20 September 2012

EMA/142164/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hizentra

International non-proprietary name: human normal immunoglobulin

Procedure No. EMEA/H/C/002127/P46/0012

Note

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

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Administrative information

Name of the medicinal product:	Hizentra
Name and address of the applicant:	CSL Behring AG Wankdorfstrasse 10 3000 Bern 22 Switzerland
Type of Marketing Authorisation Application:	Article 46
Active substance:	Human normal immunoglobulin (SCIg)
Pharmaco-therapeutic group	immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06BA01
Therapeutic indication(s):	Replacement therapy in adults and children in primary immunodeficiency syndromes such as: – congenital agammaglobulinaemia and hypogammaglobulinaemia – common variable immunodeficiency – severe combined immunodeficiency – IgG subclass deficiencies with recurrent infections Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections

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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_{τ}	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_{τ}	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

Background

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

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

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 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.

Clinical Studies

The MAH submitted data from continued studies for:

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

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

In addition the MAH submitted data from:

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

- **Objective(s)**

ZLB07_002CR: To continue assessing the efficacy, tolerability, and safety of IgPro20 in subjects with primary immunodeficiency (PID), who elected to continue the treatment they received previously under Protocol **ZLB06_001CR**. Additionally, long-term health-related quality of life (HRQL) was assessed.

ZLB20_3001: To assess the efficacy, tolerability, and safety of IgPro20 in subjects with PID who elected to continue IgPro20 treatment received previously in study **ZLB04_009CR**. Other objectives were to assess health-related quality of life (HRQL), treatment satisfaction, utility, and health-care related resource use.

ZLB06_002CR: To assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of IgPro20 in subjects with primary immunodeficiency (PID) as well as to assess the health-related quality of life (HRQL) and pharmacoeconomic (PhEc) aspects. The primary objective of this study was to evaluate if sustained total serum IgG trough levels with subcutaneous immunoglobulin (SCIG) therapy (IgPro20) comparable to the preceding intravenous immunoglobulin (IVIG) treatment period in the per protocol set (PPS) could be achieved. The objective of the PK substudy was to obtain PK data of IgPro20 in the Japanese subject population. PK parameters including area under the curve (AUC), maximum concentration (Cmax), and time point of Cmax (Tmax) were calculated from total serum IgG.

Assessor's comment
Given the open nature of the 3 studies, the HRQL will not be assessed in any detail in this AR

- **Design**

ZLB07_002CR: This was a prospective multicenter (n=13 in Europe), open-label, single-arm, Phase III extension study in subjects with PID who had previously been treated with IgPro20 in the pivotal

study ZLB06_001CR and were willing to switch to the extension study ZLB07_002CR. The completion visit (7 ± 2 days after the last infusion) of the pivotal study ZLB06_001CR was the same day as the first infusion for this extension study. Subjects were treated from the date of their last infusion in study ZLB06_001CR until IgPro20 became available on the market or, in the UK specifically, until 36 months from the first date of infusion of the extension study. The planned weekly dose of IgPro20 in this study was the same as the subject's last dose recommended by the investigator in the pivotal study ZLB06_001CR. Individualized dose schedules and spreading of the weekly dose over several days were permitted based upon the subject's preferences and clinical judgment of the investigator, providing that the total weekly dose remained unchanged. Subjects visited the study site for assessments every 6 months.

ZLB20_3001: This was a prospective, multicenter (n=4 in USA), open-label, single-arm, Phase III extension study to provide additional long-term data for IgPro20. Subjects with PID who had previously participated in study ZLB04_009CR and who required immunoglobulin G (IgG) replacement therapy were treated with IgPro20 between their last infusion in study ZLB04_009CR and availability of IgPro20 on the market. The initial weekly dose of IgPro20 was the same as the last dose the subject received during participation in study ZLB04_009CR. Adequate dosing during the study was monitored based on the pre-specified trough level ratio (TLR, steady-state trough level [Ctrough] value during subcutaneous [SC] replacement therapy divided by the last Ctrough value during stable intravenous replacement therapy). During the treatment period, subjects visited the study site at 12-week intervals for efficacy and safety evaluations. In addition, subjects were issued a diary in which details regarding the dose of IgPro20 administered and certain aspects of the efficacy and safety of IgPro20 were entered.

ZLB06_002CR: This was a prospective multicenter (9 in Japan), open-label, single arm, Phase III study of IgPro20 in 25 subjects with PID. The study consisted of an IVIG treatment period with 3 infusions, a 12-week SCIG wash-in/washout period, and a 12-week SCIG efficacy period (i.e. 24 weeks of SCIG treatment with IgPro20). A PK sub-study was carried out once during an infusion interval, which could take place during any infusion interval after at least 16 weeks of treatment with IgPro20 (i.e. Week 16 to Week 24). During this time, blood samples were taken to determine the PK parameters AUC, Cmax, and Tmax from total serum IgG. During the 12-week SCIG efficacy period, subjects performed IgPro20 infusions as home treatment but visited the study site at 4-week intervals for efficacy and safety evaluations. In addition to efficacy and safety analyses, a survey using questionnaires was performed prior to infusion at Baseline, Week 12, and Week 24 to obtain data on the influence of SCIG treatment on HRQL and PhEc in these subjects

- **Study population**

ZLB07_002CR: 40 patients with PID were enrolled and treated (AT= all treated), the full HRQL population consisted of 37 patients. Four subjects discontinued (1 SAE resulting in death in Subject 1505, 1 withdrawal of consent, and 1 x "other") from the study, leaving 36 subjects (90%) who completed the study.

ZLB20_3001: 21 patients with PID were enrolled and treated, 18 were per protocol efficacy (PPE), and 5 patients discontinued the study; the reasons for discontinuation were withdrawal of consent (3 subjects: 13004, 13008, and 15911), lost to follow-up (1 subject: 08007; the subject had no clinically significant abnormal laboratory values at the last measurement in the study) and other SAE (subject 15001 who discontinued because of an SAE of thyroid cancer that was unrelated to study medication)

ZLB06_002CR: 25 patients with PID were enrolled and treated (AT), the full analysis set consisted of 24 patients (FAS), 21 were per protocol (PP), 8 patients entered the PK sub-study and 1 patient discontinued the study.

