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SCIENCE MEDICINES HEALTH

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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

International non-proprietary name: human normal immunoglobulin

Procedure No. EMEA/H/C/002127/P46/018

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACS	"Abnormal, clinically significant" laboratory results in CRF
AE	Adverse event
ALAT	Alanine aminotransferase
ANCS	"Abnormal, not clinically significant" laboratory results in CRF
ARAG	Autosomal recessive agammaglobulinemia
ASAT	Aspartate aminotransferase
AT	All treated
ATC	Anatomic therapeutic chemical
AUC	Area under the curve
AUClast	Area under the concentration-time curve until last measured concentration
AUC_T	Mean values for the AUC over the dosing interval
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
Cmax	Maximum concentration
CRF	Case report form
C_T	Concentration extrapolated from the tlast using the terminal elimination rate constant
Ctrough	Concentration at trough level
CT	Computerized tomography
CVID	Common variable immunodeficiency
DAF	Drug accountability form
EMA	European Medicines Agency
ER	"Error" of the laboratory results in CRF
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GMR	Geometric mean ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IgG (A, M)	Immunoglobulin G (A, M)
IMP	Investigational medicinal product
IRB	Institutional Review Board
IVIG	Intravenous immunoglobulin
LDH	Lactate dehydrogenase
λz	Terminal elimination rate constant
LQI	Life quality index
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MHLW	Ministry of Health, Labor, and Welfare in Japan
NBS	Nijmegen breakage syndrome
PhEc	Pharmacoeconomic(s)
PID	Primary Immunodeficiency
PK	Pharmacokinetic(s)
PMDA	Pharmaceutical and Medical Devices Agency, Japan
PPK	Per-protocol pharmacokinetic set
PPS	Per-protocol set
PT	Preferred term
RCA	Range change abnormal
SAE	Serious adverse event
SAP	Statistical analysis plan
SBI	Serious bacterial infection
SCIG	Subcutaneous immunoglobulin
SD	Standard deviation
SEM	Standard error of the mean
SOC	System organ class
tlast	Time point of last measurement
Tmax	Time point of maximum concentration (Cmax)
ULN	Upper limit of normal range
W	Weekly infusion, followed by a number to denote which infusion week
w/w	Wash-in/wash-out
WBC	White blood cells
WHO	World Health Organization

XLA	X-linked agammaglobulinemia

1. Introduction

On 5th January 2015, the MAH submitted a completed extension study for Hizentra (with approx.. 45% paediatric patients), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The study "*A Multicenter Study of Long-Term Clinical Outcomes of Immune Globulin Subcutaneous (Human) (SCIG) IgPro20 in Subjects with Primary Immunodeficiency*" (**IgPro20_3006**) is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Product
Hizentra is a ready-to-use 20% protein liquid formulation of a polyvalent human immunoglobulin G (IgG) preparation for subcutaneous administration (SCIG). The protein moiety of IgPro20 is highly purified IgG (≥ 98% purity). More than 90% of the IgG consists of monomers and dimers. IgG function (Fc and Fab mediated activity) is retained. The sterile 20% IgG solution is formulated with 250 mmol/L L-proline and 20 mg/L polysorbate 80 at pH 4.8. IgPro20 contains no preservative. The manufacturing process of the subcutaneous immunoglobulin (SCIG) solution is based on the IgPro10 (Privigen: EMEA/H/C/831) process except for formulation and final protein concentration. Thus, Privigen and IgPro20 manufacturing processes are identical down to the drug substance IgPro10-SOL. Filling sizes include 5 mL (1 g), 10 mL (2 g), 15 mL (3 g) and 20 mL (4 g). The primary packaging material is Type I glass infusion vials with chlorobutyl rubber stoppers.
The active substance of Hizentra is human normal immunoglobulin prepared from pooled plasma from not fewer than 1,000 donors, containing a broad spectrum of antibodies against infectious agents reflecting those antibodies present in the normal population. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range

Packing lot numbers: 4043000005, 4358000005, 4358000006, 4358000007, and 4358000008

2.3. Clinical aspects

2.3.1. Introduction

Regulatory aspects
The company CSL Behring AG submitted a Marketing Authorisation Application (MAA) for Hizentra (IgPro20) via the Centralised Procedure according to Regulation (EC) No 726/2004 using the optional scope (Article 3(2) (b). Eligibility of Hizentra for the centralised procedure was granted on 20th Nov, 2007 (Ref: EMEA/CHMP/538848/2007) due to technical innovation
With regard to the Paediatric Regulation Paediatric Investigation Plan (PIP) application under Article 7 of Regulation (European Commission [EC]) No 1901/2006 was submitted in September 2008. The EMA's Paediatric Medicinal Products Sector concluded that IgPro20 was not considered to be a "new medicinal product", and therefore Article 7 of this regulation did not apply, nor were requirements of Article 8 applicable.
On 17 February 2011 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, and the European Commission granted Marketing Authorization on 18 April 2011

Studies submitted for initial MAA
At the time of the MAA the applicant presented data of two completed Phase III studies (ZLB06_001CR, ZLB04_009CR) and two completed Phase I studies (ZLB04_008CR, ZLB06_003CR) were performed in healthy volunteers. In these four studies a total of 148 patients were treated, 115 adults (age: 16 - < 65 years) and 33 children (age: 2 - < 16 years). During the completed Phase III

studies 100 PID patients received IgPro20 during a period of 28 to 54 weeks. Data of 4095 subcutaneous use (sc-) infusions were presented.
The then valid SCIG Guideline (CPMP/BPWG/283/00) called for data from at least 30 patients, including children, followed for 12 – 24 weeks. Therefore the submitted data set exceeded these requirements.

