London, 18 October 2018
EMA/169006/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Hizentra

human normal immunoglobulin

Procedure no: EMEA/H/C/002127/P46/024

Note

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

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Table of contents

1. Introduction

On 03 August 2018 the MAH submitted a completed study for Hizentra that includes biweekly dosing in paediatric PID patients, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that IgPro20_4005: Study of immune deficiency patients treated with subcutaneous immunoglobulin (IgPro20, Hizentra®) on weekly and biweekly schedules is a stand-alone study.

Bi-weekly dosing for all ages groups was licensed in the EU with variation II/0024 based on pharmacometric data. This led to a change in the wording of Section 5.2.

In Canada an additional small clinical study was required. Since this small study contained paediatric PID subjects, the MAH submitted this Canadian study in compliance with Article 46 of the 'Paediatric Regulation'.

2.2. Information on the pharmaceutical formulation used in the study

IgPro20 is a ready-to-use 20% protein liquid formulation of a polyvalent human immunoglobulin G (IgG) preparation for subcutaneous administration (SCIG).

Commercially available Hizentra (IgPro20) was used for this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a report for:

- IgPro20_4005 - Study of immune deficiency patients treated with subcutaneous immunoglobulin (IgPro20, Hizentra®) on weekly and biweekly schedules

2.3.2. Clinical study

IgPro20_4005
Study of immune deficiency patients treated with subcutaneous immunoglobulin (IgPro20, Hizentra®) on weekly and biweekly schedules

Description

This Phase 4, open-label, single-sequence, crossover, post-marketing study, which lasted ~ 15 months, investigated the PK, safety and efficacy of weekly and biweekly schedules of s.c. Hizentra in 25 PID/SID patients

Methods

Objectives

Primary Objectives

• To determine tolerability and safety of a biweekly Hizentra injection regimen and to assess pharmacokinetic (PK) characteristics of weekly and biweekly Hizentra therapy.

Secondary Objectives:

• To determine efficacy of a biweekly Hizentra injection regimen.

• To evaluate the dose of biweekly Hizentra injections needed for subjects switching from weekly Hizentra therapy to biweekly therapy.

• To assess the quality of life (QoL) of subjects on biweekly Hizentra injections.

Study design

In **Part 1**, all subjects were observed for 12 weeks on a weekly Hizentra home infusion treatment regimen.

In **Part 2**, subjects were observed for up to 52 weeks on a biweekly Hizentra home infusion treatment regimen. Part 2 of the study began immediately after the end of Part 1, with the first biweekly Hizentra infusion occurring 2 weeks after the last weekly infusion of Hizentra.

A separate PK sub-study was performed in 14 patients to satisfy post-approval request from Health Canada "to validate the PK model predictions by real human data".

Study population /Sample size

Twenty-five (25) patients were to be included, who had a documented diagnosis of primary immune deficiency (PID) or secondary immune deficiency (SID), who were on a stable dosing regimen of immunoglobulin (IgG) replacement therapy for at least 3 months at screening. Patients with SID were expected to require immune replacement therapy for at least 18 months at study entry.

Treatments

Hizentra
The biweekly dose in Part 2 was equal to twice the individual weekly dose subjects received in Part 1.

Concomitant treatment with plasma or other blood products including any IgGs other than Hizentra within 21 days prior to study entry and during the study was not allowed.

Outcomes/endpoints

Primary Endpoint:

• Annualized rate of local and systemic adverse events (AEs) during the biweekly treatment period.

Secondary Endpoints:

• Annualized rate of infections per subject during weekly and biweekly Hizentra therapies

• SF-36 (Short Form 36, v2)

• CHQ-PF28 (Child Health Questionnaire Parent Form 28): for age < 10 years

· CHQ-CF87 (Child Health Questionnaire Child Form 87): for age ≥ 10 years

Assessor's comment

The secondary endpoint "Annualized rate of infections per subject" does not differentiate between serious bacterial infections and "other infections".

However, as no serious bacterial infections were recorded in either the adult or the paediatric populations, this is a moot point.

