efficacy pertaining to this submission, namely Study HGT-FIR-086 (methods described above).

Study HGT-FIR-086

Tolerability and safety were assessed by injection site reactions (erythema, swelling, burning sensation, itching/pruritus, warm sensation, cutaneous pain) evaluated by the investigator, adverse events, vital signs, electrocardiogram (ECG), physical examination, clinical laboratory parameters (liver function tests, haematology, urinalysis).

Levels of follicle stimulating hormone (FSH), luteinising hormone (LH), oestradiol, progesterone for female participants and FSH, LH, testosterone for male participants were assessed pre-treatment, and 6 hours, 8 days, and 90 days post-treatment. Record of the timing of the blood sampling with respect to the menstrual cycle was required.

Anti-icatibant antibodies were assessed pre-treatment and Days 8 and 90 post-treatment.

All 32 of participants received at least one injection of the study drug and were included in the safety population. One participant received 2 doses.

The mean time (standard deviation (SD)) from attack onset to study drug administration was similar for pre-pubertal and the pubertal/post-pubertal patients: 5.65 (3.21) hours and 6.55 (4.45) hours respectively.

Overview of TEAEs

Treatment emergent adverse events (TEAEs) are summarised in Table 15 and Table 16.

Table 15: Study HGT-FIR-086 treatment emergent adverse events by severity (safety population)

	Prepubertal (N=11)		Pubertal/ Postpubertal (N=21)		Overall (N=32)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
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 which 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

AE=adverse event; ISR=injection site reaction; SAE=serious adverse event

Table 16: Study HGT-FIR-086 Treatment-emergent adverse events by SOC (safety population)

System Organ Class/ Preferred Term	Prepubertal (N=11)		Pubertal/ Postpubertal (N=21)		Overall (N=32)	
	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)	Events
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
Injury, Poisoning, and Procedural Complications	1 (9.1)	2	0	0	1 (3.1)	2
Epiphyseal fracture	1 (9.1)	1	0	0	1 (3.1)	1
Thermal burn	1 (9.1)	1	0	0	1 (3.1)	1
Investigations	1 (9.1)	1	1 (4.8)	1	2 (6.3)	2
Nitrite urine present	1 (9.1)	1	0	0	1 (3.1)	1
Protein urine present	0	0	1 (4.8)	1	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

Note: Subjects are counted only once within each SOC and PT.
Adverse events are coded using MedDRA, Version 16.0.
MedDRA=Medical Dictionary of Regulatory Activities; PT=preferred term; SOC=system organ class

Overall, a total of 32 TEAEs reported for 9 (28.1%) participants: 9 for 2 pre-pubertal patients (18.2%) and 23 for 7 (33.3%) pubertal/post-pubertal participants.

One pubertal/post-pubertal participant experienced 2 TEAEs assessed as possibly related to study drug (dry mouth and fatigue).

No participant experienced a severe TEAE, a treatment emergent serious adverse event (SAE) or an injection site reaction deemed an SAE. There were no deaths and no discontinuations.

The most frequent TEAEs were gastrointestinal (GI) disorders with 9 events recorded for 3 (9.4%) participants. Headache, experienced by 2 participants, was the only TEAE experienced by more than 1 individual. There were no TEAEs suggesting a deterioration of cardiac function.

The participant who received 2 doses of icatibant for separate episodes of HAE recorded no adverse events (AEs) following the second dose.

Injection site reactions

Injection site reactions are summarised in Table 17. The majority were mild or moderate in intensity. Almost all injection site reactions had resolved by 6 hours post-dose. Two pubertal/post-pubertal participants experienced severe injection reactions 1 hour post-dose (burning sensation, erythema and swelling); both resolved by 6 hours post-dose.