Study **ZLB06_001CR** conducted in Europe with a total of 51 subjects with primary immunodeficiency syndromes (PID) aged between 3 and 60 years old were treated with Hizentra for up to 41 weeks. The mean dose administered each week was 0.12 g/kg body weight. Sustained IgG trough levels with mean concentrations of 7.99 – 8.25 g/l were thereby achieved throughout the treatment period. Subjects received in total 1831 weekly Hizentra infusions. Age did not seem to play a role with regard to any safety signals; in the European study less children and adolescents had AEs than adults.

Study **ZLB04_009CR** conducted in the US encompassed a total of 49 subjects with primary immunodeficiency syndromes aged between 5 and 72 years old were treated with Hizentra for up to 15 months. The mean dose administered each week was 0.23 g/kg body weight. Sustained IgG trough levels with a mean concentration of 12.53 g/l were thereby achieved throughout the treatment period. Subjects received in total 2264 weekly Hizentra infusions.

No serious bacterial infections were reported during the efficacy period in subjects receiving Hizentra during both clinical studies.(During the full period of study ZLB06_001CR subject 1505, a 5-year old female with a history of «chronic pneumonia» who was hospitalized due to recurrent episodes of pneumonia for 63 days and was treated with antibiotics for 116 days).

Hizentra contains the excipient L-proline which is a physiological, non-essential amino acid. The safety of Hizentra has been assessed in several preclinical studies, with particular reference to L-proline. Non-clinical data reveal no special risk for humans based on safety pharmacology and toxicity studies.

Studies submitted under Article P 46_012:

- **ZLB07_002CR**: A Multicenter Extension (EU) Study of the Efficacy, Tolerability, and Safety of Immune Globulin Subcutaneous (Human) IgPro20 in Subjects with PID
- **ZLB20_3001**: A Multicenter Extension (US) Study of the Efficacy, Tolerability, and Safety of Immune Globulin Subcutaneous (Human) IgPro20 in Subjects with PID

- **ZLB06_002CR**: A Multicenter Phase III Study (Japan) of Efficacy, Safety, Tolerability, and Pharmacokinetics of Immune Globulin Subcutaneous (Human) IgPro20 in Subjects with PID

This procedure was successfully concluded on 27 September 2012

Study submitted under Article P 46_013:

- **Study ZLB07_001CR**: a follow-up study of **ZLB06_002CR** (Japan).

2.3.2. Clinical study

For the current **P46_18** procedure the company has submitted data from **Study IgPro20_3006**

- **Objective(s)**

The objective of this study was to assess the long-term efficacy, tolerability, and safety of IgPro20 in subjects with primary immunodeficiency (PID) as an extension to the preceding follow-up study ZLB07_001CR.

CHMP comment
The objectives of the extension study are endorsed.

- **Design**

This was a prospective multicenter, open-label, single-arm, extension study in Japan for the treatment of subjects with PID who had completed their participation in the preceding follow-up study ZLB07_001CR. The study phase was initially Phase 3 and was changed to “post-marketing approval” after approval of Hizentra in Japan, in line with Japan regulatory requirements. The completion visit of follow-up study ZLB07_001CR (7 ± 2 days after the last infusion) was on the same day as the first

IgPro20 infusion of this extension study. For a treatment period of up to 36 months, each subject was planned to receive the weekly dose of IgPro20 (rounded to the nearest mL), the same as that was recommended by the investigator in the follow-up study.
IgPro20 treatment was home-based and the spreading of the weekly dose over 2 days was allowed, provided that the total weekly dose remained unchanged. Visits at the study site were scheduled at Weeks 1, 12, and every 12 weeks interval thereafter.
Health Related Quality of Life (HRQL) questionnaires were completed at the baseline (Visit 1 [V1], prior to infusion at Week 1 [W1]), prior to infusions at Month 6 and every 6 months thereafter, and at completion/discontinuation visit to obtain data on the influence of SCIG treatment on HRQL in these subjects.

- **Study population**

Study IgPro20_3006: 22 patients with PID were enrolled, treated (all treated=AT), and belong to the full analysis set (FAS), 17 were per protocol (PP), 3 patient discontinued the study.

- **Inclusion criteria**

Subjects who had completed the follow-up study ZLB07_001CR and who had tolerated IgPro20 well. Written informed consent by the subject/parent/legally accepted representative. Written assent for an underage subject (≥7 years to <20 years of age at the time of obtaining informed consent), was required, as far as possible.

- **Main exclusion criteria**

Female subjects of childbearing potential either not using, or not willing to use, a medically reliable method of contraception etc., pregnancy or nursing mother. Participation in a study with an investigational medicinal product (IMP) within 3 months prior to enrollment except for ZLB07_001CR. Subjects planning to donate blood during the study. Known or suspected antibodies to the IMP, or to excipients of the IMP.