Statistical Methods

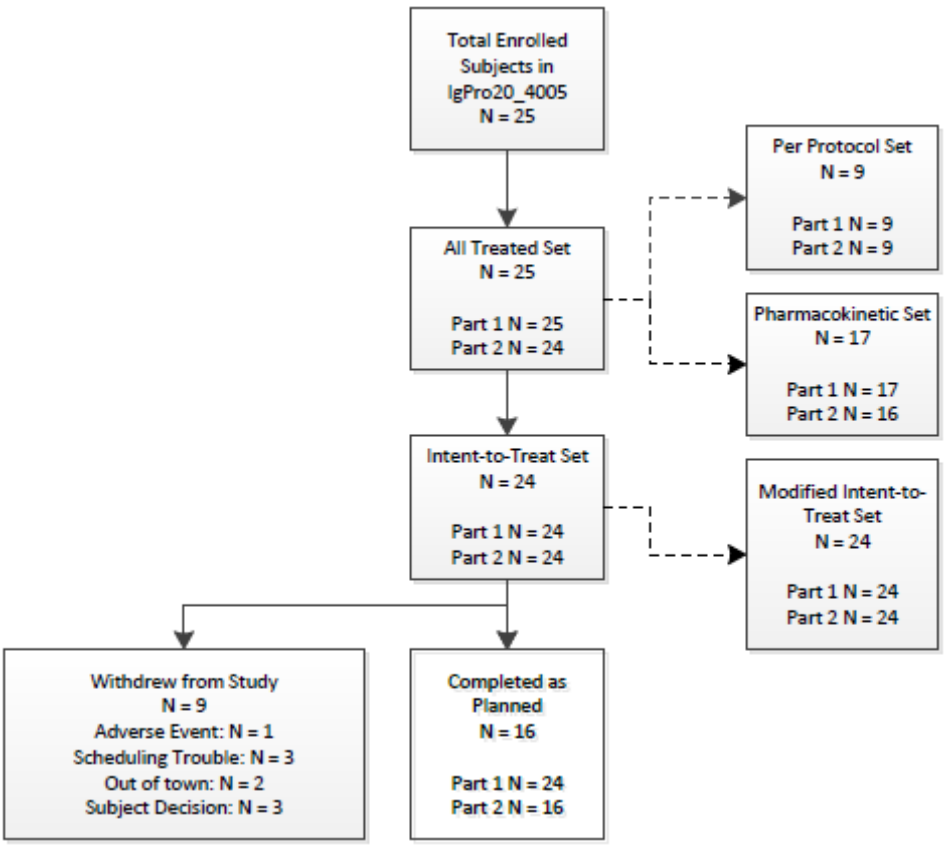
No formal sample size calculation was performed.

No formal statistical tests of hypothesis were planned for the primary or secondary endpoints. Statistical analyses and conclusions were based on descriptive statistics of the study data. The assessment of safety, tolerability and efficacy of biweekly Hizentra therapy, evaluation of the biweekly Hizentra therapy for subjects who switch from a weekly to a biweekly regimen, and QoL assessments were based on the review of subject listings and descriptive statistics.

Results

Recruitment/ Number analysed

A total of 25 subjects were enrolled in the study and treated in Part 1. Of these, 24 (96.0%) were treated in Part 2. A total of 16 subjects (64.0%) completed the study and 9 subjects (36.0%) withdrew (see below). Of the 16 subjects who completed the study, 9 subjects (36.0% of the enrolled population) completed the study per protocol.



Protocol violations

Table 10-1 Major protocol deviations

Type of Protocol Deviation	Screened Analysis Set N = 26 n (%)
Total subjects with major protocol deviation[a]	16 (61.5)
Treatment schedule	12 (46.2)
Planned number of infusions	7 (26.9)
Did not start biweekly regimen	1 (3.8)

Assessor's comment

The PP population that completed the study (n=9) is small, and the protocol deviations are prevalent (61%), so that the value of the study is questionable. However, this study is merely seen as "nice to know" since the biweekly dosing is already granted in in the EU and the current findings do not in any way contradict that evaluation.

Baseline data

Demographics

There were 14 male subjects (56.0%) and 11 female subjects (44.0%) in the All Treated Subjects analysis set (ATS) and almost all subjects were white (24 subjects, 96.0%). The mean (range) age was 23.6 (6 to 66) years.