Table 17: Study HGT-FIR-086 Injection site reactions (safety population)

Injection Site Reaction	Icatibant Exposure n (%)
Pre-pubertal (n = 11)	
Any Reaction	9(81.8)
Erythema	9(81.8)
Swelling	7(63.6)
Warm Sensation	4(36.4)
Skin Pain	3(27.3)
Burning Sensation	1(9.1)
Itching/Pruritis	1(9.1)
Any Severe Reaction	0
Burning Sensation	0
Skin Pain	0
Erythema	0
Itching/Pruritis	0
Swelling	0
Warm Sensation	0
Pubertal/post-pubertal (n = 21)	
Any Reaction	20(95.2)
Erythema	18(85.7)
Swelling	15(71.4)
Burning Sensation	9(42.9)
Warm Sensation	6(28.6)
Skin Pain	4(19.0)
Itching/Pruritis	3(14.3)
Any Severe Reaction	2(9.5)
Erythema	2(9.5)
Burning Sensation	1(4.8)
Swelling	1(4.8)
Warm Sensation	1(4.8)
Skin Pain	0
Itching/Pruritis	0

Clinical laboratory values

Two participants had changes in laboratory values assessed as TEAEs: nitrate urine present; protein urine present. Both were considered mild in intensity and unrelated to the study drug.

Vital signs

No clinically meaningful changes were noted in temperature, pulse, blood pressure and respiratory rate.

ECG results

No participant was reported to have clinically significant change to ECG.

Immunogenicity

No participant was positive for anti-icatibant antibodies at any pre-specified study time point.

Female reproductive hormones

Results based on Tanner Stage assessment of pubertal status, and change from pre-treatment to Day 90 post-treatment are summarised in Table 18. Other than progesterone

levels in pre-pubertal participants, the majority were categorised as being within the normal range at all time points. Three pre-pubertal participants had low progesterone levels at pre-treatment, 6 hours post treatment, and Day 8 post treatment and 2 continued to have low levels of progesterone at Day 90.

Table 18: Study HGT-FIR-086 Reproductive hormone assessments (female subjects, safety population) (pubertal status defined by Tanner Stage)

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 Posttreatment	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 Posttreatment	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 Posttreatment	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 Posttreatment	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 Posttreatment	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 Posttreatment	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)
Luteinizing Hormone (miU/mL)									
Pretreatment	5	2.23 (3.25)		8	3.94 (2.69)		13	3.28 (2.91)	
6 hours Posttreatment	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 Posttreatment	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 Posttreatment	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/dL)									
Pretreatment	5	0.21 (0.22)		8	3.18 (5.22)		13	2.03 (4.26)	
6 hours Posttreatment	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 Posttreatment	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 Posttreatment	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)

FSH=follicle-stimulating hormone

Bracketed numbers are standard deviations. Change from pre-dose based on results from participants with pre-treatment and post-treatment results.

Based on a Data and Safety Monitoring Board (DSMB) recommendation, a *post hoc* analysis categorised participants into pubertal status based on the baseline reproductive hormone levels (Table 19).

Overall, the investigator concluded that there were no clinically significant changes observed over time.

Table 19: Study HGT-FIR-086 reproductive hormone assessments (female subjects, safety population) (pubertal status defined by laboratory levels)

Time	Prepubertal (N=4)			Pubertal/ Postpubertal (N=9)			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	4	3.04 (3.22)		9	54.18 (51.02)		13	38.45 (48.39)	
6 hours Posttreatment	4	1.58 (1.11)	-1.47 (2.48)	9	52.32 (48.15)	1.90 (25.89)	13	36.70 (46.26)	0.86 (21.24)
Day 8 Posttreatment	4	1.11 (0.73)	-1.93 (2.93)	9	35.99 (22.46)	-14.43 (43.18)	13	25.26 (24.84)	-10.59 (35.80)
Day 90 Posttreatment	1	1.70 (NA)	-1.13 (NA)	9	54.86 (31.48)	4.44 (44.30)	10	49.54 (34.11)	3.88 (41.80)
FSH (miU/mL)									
Pretreatment	4	1.76 (0.75)		9	4.93 (2.15)		13	3.96 (2.50)	
6 hours Posttreatment	3	1.40 (0.62)	-0.25 (0.39)	8	4.90 (2.71)	0.59 (2.24)	11	3.94 (2.81)	0.36 (1.92)
Day 8 Posttreatment	4	0.99 (0.30)	-0.77 (0.81)	9	5.11 (1.96)	0.66 (1.45)	13	3.84 (2.55)	0.22 (1.43)
Day 90 Posttreatment	2	1.85 (0.21)	-0.25 (0.35)	9	4.53 (2.17)	0.08 (2.64)	11	4.05 (2.23)	0.02 (2.37)
Luteinizing Hormone (miU/mL)									
Pretreatment	4	0.02 (0.01)		9	4.73 (2.25)		13	3.28 (2.91)	
6 hours Posttreatment	4	0.03 (0.03)	0.01 (0.02)	8	4.07 (2.72)	-0.34 (3.90)	12	2.72 (2.94)	-0.22 (3.11)
Day 8 Posttreatment	4	0.02 (0.01)	-0 (0.01)	9	4.98 (3.47)	0.70 (4.29)	13	3.45 (3.70)	0.49 (3.52)
Day 90 Posttreatment	2	0.03 (0)	0 (0)	9	4.70 (2.95)	0.43 (3.00)	11	3.85 (3.25)	0.35 (2.69)
Progesterone (ng/dL)									
Pretreatment	4	0.20 (0.25)		9	2.85 (4.98)		13	2.03 (4.26)	
6 hours Posttreatment	4	0.24 (0.27)	0.03 (0.04)	9	2.70 (4.84)	-0.23 (0.54)	13	1.94 (4.12)	-0.15 (0.46)
Day 8 Posttreatment	4	0.36 (0.56)	0.16 (0.31)	9	1.04 (1.34)	-1.88 (3.73)	13	0.83 (1.18)	-1.25 (3.20)
Day 90 Posttreatment	2	0.28 (0.29)	-0.05 (0.06)	9	1.96 (2.72)	-0.96 (3.56)	11	1.65 (2.53)	-0.80 (3.21)