- **Inclusion criteria**

ZLB07_002CR: Male or female subjects with primary humoral immunodeficiency (i.e., common variable immunodeficiency [CVID], X linked agammaglobulinaemia [XLA], or autosomal recessive agammaglobulinaemia who participated in study ZLB06_001CR, tolerated IgPro20 well and gave written informed consent.

ZLB20_3001: Male or female subjects with PID (i.e., CVID or X-linked agammaglobulinemia) who participated in study ZLB04_009CR were offered the opportunity to participate in this extension study, provided none of the exclusion criteria were met.

ZLB06_002CR: Male or female subjects up to 75 years of age with PID with hypo- or agammaglobulinemia who required IgG replacement therapy and had a diagnosis of CVID, XLA, ARAG, Nijmegen breakage syndrome (NBS), hyper IgM syndrome, or ataxia telangiectasia. The diagnosis was confirmed by using the diagnostic criteria as defined by the Pan-American Group for Immunodeficiency (PAGID) and the European Society for Immunodeficiencies (ESID).Subjects must have received IVIG therapy at regular 3- or 4-week intervals at a stable dose (variations of ± 10% were allowed) for at least 3 doses prior to signing of informed consent. Written informed consent by the subject/parent/legally acceptable representative was required. For the SCIG period, subjects were included if they had an IgG trough level ≥5 g/L at least once between screening or first IVIG infusion until third IVIG infusion, IgG trough levels ≥4 g/L between screening or first IVIG infusion until third IVIG infusion, and no development of serious bacterial infections (SBIs) during the IVIG period. For the PK sub-study, subjects had to be aged ≥6 years at the time informed consent was obtained.

- **Treatments and duration**

ZLB07_002CR: The planned weekly dose of IgPro20 in this study was the same as the subject's last dose recommended by the investigator in study ZLB06_001CR. Individualized dose schedules and spreading of the weekly dose over several days were permitted based upon the subject's preferences and clinical judgment of the investigator, providing that the total weekly dose remained unchanged. Dose adjustments could be performed if medically indicated and in an amount according to the investigator's discretion. Changes in weight of more than ± 5% required a dose adjustment.

Filling lot numbers: 2024800005, 2024800007, 2024800008, 2024800009, 2024800010, 2024800011, 2044300006, 2044300014, 2044300017, 2044300022, 2072400054, 2072400078.

Duration of treatment: up to 36 months (UK sites only) or up to 42 months (all other sites).

ZLB20_3001: IgPro20 was administered as an SC infusion weekly or twice weekly, depending on the investigator's medical judgment and the subject's preference. The initial weekly dose of IgPro20 was the same as the last dose the subject received during study ZLB04_009CR. Dose adjustments could be made per investigator's judgment if the TLR for IgG differed from the threshold value of 1.29 (calculated from the results of the ZLB04_009CR pharmacokinetic sub-study) by more than 15% (i.e., was below 1.10 or above 1.50).

Packing lot numbers: 4310900004, 4310900005, 4310900006, 4310900007, 4310900008, 4310900009, 4310900010, 4310900011, 4310900012

Efficacy period: between last infusion in study ZLB04_009CR and availability of IgPro20 on the market (treatment duration of up to ~30 months).

ZLB06_002CR: IgPro20 was administered as SC infusions at weekly intervals at home by the subject/parent/guardian after a training period at the study site for a total of approximately 24 weeks. The initial weekly IgPro20 dose was equivalent to a subject's previous IGIV dose divided by the dosing interval in weeks. Dose adjustments could be performed during the wash-in/wash-out period at the discretion of the investigator in order to produce IgG trough levels of no less than 5 g/L.

Packing lot numbers: 4358000001, 4358000002, 4358000003.

IVIG period: 3 consecutive infusions at 3- or 4-week intervals; SCIG wash-in/wash-out period: 12 weeks; SCIG efficacy period: 12 weeks

- **Outcomes/endpoints**

ZLB07_002CR:
Efficacy variables: Descriptive comparison of serum IgG levels at Visits 1, 3, 5, 7, 9, 11, 13, and 15. Rate of clinically documented serious bacterial infections (SBIs; defined as bacterial pneumonia, bacteraemia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, or visceral abscess), number of infection episodes, number of days out of work/school/kindergarten/day care or unable to perform normal activities due to infections, number of days of hospitalization due to infections, and use of antibiotics for infection prophylaxis and treatment.

HRQL: The influence of long-term SCIG treatment on HRQL in subjects with PID who switched from the pivotal study ZLB06_001CR to the extension study ZLB07_002CR was assessed using validated HRQL questionnaires. Questionnaires were completed at Visits 3, 5, 7, 9, 11, 13 and 15 and examined both generic and treatment-specific subject status.

Safety and tolerability: Rate, severity, and relatedness to the study drug of any adverse events (AEs) per infusion and per subject; changes in vital signs; and changes in routine laboratory parameters (blood chemistry, haematology, urinalysis) as compared to baseline status.

ZLB20_3001: Efficacy: Annual rate of clinically documented serious bacterial infections (SBIs) as defined in the FDA guidance, total serum IgG C-trough values, any infection episodes, days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections, days of hospitalization due to infections, and use of antibiotics for infection prophylaxis and treatment.

Safety and tolerability: Local tolerability of SC infusions, adverse events (AEs), changes in routine laboratory parameters, vital signs changes before and after infusions at the study site, concomitant medications, and viral safety.

Other outcomes: Ratings of HRQL, treatment satisfaction, utility, and health-care related resource use.

ZLB06_002CR:
Primary efficacy variable: The geometric mean ratio (GMR) of SCIG versus IVIG trough levels of IgG along with a 2-sided 90% confidence interval (CI). Mean trough levels of 3 IVIG infusions in the IVIG study period were compared to trough levels measured at steady-state of 3 SCIG infusions (Week 16, Week 20, and Week 24) by way of descriptive comparison.

Secondary efficacy variables: Number of infection episodes (serious and non-serious), number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections, number of days of hospitalization due to infections, duration of use of antibiotics for infection prophylaxis and treatment.

PK parameters: AUC, Cmax, Tmax from total serum IgG.

HRQL and PhEc: To assess the influence of SCIG treatment on subject HRQL and PhEc, questionnaires were applied at baseline, Week 12, and Week 24. HRQL was assessed with the disease/application specific questionnaires “Satisfaction of the current IgG replacement therapy” and “Life Quality Index” (LQI). For the PhEc assessment the “Medical expenditures of IVIG and SCIG treatments” questionnaire was used.

