



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## Assessment report

### **Hizentra**

**Common name: human normal immunoglobulin**

**Procedure No. EMEA/H/C/002127**

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



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# 1. Background information on the procedure

## 1.1. Submission of the dossier

The applicant CSL Behring GmbH submitted on 2 March 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Hizentra, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on November 2007. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The applicant applied for the following indication: 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 lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections

### **The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The active substance is known. The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

### ***Information on Paediatric requirements***

Not applicable

### ***Information relating to orphan market exclusivity***

#### **Similarity**

Not applicable.

#### **Market Exclusivity**

Not applicable.

### ***Scientific Advice:***

The applicant did not seek scientific advice at the CHMP.

### ***Licensing status***

Hizentra has been given a Marketing Authorisation in US on 4 March 2010.

A new application was filed in the following countries: Switzerland and Canada.

The product was not licensed in any country at the time of submission of the application.

## ***1.2. Steps taken for the assessment of the product***

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

Rapporteur: **Christian Schneider**      Co-Rapporteur: **Pierre Demolis**

- The application was received by the EMA on 2 March 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2010.
- During the meeting on 22 July 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 December 2010 .
- During the CHMP meeting on 16 December 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 February 2011.
- During the meeting 14-17 February 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Hizentra on 17 February 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 February 2011.

## **2. Scientific discussion**

### **2.1. Introduction**

#### ***Problem statement***

The first use of purified human immunoglobulin G (IgG) for treatment of PID was described by Bruton, and involved the administration of intermediate purity IgG by subcutaneous injection (SCIG). Subsequent investigators reported treatment primarily administered by intramuscular injection. In the early 1980s, highly purified, lyophilized preparations of IgG for intravenous administration (IVIG) were developed by a number of manufacturers. These highly purified IVIG products became the standard of care for treatment of PID, offering the possibilities of higher and more effective dosing than intramuscular administration. However, the subcutaneous route has experienced a revival as it offers a number of advantages: it has a low rate of adverse effects and can often be used for patients with previous adverse effects to IVIG; the fluctuations in IgG levels are less than with IVIG; home therapy can be employed, as the infusion technique is easy for children, adults and elderly people to learn and there is no requirement for venous access; thus SCIG home therapy may lead to improved life situations for the patients.

PID disorders result in increased susceptibility to recurrent infections, secondary to the underlying defects in humoral and/or cell-mediated immunity. To date, more than 100 different PID syndromes have been reported in the literature. The best described of these include X-linked agammaglobulinemia, common variable immune deficiency disease, selective IgA deficiency, severe combined immune deficiency, chronic granulomatous disease, Wiskott Aldrich syndrome, X-linked hyper IgM syndrome, DiGeorge syndrome, IgG subclass deficiency, ataxia telangiectasia, leukocyte adhesion deficiency, and complement deficiencies.

Therapeutic options for the treatment of infections in PID include standard antibiotic treatment and intravenous or subcutaneous administration of IgG. Therapeutic options for treatment of PID are transplantation of bone marrow-derived stem cells, and recently, gene therapy.

SCIG also has been used in the treatment of secondary immunodeficiencies such as those occurring in patients with multiple myeloma (MM) and B-cell chronic lymphocytic leukemia (CLL), and data derived from PID patients can be extrapolated to patients with MM and CLL so that no further studies are required in these patient populations.

The main mechanism of action of immunoglobulin in the case of immunodeficiency (primary and secondary) is replacement of immunoglobulins.

With this submission and in the case of an approval, a new subcutaneous product will enter the market that has a higher protein content than other marketed SCIGs hitherto. As the relevant Monograph (01/2002: 0388) of the European Pharmacopeia does not encompass higher protein content than 160 g/L (=16%), changes to the monograph are foreseen.