- **Treatments and duration**

IgPro20 was administered as subcutaneous (SC) infusions at weekly intervals at home by the subject/parent/guardian. The weekly IgPro20 dose was equivalent to the subject's last dose, recommended by the investigator in the follow-up study ZLB07_001CR. Dose adjustments could be performed at the discretion of the investigator in order to produce IgG trough levels of no less than 5 g/L.

Concomitant medication not intended for the primary purpose of masking signs of AEs to the infusions, and which was (were) taken by the subject on a regular basis could be continued. Steroids were allowed at the discretion of the investigator.

Duration: 36 months

- **Outcomes/endpoints**

Primary efficacy variable: Number of infection episodes (serious/non-serious), assessed in frequency and duration of each infection during the study.

Secondary efficacy variables:
(1) Annualized rate of serious bacterial infections (SBIs [defined as bacterial pneumonia, bacteremia and septicemia, osteomyelitis/septic arthritis, bacterial meningitis, or visceral abscess]), assessed by symptoms, physical findings, laboratory tests, and computed tomography/magnetic resonance imaging.
(2) Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections, assessed from the first study day treatment (Day 1, W1) until study completion/discontinuation visit.
(3) Number of days of hospitalization due to infections, assessed from the Day 1, W1 until study completion/discontinuation visit.
(4) Duration of use of antibiotics for infection prophylaxis and treatment, assessed from the Day 1, W1 until study completion/discontinuation visit.
(5) Serum IgG concentrations at baseline (V1, W1) and all 3-monthly visits during the treatment period.

Secondary safety variables: Overall rate of adverse events (AEs) per infusion, assessed in total, by severity, and by causal relationship to study medication; incidence of AEs on subject level, assessed in total, by severity, and by causal relationship to study medication.

Exploratory safety variables: Routine laboratory parameters (blood chemistry, hematology, and urinalysis), assessed every 6 months during the treatment period and at the completion/discontinuation visit, except urine pregnancy and urinalysis were done at the Completion/Discontinuation visit. Due to non-availability of normal ranges for children, assessments for low, normal or high values were to be done by the investigator.

HRQL: HRQL questionnaires at baseline and every 6 months thereafter, assessed with the disease/application specific questionnaires "Life Quality Index" (LQI) and the "Treatment Satisfaction Questionnaire of Medication" (TSQM) questionnaires.

- **Statistical Methods**

Primary safety analysis: Descriptive (summary) statistics included continuous variables (summarized by number of subjects, mean, standard deviation [SD], median, minimum, maximum, interquartile range [25% and 75%]). For categorical variables, the observed absolute and relative frequencies were presented. Whenever appropriate, graphs were used to illustrate data. No formal sample size calculation was applied in this study.

The number and annualized rate of infections (serious/non-serious, primary efficacy variable) and the SBIs were calculated as follows: Annualized rate = 365 x observed episodes/total exposure days.

IgG concentrations
The steady-state IgPro20 IgG concentrations per subject within the study, i.e., IgG concentrations determined at all 3-monthly visits were summarized descriptively by visit and compared descriptively. In addition, the IgG concentrations per subject were aggregated to the mean and median value, and then median values across subjects were summarized using descriptive statistics.

Safety
Analyses of the safety endpoints were based on the AT safety data set. AEs were analyzed on a subject level as well as on infusion level. Absolute and relative frequencies were calculated. These analyses were presented also by severity, temporal association (within 72 h after last infusion) and causal relationship.
For the exploratory analyses of AEs, the overall incidences of subjects with AEs as well as AE rates per infusion were further analyzed by gender and age class.

CHMP comment
In general, the design of the extension study is endorsed. As mentioned in the last P46 ARs the relevance of a HRQL questionnaire is minimal in an open study setting. The primary endpoint (Number of infection episodes (serious/non-serious), assessed in frequency and duration of each infection during the study) is acceptable. The secondary efficacy variable (annualized rate of SBIs) corresponds to the primary endpoint of the current draft EMA SCIG Guideline (CHMP/BPWP/410415/2011). However, in this extension Japanese study no acceptability threshold has been set; the remaining secondary efficacy variables are also in line with the EMA GL.

Results

- **Recruitment/ Number analysed**

All 22 subjects enrolled in this study were treated with IgPro20 and included in the AT set.
Three subjects (13.6%) who received treatment at baseline discontinued during the study (1 of these 3 subjects discontinued due to an AE of infusion site reaction). A total of 19 subjects (86.4%) completed the study. A total of 5 AT subjects were excluded from the PPS due to major protocol deviations (i.e. an increase of >10% from the planned dose).

- **Demographic characteristics**

The demographic data (date of birth, height, and gender only) and characteristics at baseline were previously described in the pivotal study ZLB06_002CR and the follow-up study ZLB07_001. Overall, the demographic characteristics of the AT set and PPS subjects were comparable. With the exception of 2 subjects who did not continue treatment after the pivotal study and 1 subject after followup study, all the subjects included in this study were the same as those in pivotal study ZLB06_002CR and follow-up study ZLB07_001. In the AT set, 13 subjects (59.1%) were male and all subjects were of Asian origin from Japan and had a mean body weight of 47.7 kg. The mean age was 21.6 years including 10 subjects (45.5%) of ≥2 to ≤16 years. The mean body mass index was 19.2 kg/m² in the AT set and 19.5 kg/m² in the PPS.