Safety: Number, rate, severity, and relatedness of any adverse events (AEs) per infusion and subject, assessment of local tolerability of SC infusions, vital sign changes before and after infusions at the

study site, changes in routine laboratory parameters (blood chemistry, hematology, urinalysis) as compared to baseline assessments, changes in viral safety markers of IgPro20 treatment as compared to baseline assessments.

- **Statistical Methods**

ZLB07_002CR: Total serum IgG trough levels and changes from baseline (using 2 definitions of baseline: the baseline visit of the pivotal study ZLB06_001CR, and the baseline visit [Visit 1] of the extension study) were analysed descriptively to investigate the maintenance of consistent IgG trough serum levels throughout the study. Further efficacy and safety data and changes in HRQL scores over time were analysed descriptively.

ZLB20_3001: The 12-month rate of SBIs was estimated along with the 1-sided 99% upper confidence limit in the ITT and PPE populations. Analyses of all other efficacy endpoints were based on the ITT population. All endpoints were analyzed descriptively.

ZLB06_002CR: The primary analysis was a descriptive comparison of 3 IgPro20 IgG C trough values per subject during the SCIG efficacy period with the last 3 IgG C-trough values obtained during the IVIG period in the PPS population expressed as GMR. Further efficacy and safety data were analyzed descriptively. PK parameters were derived by non-compartmental analysis and summarized descriptively. Absolute values and changes in HRQL and PhEc scores compared to baseline were analyzed descriptively

Assessor's comment
The study designs, objectives, inclusion criteria of the 3 studies are endorsed.

Results

- **Baseline data/ Demographic characteristics**

ZLB07_002CR: All 40 subjects enrolled in the extension study were treated with IgPro20 and were included in the AT set and the ITT set. The ITT population consisted of 12 females (30%) and 28 males (70%). Subjects had a mean age of 21.6 years (range: 4 to 52 years). A total of 15 subjects (37.5%) were 2 to <12 years of age, 4 subjects were 12- < 16 (10%) years and 21 subjects (52.5%) were <16 years of age. All subjects were Caucasian (White) with a mean body weight of 52.4 kg (range 15 to 95 kg) and a mean BMI of 20.5 kg/m2 (range 13.9 to 31.4 kg/m2).

CVID was the primary disease in 23 subjects (57.5%), 16 subjects had XLA, which explains the male vs. female imbalance in this study, 1 subject had ARAG.

The mean IgG trough values in the previous pivotal study ranged between 7.99 and 8.25 g/L.

Dose:
The mean IgPro20 dose per week was 115.5 mg/kg and doses ranged from 54 to 406 mg/kg bw. The mean and the median of individual median doses was 117.9 mg/kg bw (standard deviation [SD] 31.01) and 116.0 mg/kg, respectively.

ZLB20_3001: Of the 21 subjects treated with IgPro20 in this study for a median duration 87 weeks (range: 11 to 104 weeks), 15 were female and 6 were male. The mean age was 42.4 years (2 children <16 years of age); all subjects were Caucasians. Mean body weight was 71.8 kg; mean BMI was 26.4 kg/m2

CVID was the primary disease in all subjects, and all subjects had the disease for >2 years at enrollment into the study.

The mean of individual median IgG Ctrough values during the last 3 month before the Screening Visit, i.e., during the preceding study ZLB04_009CR, was 12.20 g/L (range: 7.78 to 21.01 g/L)

Dose:
The mean of individual median weekly IgPro20 doses administered during the study was 221.3 mg/kg. Over time, the mean IgPro20 doses per week ranged between 216.6 and 239.7 mg/kg
The majority of subjects were using 2 infusion pumps simultaneously. The mean of individual median total body infusion rates was 48 mL/h. A total of 8 subjects had infusions with the maximum total body infusion rate of 70.0 mL/h. The mean duration of IgPro20 infusions was 2.08 hours.

ZLB06_002CR: In the FAS, 15/24 (62.5%) subjects were male and all subjects were of Asian origin. Mean age was 20.5 years (11 subjects [45.8%] ≤16 years) in the FAS. Mean body weight in the FAS was 46.0 kg. The mean body mass index (BMI) was 18.8 in the FAS, 19.1 in the PPS and 21.3 in the PK analysis set.
Primary humoral immunodeficiency was XLA in 12 subjects (50.0%), CVID in 10 subjects (41.7%), ARAG and hyper IgM syndrome in 1 subject (4.2%), each.

Assessor's comment
The baseline data in the 3 studies are representative of the PID population

- **Efficacy results**

ZLB07_002CR: (ITT population):
In the AT population, mean IgG trough values were measured every 6 months for 36 months and in 4 subjects up to 42 months.

Mean serum IgG trough levels were stable throughout the extension study, falling within a range of 7.5 to 8.5 g/L, with a mean (standard deviation, SD) median value of 7.97 (1.17) g/L, and a median value of 8.12 g/L (range: 5.8 g/L to 11.1 g/L). Stable median IgG trough levels were maintained within a narrow range throughout the treatment periods of the pivotal study ZLB06_001CR and the extension study, constituting a combined observation period for the majority of ITT subjects of 3 years.

One subject (Subject 1905, a 10-year-old female with CVID) had IgG trough levels <5 g/L at several visits (4.76 g/L at Visit 9, decreasing further to 3.32 g/L at Visit 11, and increasing after dose adjustment to 4.23 g/L at Visit 13), with a median trough level for the full study duration of 5.77 g/L; there was no increased incidence of infections in this subject. Low IgG trough levels could have been caused by protein-losing enteropathy due to coeliac disease.

Five SBIs (all bacterial pneumonia) in 5 subjects were reported during the extension study (annualized rate: 0.0478 SBIs/subject/year; upper 1-sided 99% confidence limit: 0.1252).

A total of 38 subjects (95%) had at least 1 infection during the study period (38208 subject days) (rate: 3.334 infections/subject/year; 95% confidence limits: 2.993; 3.703). The most common infections were bronchitis (51 events; rate: 0.487 infections/subject/year), upper respiratory tract infection (49 events; rate: 0.468 infections/subject/year), sinusitis (31 events; rate: 0.296 infections/subject/year), cough (26 events; 0.248 infections/subject/year), and nasopharyngitis (19 events; 0.182 infections/subject/year).