#### ***About the product***

Hizentra (IgPro20), is a new ready-to-use 20% protein liquid formulation of a polyvalent human immunoglobulin G (IgG) preparation for subcutaneous administration (SCIG) developed by CSL Behring. It has twice the IgG concentration of Privigen (IgPro10, a 10% IgG solution; marketed in several countries including Canada, the European Union, Switzerland, and the US), which contains the

same active drug substance as IgPro20. Hizentra is indicated for replacement therapy in primary immunodeficiency (PI) and in myeloma and CLL with severe secondary hypogammaglobulinaemia and recurrent infections. On account of its higher IgG concentration, the use of a 20% SCIG formulation is expected to reduce the infusion volume and duration of infusion compared to the 10% and 16% SCIG products currently used for IgG replacement therapy.

The protein moiety of Hizentra (IgPro20) is highly purified IgG ( $\geq 98\%$  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 Hizentra is based on the IgPro10 (Privigen: EMEA/H/C/831) process except for formulation and final protein concentration. 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 rubber stoppers.

The claimed indications and posology are consistent with those covered in the Core SPC for human normal immunoglobulin for subcutaneous and intramuscular use CPMP/BPWG/282/00, July 2002 namely:

“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 lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.”

“A loading dose of at least 0.2 to 0.5 g/kg (1.0 to 2.5 ml/kg) bodyweight may be required. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4 to 0.8 g/kg (2.0 to 4.0 ml/kg) bodyweight.”

This medicinal product is subject to medical prescription.

### ***The development programme/Compliance with CHMP Guidance/Scientific Advice***

This is a new centralised application for marketing authorisation of a Human Immunoglobulin normal for Subcutaneous Administration. It is a complete and independent application under article 8.3 of Directive 2001/83/EC as amended, with a known active substance. The submission is in CTD format.

No formal scientific advice was obtained from CHMP. A meeting was held with the PEI in Germany in June 2006 to obtain advice on the development of IgPro20 (PEI Meeting Minutes were submitted with the Applicant dossier - 5.4 ). The PEI encouraged CSL Behring to perform separate Phase III studies in Europe and the US to account for the different dosing concepts established in these 2 regions.

The studies performed to support the requested indications are in line with the relevant CHMP Note for Guidance on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use (SCIG/IMIG) CPMP/BPWG/283/00 and encompass the following trials:

<b>Type of study</b>	<b>Study identifier</b>	<b>Description of the study</b>
Phase III (Europe)	ZLB06_001CR	Pivotal study in subjects with PID to assess efficacy, safety, tolerability, PK, and HRQL of IgPro20
Phase III (USA)	ZLB04_009CR	Supportive study in subjects with PID to assess efficacy, safety, tolerability, and PK of IgPro20
Phase I	ZLB04_008CR	Supportive study in healthy subjects to assess safety and local tolerability of IgPro16 and IgPro20 in comparison to Vivaglobin
Phase I	ZLB06_003CR	Supportive study in healthy subjects to compare safety and tolerability of IV administration of IgPro20 (at the SC dose) in comparison to Privilgen

HRQL = Health-related quality of life; IV = Intravenous; PID = Primary immunodeficiency; PK = Pharmacokinetic(s); SC = Subcutaneous; USA = United States.

The applicant has applied the Guideline on the core SmPC for human normal immunoglobulin for subcutaneous and intramuscular use (CPMP/BPWG/282/00) accordingly.

No separate paediatric development has been described by the applicant, as it is not specifically required according to the Paediatric Regulation (2006/1901 EC).

## **2.2. Quality aspects**

### **2.2.1. Introduction**

The drug product, Hizentra (IgPro20), is a new ready-to-use 20% protein liquid formulation of a polyvalent human immunoglobulin G (IgG) preparation for subcutaneous administration (SCIG). The active ingredient IgG, manufactured from human source or recovered plasma, is neither isolated, characterised nor stored but continuously processed to the drug substance solution, (called IgPro10-SOL) and further on to the bulk drug product Hizentra (IgPro20). As a consequence no specifications were defined and no batches of drug substance were analysed.