In the AT set, X-linked agammaglobulinemia (XLA) and common variable immunodeficiency (CVID) were the primary humoral immunodeficiencies in 10 subjects (45.5%) each. One subject each had autosomal recessive agammaglobulinemia, and hyper immunoglobulin M syndrome as primary humoral immunodeficiency.

At enrollment into the study, the median duration of disease was 11.4 years in subjects with XLA and 7.0 years in subjects with CVID.

Concomitant medication

The most frequent concomitant medications (ATC level 2, ≥40% of subjects) administered during the study were antibacterials for systemic use (22 subjects [1000%]), and cough and cold preparations (21 subjects [95.5%]), antihistamines for systematic use (14 subjects [63.6%]), drugs for obstructive airway disease (13 subjects [59.1%]), and corticosteroids, dermatological preparations (12 subjects [54.5%])

CHMP comment
The demographic characteristics are essentially the same as previously described for the pivotal study ZLB06_002CR, and the follow-up study ZLB07_001 and can be seen as representative of the PID population

- **Treatment and duration**

All 22 subjects received total of 2,665 infusions during 2,660 treatment weeks. Some subjects administered 2 doses within 1 week or split the weekly dose.
The median number of injection sites per infusion was 1 for both data sets, based on 2,660 total infusion weeks in the AT set and 2,123 total infusion weeks in the PPS. The range of the number of injection sites was from 1 to 5 for both data sets.
The mean (SD) weekly IgPro20 dose was 98.94 (38.834) mg/kg body weight (bw) for the AT set and 90.31 (31.382) mg/kg bw for the PPS, with a range of 31.7 to 376.5 mg/kg bw for AT set and 31.7 to 159.1 mg/kg bw for PPS.
The mean individual infusion rates were 28.14 mL/h for AT set and 27.91 mL/h for PPS, with a range from 18.0 to 38.0 mL/h (the maximum technically achievable rate) for both data sets.
The mean duration of infusion was 1.05 h for the AT set and 1.07 h for the PPS.
The total study duration was 18,701 subject days (51.24 subject years) for AT set and 14,913 subject days (40.86 subject years). The mean (SD) study duration per subject was 850 (157.6) days for AT set and 877 (48.1) days for PPS, with a range of 175 to 947 days in the AT set and 776 to 947 days in PPS.

- **Efficacy results**

Primary endpoint

Overall, 21 subjects (95.5%) in the AT set experienced at least 1 infection. The overall number of infection episodes was 124 during 18,701 study days. In the PPS, 16 (94.1%) subjects experienced 78 episodes during 14,913 study days. The total annualized rate of infection was 2.42 infections/subject/year (upper 1-sided 99% confidence limit: 2.976 infections/subject/year) in the AT set. It was slightly lower in the PPS (1.91 infections/subject/year, upper 1-sided 99% confidence limit: 2.475 infections/subject/year).

CHMP comment
The overall infection rate of 2.42 infections/subject/year (upper 1-sided 99% CI: 2.9 infections /subject/year) is in keeping with the literature for immunoglobulins (approx. 4 infections/Pt/y)

Secondary Efficacy Endpoints (AT and PPS)

Secondary efficacy endpoints	AT		PPS	
	Number (%) of subjects (N=22)	Number (annualized rate) of events or days (N=18,701)	Number (%) of subjects (N=17)	Number (annualized rate) of events or days (N=14,913)
Serious bacterial infections	0	0	0	0
Use of antibiotics for				
Infection prophylaxis	8 (36.4)	4,832 (94.31)	6 (35.3)	4,490 (109.89)
Infection treatment [a]	22 (100.0)	6,068 (118.43)	17 (100.0)	5,650 (138.29)
Days hospitalized due to infections	2 (9.1)	14 (0.27)	2 (11.8)	14 (0.34)
Days missing work/school/ kindergarten/day care or unable to perform normal activities due to infections	16 (72.7)	166 (3.24)	13 (76.5)	133 (3.26)

AT = all treated; N = total number of subjects/days in analysis set; PPS = per-protocol set.

[a] Treatment is defined as either 'treatment of medical/surgical/current condition' or 'adverse event'.

Serum IgG trough levels

The mean (SD) IgG trough levels were stable from baseline (8.13 [1.479] g/L) to V10 (8.53 [1.677] g/L) in the AT set and in the PPS (baseline [7.89 {1.324} g/L] to V10 [8.46 {1.702} g/L]). Except for V3 in the AT set, the levels did not fall below the baseline mean (SD) value throughout the study. There were no subjects with IgG trough levels <5 g/L. One subject had a minimum trough level of 5.39 g/L. All other subjects had trough levels from ≥6.0 to 12.42 g/L.

CHMP comment

The IgG trough levels seen in the extension study are adequate (completion visit: mean 8.53 g/L) and in line with the coreSPC (> 5 g/L). There were no subjects with IgG trough levels <5 g/L.