Pubertal status classifications were based on reproductive hormone lab values.
and were reclassified as pubertal/postpubertal; was reclassified as prepubertal.
FSH=follicle-stimulating hormone; NA=not applicable; SD=standard deviation

Bracketed numbers are standard deviations. Change from pre-dose based on results from participants with pre-treatment and post-treatment results.

Male reproductive hormones

Results based on Tanner Stage assessment of pubertal status, and change from pre-treatment to Day 90 post treatment are summarised in Table 20. Levels for the majority of participants were categorised as normal at all time points.

Table 20: Study HGT-FIR-086 Reproductive hormone assessments (male subjects, safety population) (pubertal status defined by Tanner Stage)

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 Posttreatment	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 Posttreatment	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 Posttreatment	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)
Luteinizing Hormone (miU/mL)									
Pretreatment	6	0.30 (0.27)		11	3.00 (2.60)		17	2.03 (2.45)	
6 hours Posttreatment	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 Posttreatment	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 Posttreatment	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 Posttreatment	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 Posttreatment	6	31.62 (44.46)	19.65 (45.47)	13	290.59 (234.34)	2.99 (155.86)	19	208.81 (229.03)	8.86 (126.08)
Day 90 Posttreatment	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)

FSH=follicle-stimulating hormone

As for females, a *post hoc* analysis was conducted categorising participants into pubertal status according to baseline reproductive hormone levels (Table 21).

Table 21: Study HGT-FIR-086 reproductive hormone assessments (male subjects, safety population) (pubertal status defined by laboratory levels)

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	1.47 (0.98)		11	3.65 (2.33)		17	2.88 (2.20)	
6 hours Posttreatment	5	1.12 (0.79)	-0.30 (0.34)	13	3.50 (2.39)	0.09 (0.79)	18	2.84 (2.32)	-0.03 (0.69)
Day 8 Posttreatment	6	1.30 (1.13)	-0.17 (0.58)	13	3.55 (2.27)	0.17 (0.52)	19	2.84 (2.22)	0.05 (0.55)
Day 90 Posttreatment	5	1.35 (1.23)	-0.06 (0.65)	12	3.80 (2.79)	0.46 (1.13)	17	3.08 (2.66)	0.28 (1.00)
Luteinizing Hormone (mIU/mL)									
Pretreatment	6	0.21 (0.17)		11	3.02 (2.55)		17	2.03 (2.45)	
6 hours Posttreatment	5	0.13 (0.19)	-0.06 (0.09)	13	2.89 (1.95)	-0.13 (2.28)	18	2.12 (2.07)	-0.11 (1.87)
Day 8 Posttreatment	6	0.37 (0.66)	0.15 (0.52)	13	3.38 (2.70)	0.37 (1.26)	19	2.43 (2.65)	0.29 (1.04)
Day 90 Posttreatment	5	0.22 (0.42)	0.02 (0.28)	12	3.27 (1.63)	0.19 (1.46)	17	2.37 (1.98)	0.14 (1.18)
Testosterone (ng/dL)									
Pretreatment	6	8.6 (11.96)		11	319.49 (269.54)		17	209.76 (262.50)	
6 hours Posttreatment	5	3.36 (1.76)	-0.43 (0.99)	13	219.55 (198.23)	-94.61 (187.09)	18	159.50 (194.08)	-65.18 (159.27)
Day 8 Posttreatment	6	21.59 (41.81)	12.93 (44.25)	13	295.25 (228.74)	6.65 (156.34)	19	208.81 (229.03)	8.86 (126.08)
Day 90 Posttreatment	5	5.81 (5.61)	2.02 (3.80)	12	288.05 (184.86)	-12.70 (185.86)	17	205.04 (202.67)	-7.79 (149.21)