The manufacturing process of the subcutaneous immunoglobulin (SCIG) solution Hizentra is based on the IgPro10 (Privilgen: EMEA/H/C/831) process except for formulation and final protein concentration

### **2.2.2. Active Substance**

#### ***Manufacture***

The production site of the drug substance (IgPro10-SOL) is CSL Behring AG, Bern (Wankdorfstrasse) and the production site of the intermediates is either CSL Behring AG, Bern (Wankdorfstrasse) (manufacturer of the intermediate Precipitate A (NA PPT), obtained by fractionation of human plasma according to Kistler-Nitschmann) or CSL Behring L.L.C, Kankakee (USA) (manufacturer of the intermediate fraction II+III precipitate (II+III PPT), obtained by fractionation of human plasma according to Cohn).

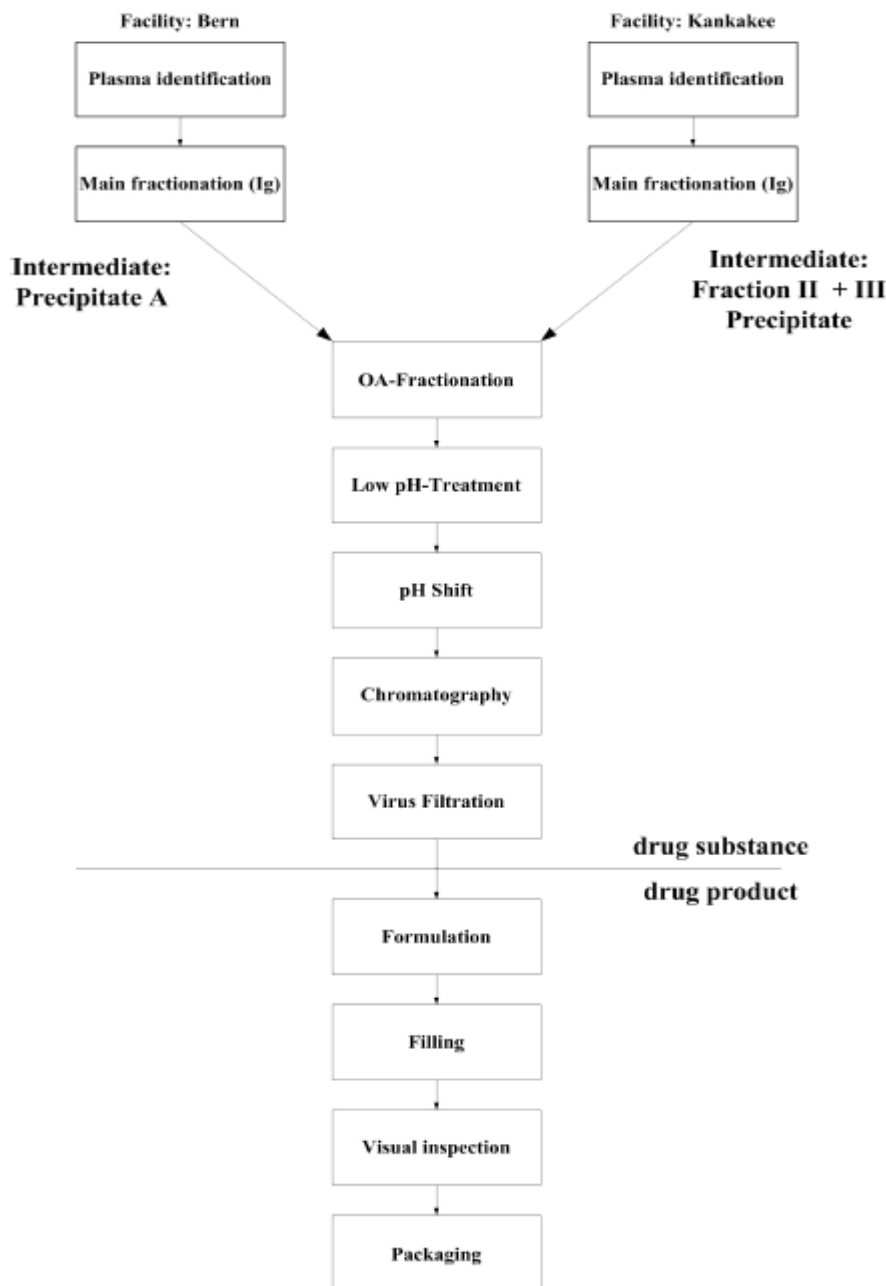
#### ***Description of Manufacturing Process and Process Controls***