Fifteen (of 25) were paediatric subjects:

- < 12 y – n=8
- ≥12 to < 16 y – n= 3
- ≥16 to < 18 y – n= 4

The mean (range) baseline body weight was 57.28 (19.0 to 96.0) kg and the mean body mass index (range) was 22.41 (13.7 to 37.0) kg/m2. Half of the subjects (13 subjects, 52.0%) were reported to be diagnosed with common variable immunodeficiency, 2 subjects (8.0%) were reported to be diagnosed with severe combined immunodeficiency, and 10 subjects (40.0%) were reported to be diagnosed with other immunodeficiencies.

The concomitant medications most frequently used at any time during the study were anti-bacterials for systemic use (16 subjects, 64.0%), analgesics (10 subjects, 40.0%), and drugs for obstructive airway diseases (8 subjects, 32.0%). All other concomitant medications were reported in < 30% of subjects

Assessor's comment
The patient population is considered to be representative for PID.

Efficacy results

The annualized rate of infections per subject during biweekly treatment for up to 52 weeks of dosing was 1.22; by age group, annualized rates were largely similar to those of the full study population.

Table 11-3 Annualized rate of infections by treatment regimen - ATS

Statistic	Part 1 (weekly treatment) (N = 25)	Part 2 (biweekly treatment) (N = 24)	Total (N = 25)
Number of subjects with any infection, n (%)	12 (48.0)	13 (54.2)	18 (72.0)
Total number of infections	16	17	33
Study days in treatment regimen[a]	2414	6878	9268
Annualized rate of infections[b]	2.42	0.90	1.30
Annualized rate of infections per subject			
Mean (SD)	2.43 (3.146)	1.22 (1.641)	1.41 (1.501)
Median	0	1.02	0.83
Minimum, Maximum	0, 11.91	0, 5.14	0, 6.23

ATS = All Treated Subjects Analysis Set; SD = Standard Deviation.

[a] The first day of the biweekly treatment regimen is counted in both Parts 1 and 2; therefore the sum of Part 1 and Part 2 does not equal the Total study days.

[b] The annualized rate of infections was calculated as the number of infection episodes in the respective regimen divided by the study days in the respective treatment regimen multiplied by 365.25.

Notes: The scheduled duration of the weekly regimen is 12 weeks compared to 52 weeks for the biweekly regimen. As the risk of observing an infection changes with time, the comparison may be biased.

All subjects started with the weekly regimen (Part 1) and were subsequently to be treated in the biweekly regimen (Part 2), thus subjects in Part 2 are a subset of subjects in Part 1. The total column refers to the whole study period.

Table 11-4 **Annualized rate of infections by treatment regimen and by age group - ATS**

Statistic	Part 1 (weekly treatment) (N = 25)	Part 2 (biweekly treatment) (N = 24)	Total (N = 25)
< 12 years old (N)	8	8	8
Number of subjects with any infection, n (%)	5 (62.5)	4 (50.0)	7 (87.5)
Total number of infections	7	5	12
Study days in treatment regimen[a]	766	2246	3004
Annualized rate of infections[b]	3.34	0.81	1.46
Annualized rate of infections per subject			
Mean (SD)	3.40 (3.926)	1.16 (1.779)	1.60 (1.302)
Median	3.69	0.51	1.22
Minimum, Maximum	0, 11.91	0, 5.14	0, 4.13
12 to <18 years old (N)	7	7	7
Number of subjects with any infection, n (%)	2 (28.6)	4 (57.1)	4 (57.1)
Total number of infections	2	5	7
Study days in treatment regimen[a]	649	2001	3643
Annualized rate of infections[b]	1.13	0.91	0.97
Annualized rate of infections per subject			
Mean (SD)	1.13 (1.939)	1.33 (1.849)	1.03 (1.093)
Median	0	1.04	0.83
Minimum, Maximum	0, 4.06	0, 5.14	0, 2.43
≥ 18 years old (N)	10	9	10
Number of subjects with any infection, n (%)	5 (50.0)	5 (55.6)	7 (70.0)
Total number of infections	7	7	14
Study days in treatment regimen[a]	999	2631	3621
Annualized rate of infections[b]	2.56	0.97	1.41

Annualized rate of infections per subject			
Mean (SD)	2.57 (3.122)	1.18 (1.547)	1.51 (1.933)
Median	1.52	1.04	0.83
Minimum, Maximum	0, 7.94	0, 4.30	0, 6.23

ATS = All Treated Subjects Analysis Set; SD = Standard Deviation.