Days of absence

A total of 16 subjects (72.7%) in the AT set missed work/school/kindergarten/day care or were unable to perform normal activities due to infections over a total of 166 days (annualized rate 3.24 days/subject/year)

Days of hospitalization

Two subjects (9.1%; Subjects 501 and 606) were hospitalized due to an infection: bacterial bronchitis and aseptic meningitis, respectively. Both subjects were hospitalized total for 14 days (annualized rate 0.27 days/subject/year)

Use of antibiotics

Indication	Number (%) of subjects (N=22)	Number (annualized rate) of days (N=18,701)
Total	**22 (100.0)**	**8,715 (170.10)**
Treatment	22 (100.0)	6,068 (118.43)
Adverse event	22 (100.0)	4,241 (82.77)
Treatment of medical/surgical/current condition	8 (36.4)	3,051 (59.55)
Prophylaxis	8 (36.4)	4,832 (94.31)

AT = all treated; N = total number of subjects/study days
Source: Table 14.2.2.5

- **Health-related Quality of Life**

Life Quality Index at Baseline and Completion (FAS and PPS)

The mean (SD) scores of all LQI parameters were high and stable for all parameters at all assessment time points, both in the AT set and PPS. The mean scores above 65 on the scale from 0 (worst) to 100 (best) were observed in the total score and every domain/scale of the LQI questionnaire at the end of the study.

		Mean (SD) score	
Scale	Visit	AT (N=22)	PPS (N=17)
Total	**Baseline [a]**	**73.4 (14.42)**	**71.8 (15.78)**
	Completion	**69.3 (19.82)**	**69.9 (21.42)**
Treatment interference	Baseline [a]	74.2 (15.36)	72.7 (16.87)
	Completion	69.3 (22.11)	70.4 (24.23)
Therapy-related problems	Baseline [a]	65.2 (16.14)	64.2 (17.62)
	Completion	64.8 (19.49)	64.7 (19.93)
Therapy setting	Baseline [a]	79.3 (18.16)	76.8 (19.37)
	Completion	76.8 (22.07)	75.5 (23.82)
Costs	Baseline [a]	78.8 (18.85)	76.5 (20.46)
	Completion	67.0 (19.50)	70.1 (20.00)

AT = all treated; N = total number of subjects; PPS = per-protocol set; SD = standard deviation.
Note: Scores range from 0 to 100, 0 presents the worst possible result and 100 the best possible result.
[a] Baseline is W1 of the extension study IgPro20_3006. Data transcribed from completion visit (W24) of the follow-up study ZLB07_001CR.
Source: Table 14.4.1.4

CHMP comment:
In this open label extension study the mean scores of all Life Quality Index parameters were slightly reduced at completion compared to baseline (however with overlapping SDs)

Treatment Satisfaction Questionnaire of Medication:

Twenty-one subjects (95.5%) in the AT set and 16 (94.1%) in the PPS at completion were on SCIG therapy, that was conducted mainly at home (90.9% in the AT set). In the AT set, 13 subjects (59.1%) performed home infusion themselves, and 6 subjects (27.3%) needed assistance from their relative or friend. Q2 and Q5 for the TSQM, showed high mean scores regarding SC therapy with IgPro20 performed at home. Q6 regarding performing SC therapy with IgPro20 at hospital/doctor's practice showed a lower mean score at baseline 55.6 decreasing to 40.2 at completion visit.

Overall Comparison of efficacy data in Hizentra studies

	ZLB06_001CR (Europe) N=51 (22-<16y)	Extension ZLB07_002CR (Europe) N=40 (19-<16y)	ZLB04_009CR (USA) N=49 (10-<16y)	Extension ZLB20_3001 (USA) N=21 (2-<16y)	ZLB06_002CR (Japan) N=25 (11-<16y)	ZLB07_001CR (Japan — follow-up) N=23 (11-<16y)	**Extension IgPro 20_3006 (Japan) N=22 (10-<16y)**
IgG Trough level g/L	7.99--8.25	8.12	12.53	11.98	7.15	8.91	**8.53**
Annualised per subject							
Absolute No. of SBIs (Rate; upper 99% CI)	0 (0;0.192)	5 (0.047;0.125)	0 (0;0.132)	2 (0.06;0.257)	0	0	**0**
Other infections (95% CI)	5.18 (4.30;6.17)	3.33 (2.99;3.70)	2.76	2.38 (1.88;2.97)	2.98 (upper 99% CI:5.305)	4.20	**2.42** (upper 99% CI:2.976)
Days missed work/school/KG	8.00	6.77	2.06	4.28	3.45	3.81	**3.24**
Days hospitalized due to infections	3.48	1.06	0.2	0.55	0.55	1.07	**0.27**
Days on antibiotics	72.75	72.13	48.5	83.87	167.42	143.11	**118**

- **Efficacy Conclusions**

Most patients (21/22) experienced at least one infection during the extension study – this can be expected in this population - it is well known that despite immunoglobulin replacement treatment, patients with antibody deficiency remain at risk of developing acute "breakthrough" or chronic infections. The annualized number of all infections per patient was 2.42 infections/subject/year (upper 1-sided 99% confidence limit: 2.97 infections/subject/year), which is in keeping with the average range reported with other IVIgs/SCIGs and can be seen in the other Hizentra studies.

The secondary efficacy endpoints seen in the extension study are comparable to those of the original study. No SBIs were seen in either study.

All patients received antibiotic therapy – this is deemed rather high considering that not all infections will have been bacterial in nature. The mean annualized number of days on antibiotics at 118 (138 in the PPS) is also very high. In general, in the Japanese studies, the use of therapeutic antibiotics (when measured as annualized days per year) is noticeably higher than in the US or European studies.

The median IgG trough levels (completion visit: mean 8.53 g/L) were comparable in the extension study with the follow-up and pivotal Japanese studies and also with the EU studies (it is known that the higher trough levels in the US studies are due to higher doses given there). These IgG trough levels are adequate and in line with the coreSPC (> 5 g/L). There were no subjects with IgG trough levels <5 g/L. This is considered the threshold level below which more infections can occur.