Pooled plasma or recovered plasma is either cold ethanol fractionated in Berne (Precipitate A; Kistler-Nitschmann fractionation) or in Kankakee (Fraction II + III Precipitate; Cohn fractionation). Both Precipitate A and Fraction II+III Precipitate are approved intermediates for the manufacturing of IgPro10 (Privilgen). These precipitates are the only stored intermediates between plasma pooling and drug substance isolation. These intermediates are resuspended in a buffer and fractionated with

octanoic acid (also called caprylic acid) to selectively remove certain proteins and plasma derived lipids. The pH shift step removes IgM and aggregates whereas anion exchange chromatography removes almost all IgA and IgM molecules leading to an IgG purity of greater than 98%. The process also includes four virus reduction steps; octanoic acid fractionation, low pH inactivation, depth filtration, and virus filtration. The purified, ultrafiltrated IgG solution of IgG before final formulation can be considered the drug substance and is referred to as "IgPro10-SOL" for IgPro10 solution. Down to this stage, the manufacturing process for IgPro10 (Privigen) and IgPro20 are identical.

The drug substance, IgPro10- SOL, is immediately further processed and formulated to the product (IgPro20-Bulk), which can be stored up to 8 days prior to aseptically filling into vials. The following flow charts show the manufacturing process.

*Entire manufacturing process:*





### ***Control of Materials***

The starting material containing the active ingredient is human plasma which complies with the requirements of the Ph. Eur. Monograph *Human Plasma for Fractionation* and with the Note for Guidance on Plasma-Derived Medicinal products CPMP/BWP/269/95 rev.3. The starting material is registered in a Plasma Master File and is updated annually in accordance with Commission Directive 2003/63/EC. The actual PMF certificate of the PMF Holder CSL Behring GmbH was provided (EMA/H/PMF/000001/04/AU/006). Ingredients used for processing meet the compendial requirements of Ph. Eur. Caprylic acid and polysorbate 80 are both of plant origin. The filter aid meets compendial requirements, whereas other auxiliary materials and filter materials meets CSLB in-house requirements.

### ***Controls of Critical Steps and Intermediates***

The manufacturing process is controlled by Process Control Parameters (PCPs) and in the In-Process Controls (IPCs) as specified in the manufacturing procedures. Standard test methods for in-process controls are identical to finished product testing. The stability of intermediate precipitates was demonstrated.

### ***Process Validation and Evaluation***

The process validation of IgPro10-SOL was described and already assessed with the marketing authorisation application or variations applications for Privigen. The process validation included the validation of precipitate A manufacturing and the validation of Fraction II+III precipitate manufacturing. Two significant changes "Precipitate A Manufacturing with Alternative Filter Aids" and "Fraction II+III Precipitate manufacturing optional prothrombin adsorption" have been made to the manufacturing process of IgPro10-SOL and were also specifically validated for Hizentra. It was demonstrated that the purification process of the drug substance solution (IgPro10-SOL) was robust, reliable and high yielding.