Pubertal status classifications were based on reproductive hormone lab values.
was reclassified as pubertal/postpubertal; was reclassified as prepubertal.
FSH=follicle-stimulating hormone

Overall, the investigator concluded there were no clinically significant changes in reproductive hormones were observed.

Post-market data

Periodic safety update reports (PSUR)/periodic benefit-risk evaluation reports (PBRER) appear not to have been provided in the dossier.

Risk management plan

Safety specification, pharmacovigilance and risk minimisation activities[5]

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 22.

[5] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 22: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Injection site reactions	ü	ü	ü	–
Important potential risks	Deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism	ü	ü	ü	–
	Partial bradykinin agonism (excluding injection site reactions)	ü	ü	ü	–
	Antigenicity manifesting as drug hypersensitivity and lack of efficacy	ü	ü	ü	–
	Lack of efficacy	ü	ü	ü	–
	Medication errors	ü	ü	ü	–
	Effect on reproductive hormone levels in pubertal/ post-pubertal children*	ü	ü	ü	–
Missing information	Use in pregnant and lactating women	ü	ü	ü	–
	Use in children below 2 years of age	ü	ü	ü	–

*safety concern not included in the ASA for risk minimisation

Routine pharmacovigilance activities are proposed for all safety concerns.

There is one additional pharmacovigilance activity assigned to all Safety Concerns and Missing Information items: A prospective, long-term Icatibant Outcome Survey (NCT01034969);[6] which is a voluntary registry, is being carried out to gain a better understanding of the long-term safety of icatibant treatment in real-world clinical practice.

Only routine risk minimisation measures have been proposed. Routine risk minimisation measures are acceptable to mitigate the risks associated with this product.

Recommended condition/s of registration

The Firazyr EU-Risk Management Plan (RMP) (version 6.2, dated 13 July 2017, data lock point 31 May 2016), with Australian Specific Annex (version 1.1, dated 15 February 2019), included with submission PM-2018-0250-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

[6] https://clinicaltrials.gov/ct2/show/NCT01034969

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

As the indications for Firazyr are being extended into a significantly different population it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Firazyr (Icatibant) is to be included in the Black Triangle Scheme. The PI and Consumer Medicines Information (CMI) for Firazyr must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

Risk-benefit analysis

Delegate's considerations

Discussion

Main issues

The main issues in this submission are as follows:

- Efficacy data paucity, in particular with regard to children aged 2 to 5 years;
- Safety data paucity, in particular with regard to reproductive hormone assessment; and
- Dosing regimen, weight based dosing versus step dosing.

These are discussed below.

Efficacy

HAE is a relatively rare condition, and this makes it difficult to recruit a large number of patients. This particularly applies to children under 5 years, as first clinical symptoms often only occurring at an older age.

In StudyHGT-FIR-086, there were only 2 patients in the 2 to < 5 year age group with the youngest patient aged 3.4 years. Despite this, the sponsor proposes to include that age group in the indications.

Only one study provided efficacy results, namely Study HGT-FIR-086. The study was open label; there was no control group and hence no randomisation or statistical comparison between groups. The assessment of efficacy was constrained by the low number of paediatric HAE patients, in particular in younger patients. It may not have been appropriate to assign some patients to a non-active placebo group, but a comparison to an active treatment group could have been possible, but was not undertaken.