In the ITT population, 27 subjects (67.5%) missed work/school/kindergarten/day care or were unable to perform normal activities due to infections on a total of 706 days (rate: 6.773 days/subject/year), 7

subjects (17.5%) were hospitalized for a total of 110 days due to infections (rate: 1.055 days/subject/year), and 36 subjects (90.0%) used antibiotics on 7551 days (rate: 72.13 days/subject/year). Antibiotics were used mainly for treatment of the corresponding medical condition (35 subjects, 87.5%), while 6 subjects (15.0%) used antibiotics for prophylaxis. No subgroup analyses were performed for this study.

	Pre-extension period (Pivotal study ZLB06_001CR)		Extension period (Study ZLB07_002CR)	
Efficacy endpoint	**Number (%) of subjects**	**Number (annualized rate) of events/days**	**Number (%) of subjects**	**Number (annualized rate) of events/days**
	(N=46)	(N=8745)	(N=40)	(N=38208)
Serious bacterial infections (ITT)	0	0	5 (12.5)	5 (0.048)
Infection episodes	36 (78.3)	124 (5.18)	38 (95.0)	349 (3.33)
Days with antibiotics for infection prophylaxis or treatment	32 (69.6)	1743 (72.75)	36 (90.0)	7551 (72.13)
	(N=46)	(N=9033)	(N=40)	(N=38045)
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections	20 (43.5)	198 (8.00)	27 (67.5)	706 (6.77)
Days hospitalized due to infections	4 (8.7)	86 (3.48)	7 (17.5)	110 (1.06)

HRQL results (Full HRQL population, n=37):
As PID is a chronic disease, and subjects entering the study were already pre-treated with IgPro20 given as SCIG, relevant changes in HRQL outcomes were not expected. Overall, HRQL scores from each instrument appeared stable through Month 36, which was the last time point with a large enough sample size of study subjects to provide meaningful results

Assessor's comment
The extension study ZLB07_002CR shows adequate efficacy outcomes that are in line with the original MAA study.

ZLB20_3001:
Two subjects had an SBI (bacterial pneumonia), resulting in an annual rate of SBIs per subject year of 0.06 (upper 99% confidence limit: 0.257). IgG Ctrough values in these 2 subjects with SBIs ranged between 6.81 and 9.63 g/L throughout the study.
A total of 20 subjects (95.2%) in the ITT population had at least 1 infection during the study. The total rate of infection was 2.38 per subject year (95% confidence interval: 1.883; 2.973). The most frequent infections (rate of ≥0.15 per subject year) were sinusitis, bronchitis, upper respiratory tract infection, and nasopharyngitis.

In the ITT population 9 subjects (42.9%) missed work/school/kindergarten/day care or were unable to perform normal activities due to infections on a total of 140 days during the study, resulting in an annual rate of 4.28 days per subject year. 2 subjects were hospitalized for a total of 18 days due to infections, which amounted to an annual rate of 0.55 days per subject year. 19 subjects (90.5%) were treated with antibiotics for a total of 2746 days, which amounted to an annual rate of 83.87 days per subject year. Antibiotics were used mainly for treatment of medical/surgical/current conditions.

The mean of individual median IgG Ctrough values was 11.98 g/L; none of the subjects had an IgG Ctrough value <5 g/L during IgPro20 treatment in this study. Mean IgG Ctrough values were generally stable throughout the study (between 11.71 and 12.76 g/L).

HQRL results

The evaluation of HRQL, treatment satisfaction, and utility showed a trend towards maintenance of HRQL and high treatment satisfaction throughout the study. Health-care related resource use and associated costs were in line with the expectations for patients with PID.

Assessor's comment
The extension study ZLB20_3001shows adequate efficacy outcomes that are in line with the original MAA study.

ZLB06_002CR: The primary efficacy analysis was the comparison of median individual IgG Ctrough levels of the SCIG (IgPro20) efficacy period with those of the IVIG period in the PPS by GMR. The IgG Ctrough levels increased from 6.53 g/L in the IVIG period to 7.15 g/L in the SCIG efficacy period. The GMR calculated was 1.09 (90% CI: 1.06 to 1.13), showing that the objective of achieving comparable IgG Ctrough levels was met.
Only one patient had a trough level of under 5 g/L and despite increases in SCIG the IgG trough levels dropped to 2.82 g/L. Temporally related to the decrease in IgG trough levels, the subject experienced acute gastroenteritis with symptoms of diarrhea, nausea, vomiting and stomach pain.

No subject had a SBI during any part of the study.

11 subjects (52.4%) had at least 1 non-serious infection during the SCIG efficacy period (annualized rate of 2.98 infections/subject [upper 99% confidence limit: 5.305 infections/subject]). The most frequent types of infections were nasopharyngitis (3 subjects [14.3%], annualized rate of 0.79 infections/subject), upper respiratory tract infection (3 subjects [14.3%], annualized rate of 0.60 infections/subject) and gastroenteritis (2 subjects [9.5%], annualized rate of 0.79 infections/subject). During the SCIG efficacy period, 7 subjects (33.3%) missed work/school/kindergarten/day care or were unable to perform normal activities due to infections on a total of 19 days (annual rate of 3.48 days/subject) and 1 subject (4.8%) was hospitalized once due to an infection for a total of 3 days). 16 subjects (76.2%) were treated with antibiotics on a total of 844 days (annualized rate of 167.42 days/subject). 13 subjects (61.9%) received antibiotics because of AEs or treatment of current medical condition (annualized rate 90.85 days/subject) and 5 subjects (23.8%) were treated for prophylaxis (annualized rate of 83.71 days/subject). The annualized rate of infections and all other secondary efficacy results were similar for the IVIG and SCIG periods.

Assessor's comment
The Phase III study shows good efficacy outcomes and comparable IgG trough levels under IVIG and SCIG treatment.

- Pharmacokinetic results [PK analysis set]

Prior treatment
All 24 FAS subjects were pretreated with IVIG, 16 (66.7%) in a 4-weekly and 8 (33.3%) in a 3-weekly treatment schedule. The average IVIG dose in subjects who received a 4-weekly treatment schedule was 291.5 mg/kg (SD: 136.93, number of injections: 47, FAS), and 236.2 mg/kg (SD: 71.58, number of injections: 24, FAS) in subjects who received a 3-weekly treatment schedule.
The FAS mean serum IgG concentration at trough level (Ctrough) levels during the last 3 months before study enrolment (prior to IVIG treatment period in the study) based on each subjects' median IgG trough level were 6.48 g/L (SD: 1.385) with a median of 5.90 and a range of 4.67 to 10.01 g/L. The IgG trough levels of the AT, PPS, and PK analysis sets were very similar.