The quality of life measurements have to be viewed with caution in an open-label setting. However, in general, the ratings were relatively high and stable and patients seemed to feel comfortable with home therapy.

This efficacy profile is similar to other SCIGs (and IVIGs) and is therefore acceptable.

- **Safety results**

Exposure

A total of 2,665 infusions of IgPro20 were administered to 22 subjects during the 2 year study.
All patients received their IgG therapy at home

The mean of the individual IgPro20 doses per week per kg was 98.36 ([SD] 37.48) mg/kg bw for the AT and 89.27 (31.95) mg/kg bw for the PPS, with a range of 33.8 to 181.8 mg/kg bw for the AT set.

Adverse events (AEs)

In the AT set, all 22 subjects experienced at least 1 AE. There were in total 660 AEs reported for 2,665 infusions resulting in an overall AE rate of 0.248.

Overview

	Statistic	IgPro20 (n=22)
Including local reactions		
Subjects with AEs	N (%)	22 (100)
Subjects with AEs of mild intensity	N (%)	22 (100)
Subjects with AEs of moderate intensity	N (%)	4 (18.2)
Subjects with AEs of severe intensity	N (%)	2 (9.1)
Subjects with at least possibly related AEs	N (%)	13 (59.1)
Subjects with temporally associated AEs (up to 24h)	N (%)	16 (72.7)
Subjects with temporally associated AEs (up to 48h)	N (%)	18 (81.8)
Subjects with temporally associated AEs (up to 72h)	N (%)	19 (86.4)
Subjects with at least possibly related, temporally associated AEs (up to 72h)	N (%)	13 (59.1)
Subjects with serious AEs	N (%)	2 (9.1)
Subjects with at least possibly related serious AEs	N (%)	1 (4.5)
Subjects with serious, at least possibly related, temporally associated AEs (up to 72h)	N (%)	1 (4.5)
Subjects with AEs leading to the death of the subject	N (%)	0
Subjects with at least possibly related AEs leading to the death of the subject	N (%)	0
Subjects with AEs where study drug infusion had to be stopped	N (%)	0
Subjects with at least possibly related AEs where study drug infusion had to be stopped	N (%)	0
Subjects withdrawn due to AEs	N (%)	1 (4.5)
Subjects withdrawn due to at least possibly related AEs	N (%)	1 (4.5)

AE rate by infusion
The median individual subject's rate of AEs by infusion was 0.093 (rate of mild AEs per infusion was 0.076). The median rate of AEs assessed by the investigator as at least possibly related was 0.008, with a range of 0 to 1. The median rate of AEs assessed by the investigator as not related to IgPro20 was 0.076, with a range of 0 to 0.36.

Type of AE
The most common AEs were local reactions, which occurred at a rate per infusion of 0.149 and were experienced by 12 subjects (54.0%). All local reactions were mild in severity and at least possibly related to IgPro20.
A total of 21 subjects (95.5%) experienced at least 1 AE in the SOC infections and infestations
In general, AEs in ≥4 subjects [≥18 %] encompassed nasopharyngitis, headache, upper respiratory tract infection, influenza, gastroenteritis, diarrhoea, injection site pain, rhinitis allergic, cough, arthralgia and eczema. All other AEs occurred in ≤3 subjects (≤13%).

Severity
All subjects experienced at least 1 mild AE; 4 subjects (18.2%) experienced moderate AEs and 2 subjects (9.1%) each experienced 1 severe AE that was also an SAE (bronchitis bacterial and meningitis aseptic).

Relatedness
A total of 13 subjects (59.1%) reported 399 AEs that were assessed as at least possibly related to IgPro20, the majority of which were local reactions (11 subjects, 50.0%; 397 AEs and 1 subject each with asthma (related SAE) and vitiligo).The related AEs were mostly mild and resolved within 48 h without any treatment.

Temporally associated AEs
A total of 19 subjects (86.4%) experienced 475 temporally associated AEs, i.e., AEs that occurred within 72 h after the end of infusion, resulting in a rate of 0.178 AEs per infusion. The most common temporally associated AEs (72 h) by PT were local reactions reported in 11 subjects (50.0%) with an AE rate of 0.146 per infusion (389 events). Temporally associated AEs (72 h) were assessed as at least possibly related to IgPro20 in 13 subjects (59.1%) who experienced 391 events resulting in a rate per infusion of 0.147.

SAEs + deaths
No deaths occurred during the study. Three SAEs were reported in 2 subjects; however, they continued IgPro20 and completed the study. Of these, 1 SAE (asthma) was assessed by the investigator as at least possibly related to IgPro20 and temporally associated to the infusion within 72 h. One SAE (aseptic meningitis) in the same subject was assessed as unlikely related to IgPro20 and not temporally associated to infusion within 72 h. In the second subject, an SAE of bacterial bronchitis was reported and assessed as not related to IgPro20 and not temporally associated to infusion within 72 h.