Despite the limitations, the efficacy and safety endpoints appeared to be appropriate and allowed the assessment of the therapeutic use of Firazyr in HAE and a limited comparison to use in adults.

In Study HGT-FIR-086, at 1 hour post treatment, approximately 50% of participants recorded symptom relief; at 2 hours post treatment approximately 90% of participants had experienced symptom relief. This was similar for both pre- and post-pubertal patients.

There appeared to be a beneficial pattern favouring Firazyr, but this could not be assessed against a control group.

No patients with laryngeal HAE receiving single-dose icatibant were included in Study HGT-FIR-086, and even if efficacy could be reasonably extrapolated, the longer onset time may not be suitable for more severe cases of laryngeal HAE. One patient who received a second dose for a subsequent HAE episode had laryngeal symptoms, but the TOSR and time to minimal symptoms were 4 hours.

Safety

Only one study provided safety data, namely Study HGT-FIR-086. No new safety signals emerged from that study. However, given the small sample size, the probability of rare (or even more common) adverse events to emerge was relatively low. In this case, the absence of adverse drug reactions in this study is not evidence of absence.

Safety has been studied for dose of 0.4 mg/kg. Some patients administered treatment using the five band regimen based on results of population PK modelling will be treated with up to twice the studied dose. However, even at those doses, population PK modelling indicates that the exposes would likely be lower compared to adult exposure.

Repeat use

There is no safety data on repeated use (with the exception of one study participant who received icatibant twice), or data on how frequent icatibant could be used safely.

Effect on reproductive hormones

There is potential for icatibant to have an effect on reproductive hormones. Some of the nonclinical studies showed an effect on reproductive hormones in animals, but at much higher equivalent doses. The implications for clinical use remain unknown (in particular for repeat use or longer-term effects after a sporadic use), and potential reproductive problems may only become apparent after years.

The investigation in Study HGT-FIR-086 only showed inconclusive results, mainly due to the low sample size, and lack of complete data for some patients, and the single dose administration. In the clinical evaluation report, the evaluator stated that for females, a single dose of icatibant may have the potential to decrease oestradiol, FSH and LH. In males, FSH levels dropped from baseline at each subsequent measurement. This was similar for testosterone, but there appeared to be a rebound to 2 to 3 times the pre-treatment level.

In the study of icatibant in adults (Study HGT-FIR-062) (not part of this submission), effects on reproductive hormones were also investigated, but the study was not powered to detect differences.

Effect on cardiac function

There is a potential for deterioration of cardiac function under ischaemic conditions due to bradykinin antagonism, and a theoretical risk regarding cardiac structural development following frequent, repeated use over years. Additionally, there may be a theoretical risk of cardiac function impairment in the presence of hypoxia due to airway compromise during laryngeal attacks of HAE.

Mitigation

The sponsor intends to monitor safety and efficacy data in children and adolescents through an international observational study (Icatibant Outcome Survey) recording the

safety and effectiveness of Firazyr treatment, and through its post-market pharmacovigilance activities.

However, the method of assessing reproductive outcomes has not been stated. Adverse reproductive outcomes may not be apparent for decades. The clinical evaluator recommended that a systematic approach is taken to the post-market evaluation of the safety concerns outlined in the RMP safety specification, including potential effects on heart muscle in the event of hypoxia, heart muscle growth over time and reproductive hormones, at least until patients reach maturity.

Dosing

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.

The proposed five weight band dosing regimen appears to be a compromise between weight based dosing (and its associated potential for medication errors) and the three weight band dosing (and its associated potential for larger deviations from the doses tested in the clinical studies).

From the population PK/PD modelling the exposure (AUC) in the five weight band dosing regimen appears higher relative to the weight based regimen. In the AUC versus age graph this is more prominent until approximately age 12 years. In the AUC versus weight graph, weight band dosing exposure is higher in each weight band at the lower end of the band, but converges with the exposure of the weight based regimen to at the upper end of the band, as expected.

The dose proposed for registration is higher for many patients than that used in the study, twice as high (approximately 0.8 mg/kg) for patients weighing 12 kg. And for patients aged 2 to 3.4 years, there was no observed data for the model. Exposure did not appear to approach that of 0.4 mg/kg dosing until about 6 to 8 years. The range of 2 to 8 years is a range in which considerable development occurs in number organ systems, including reproductive systems. It is unclear whether potential reproductive effects would be exposure dependent.