[a] The first day of the biweekly treatment regimen is counted in both Parts 1 and 2; therefore the sum of Part 1 and Part 2 does not equal the Total study days.

[b] The annualized rate of infections was calculated as the number of infection episodes in the respective regimen divided by the study days in the respective treatment regimen multiplied by 365.25.

Notes: The scheduled duration of the weekly regimen is 12 weeks compared to 52 weeks for the biweekly regimen. As the risk of observing an infection changes with time, the comparison may be biased.

All subjects started with the weekly regimen (Part 1) and were subsequently to be treated in the biweekly regimen (Part 2), thus subjects in Part 2 are a subset of subjects in Part 1. The total column refers to the whole study period.

Assessor's comment

The mean annualized rate of infections per subject was comparable between the age groups (paediatric patients (~1.3) vs. adults (~1.5)) and there was trend to more infections in the 1-weekly (2.43) compared to the biweekly (1.22) dosing.

No serious bacterial infections were recorded in either the adult or the paediatric populations.

Mean IgG concentrations during biweekly dosing remained consistent with IgG concentration during pre-study treatment and weekly dosing.

Table 11-5 IgG serum concentration by treatment regimen over time - ATS

Statistic	At diagnosis (historic) (N = 25)	Pre-study (within 6 months before enrollment) (N = 25)	Part 1, Week 6 (N = 25)	Part 2, Week 12 (N = 25)	Part 2, Week 24 (N = 25)	Part 2, Week 48 (N = 25)
N with data	24	21	17	19	20	19
Geometric mean (GM SD)	3.51 (3.170)	9.89 (1.197)	10.16 (1.184)	9.92 (1.186)	10.20 (1.270)	10.10 (1.253)

ATS = All Treated Subjects Analysis Set; GM SD = Geometric Mean Standard Deviation.

Assessor's comment

We concur with the applicant that the biweekly treatment regimen comprising of twice the prescribed weekly dose provided adequate Hizentra exposure during the course of the 52 week study.

Safety results

Exposure

By nature of the study design, there were more infusions per subject-years in Part 1 than Part 2 and the mean (range) of the intra-individual median dose in Part 2 (218.62 [113.0 to 473.0] mg/kg bw) was almost twice that of at Part 1 (112.14 [52.0 to 239.7] mg/kg bw).

The mean (range) volume per injection site was 12.8 (5 to 27) mL for Part 1 and 14.5 (3 to 37) for Part 2. The mean (range) of the intra-individual median duration of infusion on each treatment day was somewhat longer during Part 2 (1.23 [0.4 to 2.5] hours) than Part 1 (0.94 [0.3 to 3.9] hours).

Adverse events

A total of 22 subjects (91.7%) experienced any AE during Part 2 and 20 subjects (80.0%) experienced any AE during Part 1. There were no severe AEs and no related SAEs in either group. One unrelated SAE of gastroenteritis occurred in the study affecting a PID child.

Table 12-2 Overview summary of treatment emergent adverse events - ATS

	Part 1 (weekly treatment) (N = 25) n (%)	Part 2 (biweekly treatment) (N = 24) n (%)	Total (N = 25) n (%)
Any AE	20 (80.0)	22 (91.7)	24 (96.0)
Any local AEs	2 (8.0)	3 (12.5)	4 (16.0)
Severity of AEs			
Mild AEs	19 (76.0)	22 (91.7)	24 (96.0)
Moderate AEs	4 (16.0)	10 (41.7)	11 (44.0)
Severe AEs	0	0	0
Related AEs	4 (16.0)	3 (12.5)	6 (24.0)
Temporally associated AEs	10 (40.0)	16 (66.7)	19 (76.0)
Related or temporally associated AEs	11 (44.0)	16 (66.7)	19 (76.0)
Serious AEs	0	1 (4.2)	1 (4.0)
Related serious AEs	0	0	0
Temporally associated serious AEs	0	0	0
Related or temporally associated AEs	0	0	0
AEs leading to death	0	0	0
AEs leading to withdrawal of study drug	0	0	0
AEs leading to study discontinuation	0	1 (4.2)	1 (4.0)

AE = Adverse Event; ATS = All Treated Subjects Analysis Set.