Study treatment
The resulting mean weekly IgG dose-equivalent based on the median of the individual subjects' aggregated values was 72.9 mg/kg (range 22 to 144 mg/kg) for subjects with a 4-weekly treatment schedule and 78.7 mg/kg (range 52 to 119 mg/kg) for subjects with a 3-weekly treatment schedule.

The PK analysis in 8 subjects revealed stable serum IgG concentrations during the SCIG efficacy period. Mean IgG values over time ranged between 6.98 and 7.34 g/L. The mean Cmax IgG value was 7.63 g/L and Tmax was very variable between 0.13 and 6.98 days post-infusion, with a median of 2.56 days.

Assessor's comment
The PK data is limited in its relevance due to the small sample size (in 8 subjects) and large fluctuations in Tmax (0.13 and 6.98 days post-infusion).

HRQL results [FAS]:
The "Satisfaction with the current IgG replacement therapy questionnaire" showed that during the SCIG study period >95% of the subjects were performing their therapy mainly at home. At Week 24, 14 subjects (58.3%) were able to perform the SCIG home infusion by themselves and none needed support from a medical professional. The mean LQI total score increased from 53.7 at Week 1 (IVIG) to 71.5 at Week 24 during SCIG treatment with IgPro20. Improvements were found in all LQI subscales but were most pronounced for "costs", "therapy setting", and "treatment interference".

Assessor's comment
As mentioned above, HQRL is of limited value in an open study; nevertheless it is of interest that in the PhEc assessment, the switch to IgPro20 treatment was associated with reduction in productivity loss and hospital-related absenteeism compared to IVIG therapy.

- **Safety results**

Adverse events (AEs)
ZLB07_002CR: The safety of IgPro20 was evaluated in all 40 subjects who received IgPro20 during any study period in the extension study. A total of 5405 weekly infusions of IgPro20 were administered. The lowest number of infusions was 10 and the highest 168. Only 3 subjects received less than 100 infusions during the extension study.

Thirty-nine subjects (97.5%) had at least 1 AE, and 8 subjects (20.0%) had at least 1 AE that was considered by the investigator to be at least possibly related to study drug (i.e. causally related). No causally related AE preferred term was reported for more than 1 subject during the study. There was a total of 506 AEs (rate: 0.0936 AE/infusion) of which 14 AEs were considered at least possibly related to study drug (rate: 0.0026 AE/infusion). The causally related AEs were local reactions (7), headache (3 events), dizziness (2 events), arthritis (1 event), pancreatic enzymes increased (1 event).

There were no discontinuations in this study because of AEs.

The most common AE, experienced by 21 subjects (52.5%) was bronchitis, followed by upper respiratory tract infection (18 subjects, 45.0%), sinusitis (13 subjects, 32.5%), nasopharyngitis (12 subjects, 30.0%), cough (11 subjects, 27.5%), and rhinitis (9 subjects, 22.5%). Local reactions were reported in 6 subjects (15.0%); the rate by infusion was 0.0013. All other AEs in the extension study affected 15% (n<6) or less of the subjects.

Incidence of subjects with common adverse events (experienced by ≥4 subjects) by preferred term and rate per infusion, irrespective of causality (AT population).

Preferred term	All events	
	Number (%) of subjects (N=40)	Number (rate) of events (N=5405)
Any preferred term	**39 (97.5)**	**506 (0.0936)**
Bronchitis	21 (52.5)	51 (0.0094)
Upper respiratory tract infection	18 (45.0)	49 (0.0091)
Sinusitis	13 (32.5)	31 (0.0057)
Nasopharyngitis	12 (30.0)	19 (0.0035)
Cough	11 (27.5)	34 (0.0063)
Rhinitis	9 (22.5)	15 (0.0028)
Arthralgia	6 (15.0)	7 (0.0013)
Febrile infection	6 (15.0)	10 (0.0019)
Local site reactions	6 (15.0)	7 (0.0013)
Acute sinusitis	5 (12.5)	5 (0.0009)
Pharyngitis	5 (12.5)	10 (0.0019)
Pneumonia bacterial	5 (12.5)	5 (0.0009)
Abdominal pain upper	4 (10.0)	9 (0.0017)
Diarrhoea	4 (10.0)	6 (0.0011)
Influenza	4 (10.0)	4 (0.0007)
Pyrexia	4 (10.0)	6 (0.0011)
Viral infection	4 (10.0)	4 (0.0007)
Viral upper respiratory tract infection	4 (10.0)	5 (0.0009)

The majority of AEs in this study were mild (370 of 506 AEs) or moderate (125 of 506 AEs) in intensity; 11 (2.2%) AEs in 7 (17.5%) subjects were considered of severe intensity (rate by injection: 0.0020). Only 1 severe AE was reported more than once (pneumonia bacterial, 3 times; rate by injection: 0.0006).

Laboratory parameters

There were no major or new safety concerns regarding clinical laboratory parameters during this study. Clinically significant abnormal values were observed in only 6 subjects.

In 4 subjects (Subject 1303, 1902, 1905, and 2103) haematology values were considered clinically relevant (*narratives were provided)*. For haemoglobin and haematocrit the lower ranges declined from 116 g/L to 74 g/L and from 0.35 to 0.25, respectively; this was mainly due to Subject 1905 who had iron deficiency anaemia and coeliac disease. Subject 1303 also had coeliac disease. For 1 subject(0406) haemoglobin dropped to 137 g/L, haptoglobin decreased to 0.25 g/L, and LDH increased to 487 U/L. indicating haemolysis. This subject had a relevant medical history of haemolytic anaemia since 2004.

One subject (1503, 8 y female) with chronic ITP had a decline in platelets to 3 $x10^9$/L at Visit 11 and 9 $x10^9$/L at completion. Three subjects had a positive Coombs test at selected visits, but were negative at the completion visit. In addition, 1 subject who already had a positive direct Coombs test at screening also had positive direct Coombs tests throughout the study.