The dose band for patients weighing 12 to 25 covers approximately the 2 to 8 year age range, that is, about one third of the total proposed paediatric population. This is the third with the most organ system development to undergo and there is no subtlety of dose allowed. To reflect this, the clinical evaluator had considered the possibility of adding an additional weight band (with appropriate dosing) for the lightest patients (for example, 12 to 17 kg). However, such an approach may require an alternative syringe system to reliably administer amounts under 1 mL, and would misalign the Australian dosing with the currently approved paediatric dosing in the EU and Switzerland.

However, the exposure of either of the two regimens appears to be consistently lower compared to the adult exposure without apparent reduction in clinically relevant efficacy, although those in the lowest tertile of exposure in the small number of participants studied, appeared to take longest to respond. From the data provided, the therapeutic window appears to be relatively large.

Summary of issues

The main issues in this submission are as follows:

- Efficacy data paucity, in particular with regard to children aged 2 to 5 years;
- Safety data paucity, in particular with regard to reproductive hormone assessment; and
- Dosing regimen, weight-based dosing versus step dosing.

Proposed action

The Delegate had no reason to say, at this time, that the application for Firazyr should not be approved for registration for the paediatric indication sought.

Request for Advisory Committee on Medicines (ACM) advice

1. Given the relative data paucity for children in the 2 to 5 year age group, should the indication be restricted (for example, to age 3 and above, or age 5 and above)?
2. Is the proposed five weight band dosing regimen appropriate, in particular for patients at the lower end of the weight spectrum (for example, 12 to 17 kg)?
3. The ACM is invited to provide any other comments with regard to this submission.

Advisory committee considerations[7]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Firazyr, an injection pre-filled syringe, containing 30 mg/3 mL of icatibant as acetate.

The ACM agreed that Firazyr had an overall positive benefit-risk profile for the indication:

> *FIRAZYR is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase.*

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. Given the relative data paucity for children in the 2 to 5 year age group, should the indication be restricted (for example to age 3 and above, or age 5 and above)?

The ACM noted that HAE is a rare condition in children and therefore it is difficult to recruit a large number of patients to clinical studies. The ACM also noted that icatibant is a bradykinin type 2 receptor antagonist and that the mechanism of action is unlikely to differ physiologically between a 2 year old child compared to a 3 year old child.

Given the demonstrated efficacy and positive response to icatibant in all age groups; the severity of attacks; the infrequent use; the rapid time to onset of symptom relief; the transient nature of adverse effects; and no new safety signals in post market surveillance, the ACM was of the view that the potential for significant benefits should be extended to children 2 years and older.

The ACM agreed that the PI should outline the paucity of data in younger age groups and the uncertainties in relation to repeat dosing and the potential effects on reproductive hormones.

[7] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

2. Is the proposed five weight band dosing regimen appropriate, in particular for patients at the lower end of the weight spectrum (for example, 12-17 kg)?

The ACM noted that the proposed dosing schedule was approved in the EU and Switzerland. The ACM was of the view that, although not ideal, the benefit of the five weight dosing regimen may outweigh the risk of dosing errors with weight based dosing. The ACM advised that while patients at the lower end of the weight spectrum may receive a higher effective dose using the weight band dosing regimen, there was no evidence that this increased dose presented a clinical risk.

3. The ACM is invited to provide any other comments with regard to this submission.

The ACM advised that the proposed product may provide benefits to patients in rural and remote areas as it provides a timely and more accessible treatment option for carers, compared to the current approved treatment via intravenous injection which usually requires hospitalisation.

Outcome

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

> *Firazyr is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children aged 2 years and older with C1-esterase-inhibitor deficiency.*

Specific conditions of registration applying to these goods

- Firazyr (icatibant) is to be included in the Black Triangle Scheme. The PI and CMI for Firazyr must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.
- The Firazyr EU-Risk Management Plan (RMP) (version 6.2, dated 13 July 2017, data lock point 31 May 2016), with Australian Specific Annex (version 1.1, dated 15 February 2019), included with submission PM-2018-02506-1-2, and any subsequent revisions, as agreed with the TGA, will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.
- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Firazyr approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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