Notes: One AE (Subject 15, arthralgia) was assigned to both study periods as unambiguous assignment to a treatment period was not possible due to an incomplete AE start date.

If due to partial AE date/time information, a temporal association cannot be ruled out, the AE was conservatively assigned as temporally associated.

All subjects started with the weekly regimen (Part 1) and were subsequently to be treated in the biweekly regimen (Part 2), thus subjects in Part 2 are a subset of subjects in Part 1. The total column refers to the whole study period.

Assesor's comment:

Related or temporally associated AEs were more pronounced in the biweekly group compared to the once weekly group (66.7 % vs 44.0%). However, the numbers evaluated are fairly small to draw clear conclusions. It cannot be excluded that the higher dose may affect this variable.

Discontinuation

One AE in Part 2 led to discontinuation of a child, who experienced a migraine (mild/related) that lasted 60 days. The regimen was changed to weekly and the subject was withdrawn from the study.

Local AEs

Four subjects (16.0%) experienced at least 1 local AE during the study. The overall annualized rate of local AEs per patient year was 0.30 for Part 1, 0.21 for Part 2, and 0.24 for the whole study. Per subject, the mean annualized rate of local AEs was 0.32 for Part 1, 0.18 for Part 2, and 0.26 for the whole study.

In Part 1, the mean annualized rate of local AEs per subject in subjects < 12 years old was 0.49 and in subjects ≥ 18 years old was 0.40. In Part 2, the mean annualized rate of local AEs per subject in subjects < 12 years old was 0.13 and in subjects ≥ 18 years old was 0.35. The mean annualized rate of local AEs per subject for the whole study was 0.41 in subjects < 12 years old and 0.33 in subjects ≥ 18 years old. No subjects 12 to < 18 years old experienced a local AE.

Assesor's comment:

Seemingly, the annualized rate of local AEs (in Part 2 slightly less than in Part 1) did not account for the trend for higher rates seen in Part 2 for related or temporally associated AEs

AEs per infusion

The rate of AEs per infusion was 0.116 for Part 2, 0.139 for Part 1 and 0.124 for the whole study. The rate of local AEs per infusion was the same (0.008) for Part 2 and for the whole study and 0.006 for Part 1.

Type of AE

Table 12-5 **Adverse events occurring in at least 5% of the subjects in at least one treatment regimen by SOC and PT - ATS**

SOC PT	Part 1 (weekly treatment) (N = 25) n (%)	Part 2 (biweekly treatment) (N = 24) n (%)	Total (N = 25) n (%)
Gastrointestinal disorders			
Abdominal pain	1 (4.0)	3 (12.5)	3 (12.0)
Nausea	2 (8.0)	2 (8.3)	3 (12.0)
Infections and infestations			
Ear infection	2 (8.0)	0	2 (8.0)
Nasopharyngitis	5 (20.0)	4 (16.7)	9 (36.0)
Sinusitis	1 (4.0)	3 (12.5)	3 (12.0)
Upper respiratory tract infection	3 (12.0)	1 (4.2)	4 (16.0)
Musculoskeletal and connective tissue disorders			
Arthralgia	3 (12.0)	2 (8.3)	4 (16.0)
Tendonitis	0	2 (8.3)	2 (8.0)
Nervous system disorders			
Headache	5 (20.0)	1 (4.2)	5 (20.0)
Migraine	0	2 (8.3)	2 (8.0)

ATS = All Treated Subjects Analysis Set; PT = Preferred Term; SOC = System Organ Class.

Notes: One AE (Subject 15, arthralgia) was assigned to both study periods as unambiguous assignment to a treatment period was not possible due to incomplete AE start date.

All subjects started with the weekly regimen (Part 1) and were subsequently to be treated in the biweekly regimen (Part 2), thus subjects in Part 2 are a subset of subjects in Part 1. The total column refers to the whole study period.