CHMP comment
One SAE (aseptic meningitis) in the same subject was assessed as unlikely related to IgPro20 and not temporally associated to infusion within 72 h. The latter part of the statement is incorrect as the SAE started on the same day as the administration of Hizentra:
On 10 April 2012, 11 weeks after the first IgPro20 infusion, the subject received IgPro20: 70 mg/kg bw dose at 35 mL/h maximum infusion rate (Lot # 4358000005, 45.9 kg body weight at time of SAE 2). On the same day, the subject developed severe headache, vomiting, and nuchal rigidity, followed by pyrexia in the evening. The subject experienced difficulty in oral intake due to vomiting on the next day. She was hospitalized on 11 April 2012 and based on symptoms, aseptic meningitis was suspected.

We agree with the company's assessment that the relationship of this temporally associated SAE is possible/probable.

Discontinuations/Interruptions
One subject discontinued due to a series of events of mild and at least possibly related and temporally (72 h) associated local reactions (infusion site reaction). Four subjects had an interruption or modification of dosing due to local reactions (AEs).

Laboratory analyses:
Hematology, blood chemistry, and urinalysis analytes were evaluated (baseline) in the pivotal study ZLB06_002CR and documented for each subject who enrolled into this study. Hematology and blood chemistry were determined at every 6-month visit and at the completion/discontinuation visit of extension study.
There were no safety concerns regarding clinical laboratory parameters over the course of the study.
No thromboembolic events or cases of hemolysis were reported in this study.
No changes from baseline for HB were greater than – 1.5 g/dL.
None of the individual laboratory values was flagged as abnormally, clinical significant by the investigators during the study. All subjects were negative for human immunodeficiency virus type -1 (HIV-1), HIV-2, hepatitis C virus, and hepatitis B virus at baseline and viral safety follow-up at completion visit.

Other safety analyses:
All direct Coombs tests at baseline and study completion were negative except for 1 subject who was identified with a slightly positive Coombs test at V11, which was negative again at the next measurement (2 months later) during the completion visit iand was not considered as hemolysis. This subject was concomitantly exhibiting iron deficiency anemia which may explain Coombs test results.
One subject (Subject 603; an 18-year-old female with CVID) became pregnant and was discontinued from the study on 16 December 2013 as required by the protocol.

Subgroup analysis
- *Gender differences*

Of the 22 AT set subjects, 13 were male (reflecting the relatively high proportion of XLA subjects) and 9 were female.
The female subgroup (n=9) received 1,029 total infusions during the study and reported more AEs per infusion (506 events; rate per infusion 0.492) than the male subgroup. In the male subgroup (n=13; total infusions 1,636), less AEs (154 events) were reported with a rate per infusion of 0.094.

- *Age class*

In the AT set, most subjects were in the age class of >16 to <65 years of age (12 subjects [54.5%]); 5 subjects (22.7%) each were in the age class of ≥2 to <12 years of age (children) and ≥12 to ≤16 years of age.
There were no severe AEs reported in the youngest age group (≥2 to <12 years of age).
The youngest age class received 639 total infusions during the study and reported a higher rate of AEs per infusion (262 events; rate per infusion 0.410). Most of these AEs were of local reactions (136 events; rate per infusion 0.213), of mild severity and assessed as at least possibly related to IgPro20. This age group included Subject 304 who reported local reactions after almost every infusion.

The total number of infusions for the age classes ≥12 to ≤16 years were 513 and for >16 to <65 years were 1,513 during the study. In the age class of ≥12 to ≤16 years, the overall rate of AEs (161 events) by infusion was 0.314 and most of the events were local reactions (131 events; rate per infusion 0.255), of mild severity and assessed as at least possibly related to IgPro20. This age group included Subject 308 who reported local reactions after almost every infusion

In the age class of >16 to <65 years, the overall rate of AEs (237 events) per infusion was 0.157, and most of the events were local reactions (131 events; rate per infusion 0.087) of mild severity and mainly at least possibly related to IgPro20

Subjects with AEs analyzed by age group.

		age class		
	Statistic	>=2 to < 12 yrs (n=5)	>=12 to <=16 yrs (n=5)	>16 to < 65 yrs (n=12)
Including local reactions				
Subjects with AEs	N (%)	5 (100)	5 (100)	12 (100)
Subjects with AEs of mild intensity	N (%)	5 (100)	5 (100)	12 (100)
Subjects with AEs of moderate intensity	N (%)	0	1 (20.0)	3 (25.0)
Subjects with AEs of severe intensity	N (%)	0	1 (20.0)	1 (8.3)
Subjects with at least possibly related AEs	N (%)	5 (100)	4 (80.0)	4 (33.3)
Subjects with temporally associated AEs (up to 24h)	N (%)	5 (100)	4 (80.0)	7 (58.3)
Subjects with temporally associated AEs (up to 48h)	N (%)	5 (100)	4 (80.0)	9 (75.0)
Subjects with temporally associated AEs (up to 72h)	N (%)	5 (100)	4 (80.0)	10 (83.3)
Subjects with at least possibly related, temporally associated AEs (up to 72h)	N (%)	5 (100)	4 (80.0)	4 (33.3)
Subjects with serious AEs	N (%)	0	1 (20.0)	1 (8.3)
Subjects with at least possibly related serious AEs	N (%)	0	1 (20.0)	0
Subjects with serious, at least possibly related, temporally associated AEs (up to 72h)	N (%)	0	1 (20.0)	0

- **Conclusions on Safety**

Over the 2 year study period there were 660 AEs occurring with 2.665 infusions (rate: 0.248) in 22 patients (100%) in the home setting. This rate of AEs per infusion is low, also compared to the other studies performed with Hizentra (see table below) – however, the home setting may not lend itself to rigorous documentation of AEs.