In serum chemistry there were shifts from normal/high at baseline to low at the completion visit in 4 subjects for LDH, in 3 subjects for lipase, in 2 subjects for total protein, and in 1 subject for AP and shifts from normal/low at baseline to high at the completion visit in a further 4 subjects for ASAT, in 3 subjects for LDH, in 2 subjects each for ALAT, amylase and haptoglobin, and in 1 subject each for urea, BUN, AP and lipase. One value associated was considered clinically relevant, i.e. change in LDH in Subject 1303.

Assessor's comment
There were no new safety signals or increased rates of known signals.

ZLB20_3001: Safety results (AT population):

The safety of IgPro20 was evaluated in all 21 subjects enrolled and treated in this study. A total of 1735 IgPro20 infusions were administered; most subjects (18 subjects [85.7%]) received at least 50 infusions (range: 11 to 146 infusions)

All subjects (100%) had at least 1 AE. There were 1147 AEs and 1735 infusions in this study, resulting in an AE rate per infusion of 0.661. The rate of AEs that were causally related to study medication was 0.524 (909 events) in 21 subjects. Local reactions were the most frequent AEs experienced by all subjects; the rate of local reactions per infusion was 0.500. Excluding local reactions, the overall AE rate per infusion was 0.161. The next most frequent AEs after local reaction were sinusitis and nasopharyngitis (66.7% and 33.3% of subjects, respectively). Most AEs (98.5%) were mild or moderate in intensity. According to the subjects' assessments of local tolerability (within 24 hours after each infusion), approximately 45% of subjects experienced injection site reactions after each infusion. Almost all of these injection site reactions (99.3%) were assessed as "very slight" or "slight" in intensity.

Incidence of subjects with frequent adverse events (experienced by ≥3 subjects) by preferred term and rate per infusion, irrespective of causality (AT population)

	All events		Temporally associated (72 hours)	
Preferred term	Number (%) of subjects (N=21)	Number (rate) of events (N=1735)	Number (%) of subjects (N=21)	Number (rate) of events (N=1735)
Any preferred term	**21 (100)**	**1147 (0.661)**	**21 (100)**	**997 (0.575)**
Local reaction [a]	19 (90.5)	868 (0.500)	19 (90.5)	863 (0.497)
Sinusitis	14 (66.7)	24 (0.014)	6 (28.6)	10 (0.006)
Nasopharyngitis	7 (33.3)	10 (0.006)	3 (14.3)	3 (0.002)
Oropharyngeal pain	6 (28.6)	12 (0.007)	3 (14.3)	6 (0.003)
Upper respiratory tract infection	6 (28.6)	6 (0.003)	3 (14.3)	3 (0.002)
Fatigue	5 (23.8)	33 (0.019)	3 (14.3)	27 (0.016)
Arthralgia	5 (23.8)	5 (0.003)	2 (9.5)	2 (0.001)
Bronchitis	5 (23.8)	7 (0.004)	1 (4.8)	1 (<0.001)
Influenza like illness	4 (19.0)	7 (0.004)	4 (19.0)	5 (0.003)
Nausea	4 (19.0)	4 (0.002)	1 (4.8)	1 (<0.001)
Headache	3 (14.3)	10 (0.006)	2 (9.5)	7 (0.004)
Back pain	3 (14.3)	10 (0.006)	2 (9.5)	5 (0.003)
Abdominal pain	3 (14.3)	4 (0.002)	2 (9.5)	3 (0.002)
Anxiety	3 (14.3)	3 (0.002)	2 (9.5)	2 (0.001)
Diarrhoea	3 (14.3)	4 (0.002)	0	0

Subgroup analyses of AEs revealed no clinically relevant or consistent trends according to gender or total body infusion rate. The rate of local reactions had a tendency to increase with total IgPro20 dose volume. The numbers of subjects in some age classes and dose volume classes were too low to allow any meaningful conclusions

Almost all of the assessments for injection site reactions (99.3%) were reported by the subjects as "very slight" or "slight", 6 injection site reactions (0.7%) were reported as "moderate" and none as "severe".

Laboratory parameters

There were no safety concerns regarding clinical laboratory parameters over the course of the study. There was no indication that SC administration of IgPro20 in PID patients was associated with hemolysis, as none of the subjects had a positive DAT and a decrease in hemoglobin of ≥2.0 g/dL, together with increased LDH and decreased serum haptoglobin at any time during the study. With respect to virus safety, there were no proven cases of infections due to human immunodeficiency virus (HIV), hepatitis A/B/C virus (HAV/HBV/HCV), or parvovirus B19 during the study.

There were no clinically relevant changes from baseline in vital signs or physical examinations.

Assessor's comment

There were no new safety signals, the rates of AEs are slightly higher than in the European study, however, the majority was local reactions. The slightly higher rate in this US study is most likely due to the higher doses administered.

ZLB06_002CR: The safety of IgPro20 was evaluated in all 25 subjects enrolled and treated in this study with weekly SC infusions with IgPro20. A total of 584 IgPro20 SCIG infusions were administered. Overall, 143 (48.3%) infusions during the wash-in/wash-out period were given at home and 153 (51.7%) infusions at the investigational site. During the efficacy period 213 (74.0%) infusions were given at home and 75 (26.0%) at the investigational site.
24 subjects (96.0%) experienced at least 1 AE. AEs were at least possibly related to study drug in 21 subjects (84.0%) and temporally associated (i.e., during or within 72 h after the end of infusion) in 23 subjects (92.0%). 21 subjects (84.0%) had at least 1 AE that was considered both at least possibly related to study drug and temporally associated. 1 subject (4.0%) had 1 SAE (bacterial infection), which was assessed by the investigator to be unrelated to the study drug.
Based on the 584 SCIG infusions administered in the study, the overall AE rate per infusion was 0.457, the rate of at least possibly related AEs was 0.296, the rate of temporally associated AEs (72 h) was 0.344, and the rate of AEs that were both temporally associated and at least possibly related to study drug was 0.288. The majority of at least possibly related AEs were also temporally associated to study drug.
The most common AEs were local reactions (i.e. a group of 16 preferred terms related to the site of injection). They occurred at a rate per infusion of 0.274 and were experienced by 20 subjects (80.0%). All local reactions were mild in intensity.
Other common AEs (in ≥4 subjects [≥16%]) were nasopharyngitis, upper respiratory tract infection, and influenza. All other AEs occurred in ≤3 subjects (≤12%). All AEs were mild or moderate in intensity.
Due to the small size of the subgroups no conclusive evidence could be drawn from the subgroup analyses by age. In the eleven children no subject had an AE of severe intensity and only one had an AE of moderate intensity, the rest were all mild AEs. As with the adult local reactions were the prevalent AEs.
In the study sample, there is no sign detectable indicating higher rates of temporally related AEs with a high SCIG starting infusion rate of >25 mL/h. For all AEs by PT temporally associated with SCIG infusion (72 h), the event rate by infusion was 0.361 (172 events) in the 15 to 25 mL/h and 0.292 (28 events) in the >25 mL/h subgroup.
No clear statements can be made about the AE rate depending on the setting clinical setting vs. infusions made at home. However, it appears that there is a trend over the course of the study for the rate of AEs decreasing from the SCIG wash-in/wash-out period to the efficacy period (regardless of the setting of the infusion). This correlates with the consistent decrease of local reactions which made up the majority of the AEs reported over time on therapy.