Related AEs

Table 12-7 Incidence of subjects with causally related adverse events by treatment regimen - ATS

SOC PT	Part 1 (weekly treatment) (N = 25) n (%)	Part 2 (biweekly treatment) (N = 24) n (%)	Total (N = 25) n (%)
Any related AE	4 (16.0)	3 (12.5)	6 (24.0)
General disorders and administration site conditions	3 (12.0)	2 (8.3)	4 (16.0)
Fatigue	1 (4.0)	0	1 (4.0)
Injection site bruising	1 (4.0)	0	1 (4.0)
Injection site erythema	0	1 (4.2)	1 (4.0)
Injection site mass	0	1 (4.2)	1 (4.0)
Injection site pain	1 (4.0)	0	1 (4.0)
Nervous system disorders	1 (4.0)	1 (4.2)	2 (8.0)
Migraine	0	1 (4.2)	1 (4.0)
Paraesthesia	1 (4.0)	0	1 (4.0)

Assessor's comment

Most AEs were related to the underlying PID disorder.

Drug related AEs were comparable between the 2 treatment schedules and encompassed known ADRs for SCIGs, (mainly injection site reactions, and nervous system disorders in individual patients).

The mean annualized rates for local AEs showed comparable results for the 2 treatment schedules and between the age groups.

Quality of Life

Quality of life was assessed using the Short-Form 36 (SF-36; adults), Child Health Questionnaire Child Form 28 (CHQ-PF28; children < 10 years), and Child Health Questionnaire Child Form 87 (CHQ-CF87; children ≥ 10 years).

In adults (n=9) there was a slight trend for a decrease in the mental and physical scores from the beginning of Part 1 to the end of Part 2, albeit with large standard deviations.

In children <10 (CHQ-PF28) (n=6 at the beginning of Part 1; n=3 at the end of Part 2) the summary scores decreased slightly throughout the study. This was not deemed to be clinically relevant

For the CHQ-PF87 for children > 10 years of age (n= 9 at the beginning of Part 1; n=5 at the end of Part 2) summary scores do not exist; in general, individual scale scores remained stable throughout the study.

Assessor's comment

No clear conclusions can be drawn from the QoL data, given the open label nature of the study, and the small and dwindling numbers in each group. In general, there was no obvious difference in QoL between the 2 dosing schedules.

PK Sub-study

The PK sub-study objective was to assess PK characteristics of weekly and biweekly IgPro20 therapy.

PK Part 1 assessment was performed at Week 6 (Week 16 for subjects under IVIg at the time of enrollment) on Day 1 (pre-infusion + post-infusion), Day2, Day3, Day4, Day6, Day8.

PK Part 2 assessment was performed at Week 12 on Day 1 (pre-infusion + post-infusion), Day2, Day3, Day4, Day6, Day8, Day15.

Parameters were AUC0-tau, dose-adjusted AUC0-tau, C trough, Cmax, Cmin, tmax, clearance.

Results

Seventeen (17) subjects (thereof 7 children) were enrolled into the PK substudy. Of these, 15 had PK sampling for both the weekly and biweekly regimens. Nine (9) subjects (thereof 4 children) were included in the PK PP set, reasons for exclusions of subjects from the PK PP set included deviation of the planned dosing, insufficient PK sample collection and withdrawal during the PK study.

Mean (CV%/SD) of Serum IgG PK Parameters by Treatment Regimen – PK PP Set

PK Parameter	Summary Statistic	Treatment Regimen	
		Weekly (N=9)	Biweekly (N=9)
$AUC_{0\text{-}tau}$ (h*g/L)	Geometric Mean (CV%)	1685 (17.2)	3514 (17.8)
	Arithmetic Mean (SD)	1707 (294)	3561 (594)
dAUC ((h*g/L)/mg)	Geometric Mean (CV%)	0.24 (17.1)	0.25 (13.8)
	Arithmetic Mean (SD)	0.24 (0.04)	0.26 (0.04)
C_{max} (g/L)	Geometric Mean (CV%)	10.51 (16.1)	11.47 (18.1)
	Arithmetic Mean (SD)	10.63 (1.70)	11.63 (2.03)
t_{max} (day)	Median	2.00	3.02
	Min, Max	1.0, 5.1	2.0, 7.1
C_{trough} (g/L)	Geometric Mean (CV%)	9.92 (17.0)	9.71 (18.7)
	Arithmetic Mean (SD)	10.04 (1.63)	9.86 (1.68)
C_{min} (g/L)	Geometric Mean (CV%)	9.40 (20.5)	9.44 (15.5)
	Arithmetic Mean (SD)	9.57 (1.91)	9.53 (1.39)
CL_{ss} (mL/h)	Geometric Mean (CV%)	4.17 (17.1)	3.94 (13.8)
	Arithmetic Mean (SD)	4.22 (0.68)	3.98 (0.52)

The full PK sets (weekly n=17, biweekly n= 15) had similar results for the different PK parameters.