The severity of the AEs was mainly mild, (mainly local reactions): 17 subjects reported 650 mild AEs (rate per infusion 0.244). 4 subjects reported 8 moderate AEs (rate p.i.: 0.003) and 2 subjects reported 2 severe AEs (bronchitis bacterial and meningitis aseptic). The nature and severity of the AEs is in keeping with the SCIG administration.

The rate of at least possibly related AEs was 0.150 (399 events in 13 subjects); the rate of temporally associated AEs (72 h) was 0.178 (475 events in 19 subjects); and the rate of AEs that were both temporally associated (72 h) and at least possibly related to IgPro20 was 0.147 (391 events). This data is within the range seen in the other studies.

Three SAEs were reported in 2 subjects; 1 SAE (asthma) was assessed by the investigator as at least possibly related to IgPro20 and temporally associated to the infusion within 72 h. From the details of the narrative the CHMP agrees with the company and views a causal relationship as unlikely – the wheezing commenced 3 days after study medication and was seemingly induced by exercise. The SAE aseptic meningitis in the same subject was assessed by the investigator as unlikely to be related to IgPro20. Here again we agree with the company, - aseptic meningitis is a known side-effect of IVIGs and in some instances of SCIGS and a temporal association was given, thus making the relationship possible/probable. In the former study (ZLB07_001CR) one subject had also developed aseptic meningitis. This AE is mentioned in 4.4 and 4.8 of the Hizentra SPC and Section 4 of the PIL.
In the second subject, an SAE of bacterial bronchitis was reported and assessed as not related to IgPro20, but rather due to the underlying PID.

There were no deaths.

There were no trends arising from the laboratory- vital signs- or physical examination assessment. No thromboembolic events or cases of hemolysis were reported in this study.

Due to the small number of study subjects, results of the performed subgroup analyses by gender and age should be interpreted with caution. Except for a higher incidence of local reactions in females compared to males, probably driven by repeated reporting of injection site pain and injection site

reaction/swelling in 2 female pediatric subjects, no differences in the rates of AEs by gender or age group were found.

No changes in the safety assessment result from this Japanese extension study in 22 PID patients followed over 2 years in the home setting.
No specific safety signals arise for children.

	ZLB06_001CR (Europe) N= 51 (22 < 16y)	Extension ZLB07_002CR (Europe) N= 40 (19 < 16y)	ZLB04_009CR (USA) N=49 (10 <16y)	Extension ZLB20_3001 (USA) N=21 (2 <16y)	ZLB06_002CR (Japan) N= 25 (11 <16 y)	ZLB07_001CR (Japan – follow-up) N=23 (11 < 16y)	**Extension IgPro 20_3006 (Japan) N=22 (10 < 16y)**
Infusions	1831	5405	2264	1735	584	529	**2665**
IgG Trough level g/L	7.99 - 8.25	8.12	12.53	11.98	7.15	8.91	**8.53**
Efficacy annualised per subject (all treated)							
Absolute No. of SBIs (Rate; upper 99% CI)	0 (0; 0.192)	5 (0.047; 0.125)	0 (0; 0.132)	2 (0.06; 0.257)	0	0	**0**
Other infections (95% CI)	5.18 (4.30; 6.17)	3.33 (2.99; 3.70)	2.76	2.38 (1.88; 2.97)	2.98 (upper 99% CI: 5.305)	4.20	**2.42** (upper 99% CI: 2.976)
Days missed work/school/KG	8.00	6.77	2.06	4.28	3.45	3.81	**3.24**
Days hospitalized due to infections	3.48	1.06	0.2	0.55	0.55	1.07	**0.27**
Days on antibiotics	72.75	72.13	48.5	83.87	167.42	143.11	**118**
Safety							
Subjects with AE at least possibly related	60.8%	20.0%	100%	100%	84%	43.5%	**59.1%**
Subjects with AE temp associated (within 72 h)	94%		100%	100%	92%	87%	**86.4%**
AE rate per infusion	0.288	0.0936	0.773	0.661	0.457	0.346	**0.248**
AE rate per infusion possibly related	0.106	0.0026	0.634	0.524	0.296	0.136	**0.150**
AE rate local reaction	0.060		0.592	0.500	0.274	0.132	**0.149**
Subjects with AE local reaction	49%	15%	100%		80%	34.8%	**54%**
SAEs (rate)	7 (0.004)	18 (0.003)	10 (0.004)	5 (0.003)	1 (0.0017)	1 (0.002)	**3 (0.001)**
SAE related	0	0	0	0	0	1	**1**
Deaths	0	1	0	0	0	0	**0**

2.3.1. Discussion on clinical aspects

(See safety and efficacy conclusions)

3. CHMP overall conclusion and recommendation

The Japanese extension study IgPro 20_3006 showed results consistent with the data seen hitherto in the MAA studies and confirmed the adequate efficacy and safety profile of Hizentra when administered as weekly SC infusions to adult and paediatric subjects with PID.

One case of aseptic meningitis occurred in this extension study and one in the previous follow-up study. As this ADR is already part of the warnings (4.4.) and undesirable effects (4.8) in the SPC and in Section 4 of the PIL, further changes to the SPC/PIL are currently not deemed necessary.