Laboratory parameters
There were no safety concerns regarding clinical laboratory parameters over the course of the study, although there were clinically significant abnormal values observed reported in 6 subjects. No positive Direct Coombs' test was found during the study, and hemoglobin values were stable throughout the study. There were no clinically relevant changes in vital signs, and most physical examination findings were normal at baseline and at the completion visit. All subjects were also negative HIV-1, HIV-2, HCV, and HBV viral markers at baseline and viral safety follow-up.

Assessor's comment
There were no new safety signals. The profile is in keeping with other SCIGs.

- **Serious adverse events**

ZLB07_002CR
18 SAEs (0.003) were reported by 14 subjects (35.0%), all of which were considered as unrelated to the study drug by the investigators. Five SAEs were the 5 SBIs of bacterial pneumonia mentioned above. Eleven of the SAEs were temporally associated, i.e., occurred during or within 72 h after the end of an infusion (6x pneumonia, acute episode of ITP, dyspnea, facial oedema, bronchiolitis, bone fracture) . Seven SAEs in 5 subjects were severe in intensity: pneumonia (in Subjects 0202; 1505, and 1903), septic shock, agranulocytosis (sulfasalazine treatment), diarrhoea, and dyspnoea. Two SAEs were mild in intensity (abdominal pain, facial oedema), the remaining 10 SAEs were moderate in

intensity. One SAE each of bone fracture (Subject 1302), coeliac disease, and bronchiolitis was ongoing at final assessment. The SAE of dyspnoea resolved with sequelae, and the pneumonia in Subject 1505 had a fatal outcome (see Deaths below). All other SAEs resolved without sequelae.

- **ZLB20_3001:**

Five SAEs (0.003) occurred in 4 subjects: (01004: cellulitis; 01016: pneumonia; 15001: thyroid cancer [2 events, 1 of which had started during the preceding study ZLB04_009CR; the second event was a relapse]; and 15911: diarrhea), all of which were considered by the investigators to be unrelated to study medication. (*Narratives were provided*) One SAE of pneumonia was classified as an SBI (subject 01013)

ZLB06_002CR:

There was 1 treatment-emergent SAE in the SCIG period (Subject 1101; bacterial infection) in 584 infusions (rate: 0.0017). The investigator considered the event to be unrelated to study drug, the subject completed the study without interruption. This event did not fulfill the criteria for SBI according to the assessment of investigator and the sponsor's medical reviewer.

Assessor's comment
No new safety signals resulted from the SAEs, the reporting rates (0.003) were similar in the European and US studies and slightly lower in the Japanese study (0.0017).

- **Deaths**

ZLB07_002CR

One subject (1505) a 6-year-old female subject with CVID died from pneumonia. This subject had a known history of recurrent severe pneumonia requiring hospitalisation. An opportunistic lung infection (atypical Mycobacterium diagnosed in BAL by PCR only) was not controlled by high doses of IgG (230-260 mg/kg per week in the pivotal study; 227 mg/kg/week in this extension study) and poorly treatable with multiple courses of broad spectrum antibiotics suggest. The subject was treated for pneumonia with metamizole IV. The subject also received ciprofloxacine (100 mg, IV, 2 times a day), amikacine (200 mg, IV, once a day), ethambutol (300 mg, once a day), piperacilin/tazocain, ipratropium bromide, furosemide, dopamine, KCl, and oxygen.
No action was taken with respect to the study drug; however, the subject did not receive IgPro20 during the last hospitalization.
The SAE outcome was fatal after 41 days following hospitalization. Autopsy was not conducted. The final diagnosis is unknown. The SAE was considered an SBI. The investigator assessed the SAE as not related to the study drug, but to the underlying disease of chronic pneumonia.

Assessor's comment
It is not quite clear in the fatal outcome of this 6 year old girl why the study medication was not given during the last hospitalization. However, it is futile now to hypothesize whether this could have altered the course of the very severe disease.

- **ZLB20_3001:**

No deaths occurred in this study.

ZLB06_002CR:

No deaths or discontinuations due to AEs occurred during the study.

Rapporteur's summary

For a comparison of the current studies, initial MAA studies and the Japanese study see table below.

ZLB07_002CR:
This was an open, prospective, long-term extension study performed in 13 centres in Europe investigating the use of Hizentra in 40 PID patients; the results reflect the data seen in the pivotal study ZLB06_001CR.
We concur with the MAH that the efficacy data indicate that long-term therapy with IgPro20 at weekly doses is effective for the treatment of adult (n= 21) and paediatric subjects (n= 19 <16 y) with PID. IgG serum trough values were sustained over more than 3 years of extension study duration at the mean (SD) of the median value of 7.97 (1.17) g/L.
A total of 5 SBIs, (5x acute bacterial pneumonia), were experienced during the study by 5 subjects, translating into an annualized SBI rate per subject of 0.0478 (upper 1-sided 99% CI: 0.1252), thereby fulfilling Guideline recommendation of aiming for < 1 SBI/patient-year.
A total of 38 subjects (95%) had at least 1 infection during the study period resulting in an annualized rate of total infections was 3.33 infections/subject/year (95% CI: 2.993; 3.703), which was lower than the rate observed in the pivotal study ZLB06_001CR (5.18 infections /subject/year). The main infections were those of the respiratory tract.
HRQL assessments are of limited value in an open study, however the current data in 37 subjects indicated that for at least 36 months of stable dosing with IgPro20, PID subjects experienced stable quality of life.
Safety was evaluated in all 40 subjects who received a total of 5405 weekly infusions. Thirty-nine subjects (97.5%) had at least 1 AE, and 8 subjects (20.0%) had at least 1 AE that was considered to be at least possibly related (local reactions (7), headache (3 events), dizziness (2 events), arthritis (1 event), pancreatic enzymes increased (1 event)). The majority of the AEs were linked to the underlying disease. %). Local reactions were low (6 subjects (15.0%); rate by infusion was 0.0013).
18 SAEs (0.003) were reported by 14 subjects (35.0%), all of which were considered as unrelated.
One subject (1505) a 6-year-old female with CVID died from pneumonia. She had had a known history of recurrent severe pneumonia requiring hospitalization; it is unclear why the patient did not receive IgPro20 during the last hospitalization, however, this may not have changed the course of this unfortunate child.
There were no major or new safety concerns regarding clinical laboratory parameters over the course of the study. Clinically relevant values were observed in 5 subjects. Underlying diseases reported were coeliac disease, anaemia, chronic ITP, and respiratory tract infection. One subject had been positive for the direct Coombs test throughout the study and showed some signs of transient haemolysis on the background of chronic haemolytic anaemia.