Assessor's comment

Comparable trough serum IgG concentrations (~9.9 g/L) and dose-adjusted AUC (~0.25 h*g/L/mg) were achieved by the weekly and biweekly treatment regimens.

2.3.3. Discussion on clinical aspects

Study IgPro20_4005, a Phase 4, open-label, single-sequence, crossover, post-marketing study, which lasted ~ 15 months, investigated the PK, safety and efficacy of weekly and biweekly schedules of s.c. Hizentra in 25 PID patients.

The study was not part of any PAM, as the bi-weekly dosing for all ages groups was already licensed in the EU with variation II/0024 based on pharmacometric data. Rather it had been requested in Canada for the biweekly dosing regimen.

The EU with variation II/0024 had led to the following update of Section 5.2 in the SmPC:

PID
In a clinical trial with Hizentra (n = 46), the subjects achieved sustained trough levels (median 8.1 g/l) over a period of 29 weeks when receiving median weekly doses of 0.06 to 0.24 g/kgbw.
Simulations by empirical Population Pharmacokinetic models suggest that comparable IgG exposure levels (AUC0-14days, Cmin 14days) may be obtained if Hizentra is administered subcutaneously every two weeks using double the weekly dose during maintenance therapy.
These simulations further suggest that comparable serum IgG trough levels can be achieved when the weekly maintenance dose of Hizentra is administered in proportional amounts more frequently than once a week (e.g. 2 times per week, 3 times per week, 5 times per week or daily).
Simulation of 2-3 missed daily doses resulted in a median serum IgG level decrease of ⩽ 4% compared to consistent daily dosing. By replacing the missed doses when daily dosing was resumed, the median concentration profile recovered within 2 to 3 days. However, if missed doses were not replaced when dosing was resumed, it took up to 5-6 weeks for the IgG trough levels to return to steady-state.

<u>Paediatric population</u>
No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients.

Study IgPro20_4005 included a representative PID population of all age groups; of the 25 patients 15 were paediatric.

The study was divided into 2 parts comparing 12 weeks on a weekly Hizentra home infusion treatment regimen to 52 weeks on a biweekly infusions at double the former dose.

The main measure of efficacy was the annualized rate of infections per subject; this was comparable between paediatric and adults patients and between 1-weekly and biweekly dosing schedules (with a trend to less infections in the biweekly group). No serious bacterial infections were recorded in either the adult or the paediatric populations. IgG levels were maintained in the biweekly group and thus provided adequate Hizentra exposure.

The safety profile showed no untoward signs either in the different age groups or between the dosing schedules. Most AEs were related to the underlying disorder. Drug related AEs were comparable between the 2 treatment schedules and encompassed known ADRs for SCIGs, (mainly injection site

reactions, and nervous system disorders such as headache and migraine). Local reactions were also similar between age and dosing groups.

Only one child had to revert back to the weekly dosing after experiencing mild, but prolonged migraine under the biweekly schedule.

A PK sub-study in 17 subjects (thereof 7 children) showed comparable trough serum IgG concentrations and dose-adjusted AUC in the weekly and biweekly treatment regimens.

No new insights or safety signals can be drawn from this small study, other than it confirms the PK, safety and efficacy profile of biweekly Hizentra dosing.

3. CHMP overall conclusion and recommendation

Overall conclusion

Study IgPro20_4005, a Phase 4, open-label study, which lasted ~ 15 months, investigated the PK, safety and efficacy of weekly and biweekly schedules of s.c. Hizentra in 25 PID patients (15 thereof paediatric).

The study was not part of any PAM, as the bi-weekly dosing for all ages groups was already licensed in the EU with variation II/0024 based on pharmacometric data. The study confirmed that the biweekly Hizentra dosing regimen offers a good safety and efficacy profile.

Recommendation

☒ Fulfilled:

No regulatory action required.

4. Comments

Supporting comments were received from MS1