ZLB20_3001:
This was a prospective, multicenter (n=4 in USA), open-label, single-arm, extension study in 21 PID patients lasting approx. 30 months; here again the results reflect the data seen in the previous study ZLB04_009CR.
As above, we agree with the MAH that the data obtained demonstrate that long-term, home-based treatment with Hizentra provides good efficacy with consistent IgG levels ((between 11.71 and 12.76 g/L), thereby controlling most recurrent infections.
Two subjects had an SBI (bacterial pneumonia), resulting in an annual rate of SBIs per subject of 0.06 (upper 99% CI: 0.257). All subjects had at least 1 AE, resulting in an AE rate per infusion of 0.661 (causally related: 0.524). Local reactions were the most frequent AEs. As in study ZLB07_002CR there were no major or new safety concerns regarding clinical laboratory parameters and no indication of hemolysis.

As with the initial studies for MAA the comparison of the European extension study ZLB07_002CR and US extension study ZLB20_3001 predictably showed that the lower IgG dosing resulted in lower IgG trough levels in the European study. The rate of SBIs is similar in both (0.0478 vs. 0.06). The rates of other infections, annualized days in hospital, and annualized days on antibiotics are higher in the

European study, however, the rate of AEs, esp. local reactions are higher in the US study. This again reflects the findings of the MAA studies.
As the US study only included 2 children, the relevance for the Art. 46 submission is low.

ZLB06_002CR:
This was a prospective multicenter (9 in Japan), open-label, single arm, Phase III study of IgPro20 in 25 subjects with PID, lasting approx. 6 months. The primary efficacy analysis was the comparison of median individual IgG Ctrough levels of IgPro20 with those of the previous IVIG treatment. The geometric mean ratio of the 2 treatment modalities was 1.09 (90% CI: 1.06 to 1.13), showing that the objective of achieving comparable IgG Ctrough levels was met. The majority of infusions were given at home (74%).
No subject suffered from an SBI; 11 subjects (52.4%) had at least 1 non-serious infection.

24 subjects (96.0%) experienced at least 1 AE with 84.0% experiencing an at least possibly related (mainly local reactions). There was 1 treatment-emergent, unrelated SAE. No new or major safety concerns regarding clinical laboratory parameters emerged. No positive Direct Coombs' test was found and hemoglobin values were stable. There were no clinically relevant changes in vital signs, and most physical examination findings were normal at baseline and at the completion visit. All subjects were also negative HIV-1, HIV-2, HCV, and HBV viral markers at baseline and viral safety follow-up.

According to the HRQL data, IgPro20 therapy improved quality of life in PID subjects compared to their previous IVIG treatment. In the PhEc assessment, switch to IgPro20 treatment was associated with reduction in productivity loss and hospital-related absenteeism compared to IVIG therapy.

Overall, the extension studies showed efficacy and safety results consistent with the data seen hitherto in the MAA studies; the Japanese studies further confirmed the adequate efficacy and safety data with Hizentra when administered as weekly SC infusions to adult and paediatric subjects with PID.

Changes to the SPC/PIL are currently not deemed necessary.

Comparison of studies

	ZLB06_001CR (Europe) N= 51 (22 < 16 years of age)	Extension ZLB07_002CR (Europe) N= 40 (19 < 16 years of age)	ZLB04_009CR (USA) N=49 (10 <16 years of age)	Extension ZLB20_3001 (USA) N=21 (2 <16 years of age)	ZLB06_002CR (Japan) N= 25 (11 <16 years of age)
IgG Trough level	7.99 - 8.25 g/L	8.12 g/L	12.53 g/L	11.98 g/L	7.15 g/L
Annualised per subject					
SBI (Rate; upper 99% CI)	0 (0; 0.192)	5 (0.0478; 0.1252)	0 (0; 0.132)	2 (0.06; 0.257)	0
Other infections/ (95% CI)	5.18 (4.305; 6.171	3.334 (2.993; 3.703)	2.76	2.38 (1.883; 2.973)	2.98 (upper 99% CI: 5.305)
Days missed work/school/KG	8.00	6.77	2.06	4.28	3.48
Days hospitalized due to infections	3.48	1.05	0.2	0.55	0.55
Days on antibiotics	72.75	72.13	48.5	83.87	167.42
Safety					
Subjects with AE at least possibly related	60.8%	20.0%	100%	100%	84%
Subjects with AE temp associated (within 72 h)	94%		100%	100%	92%
AE rate per infusion	0.288	0.0936	0.773	0.661	0.457
AE rate per infusion possibly related	0.106	0.0026	0.634	0.524	0.296
AE rate local reaction	0.060		0.592	0.500	0.274
Subjects with AE local reaction	49%	15%	100%		80%
SAEs (rate)	7 (0.004)	18 (0.003)	10 (0.004)	5 (0.003)	1 (0.0017)
SAE related	0	0	0	0	0
Deaths	0	1	0	0	0

Overall conclusion and recommendation

Overall, the extension studies showed efficacy and safety results consistent with the data seen hitherto in the MAA studies; the Japanese studies further confirmed the adequate efficacy and safety data with Hizentra when administered as weekly SC infusions to adult and paediatric subjects with PID.

Changes to the SPC/PIL are currently not deemed necessary.

☒ **Fulfilled** –

No regulatory action required.

Additional clarifications requested

Not applicable