### ***Manufacturing Process Development***

The development of the product Hizentra was described in detail and the validation reports were provided. The initial development of the IgPro20 drug substance solution (IgPro10-SOL) was done according to manufacture procedure of the drug substance solution, IgPro10-SOL (Privigen). The manufacturing process development was initiated with the production of a 15% protein solution (IgPro15). Manufacturing of higher concentrated solutions (IgPro16, IgPro18 and IgPro20) demonstrated the feasibility to manufacture a 20% protein solution. At a later stage of development suitability of prothrombin adsorbed Fraction II + III Precipitate and the use of alternative filter aids for the IgPro20 manufacturing process was demonstrated.

## **2.2.3. Finished Medicinal Product**

Hizentra is a new ready-to-use 20% protein liquid formulation of a polyvalent human immunoglobulin G preparation for subcutaneous administration. With the exception of pH and protein concentration, Hizentra meets the requirements of the Ph. Eur. Monograph "Human Normal Immunoglobulin" 07/2008:0338. All IgG subclasses found in normal serum are present in the final product. IgG function (Fc and Fab mediated activity) is retained. About 98% of the IgG portion of Hizentra consists of monomers and dimers as determined by size exclusion high performance liquid chromatography (SE-HPLC). The percentage of polymers (aggregates) is typically below 0.1% and the low molecular weight fraction, IgG fragments generated by proteolysis, is typically below 2%. The sterile 20% IgG solution is

formulated with 250 mmol/L of L-proline at pH 4.8. IgPro20 is aseptically filled into vials allowing enough overage in filling volume to guarantee the removal of the claimed volume on the label.

### ***Pharmaceutical Development***

The chosen formulation (20% IgG, 250 mmol/L L-proline, 20 µg/mL polysorbate 80, pH 4.8) presents Hizentra as a stable, clear and almost colourless immunoglobulin solution. Both, L- proline and polysorbate 80, are of plant origin and fulfil the compendial requirements of Ph. Eur. Water for injections (as in Ph Eur. Monograph) is used as a solvent to adjust the concentration of the drug substance and the excipients. HCl and NaOH are used in trace amounts to adjust the pH of the drug substance to pH 4.8 if necessary.

The formulation of IgPro20 is based on the IgPro10 (Privigen) formulation and was then further developed in order to address typical features of very highly concentrated IgG solutions. Overfill, in terms of a volume or weight of the formulation filled in each container in slight excess of the labelled content is employed for IgPro20 to compensate for non-extractable volume. The overfill values were indicated.

Subclass distribution and antigenic reactivity is discussed in detail and it is demonstrated that the reactivity to a variety of investigated antigens has been retained in the final product. Five different antigens (three viral, one bacterial, one toxin) measured in final IgPro20 were compared to Privigen and Sandoglobulin. Furthermore, the reactivity to antigens of particular clinical relevance (tetanus toxoid, Haemophilus influenza B, Pneumococcal Cell Wall Polysaccharide and Cytomegalovirus) contained in the three products have also been compared. These experiments demonstrate that the reactivity to the investigated antigens is comparable to other IVIGs licensed by CSL Behring. Fc-function of IgPro20 is adequately demonstrated. The elimination of impurities in the production process revealed that octanoic acid precipitation and anion exchange chromatography also caused a slight reduction of the IgG3 and IgG4 subclass.

### ***Adventitious agents***

Hizentra is produced from human plasma. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations Plasma is collected in Belgium, Denmark, Germany, Switzerland and the USA. Single donations are screened by an adequate testing program for viral markers (anti-HIV-1/2, HBsAg, anti-HCV). Manufacturing pools are tested by NAT for HIV RNA, HBV RNA, HCV RNA and parvovirus B19 DNA (limit: less than 10<sup>4</sup> IU B19V DNA per mL). Donors with an increased risk for sporadic or variant Creutzfeldt-Jakob-Disease are excluded. The donor selection and plasma donation testing strategy for viral markers is considered adequate.

Prion reduction has been demonstrated for the octanoic acid fractionation, clarifying depth filtration and nanofiltration steps.

Several steps have been investigated for their virus clearance capacity. These include octanoic acid fractionation, Low pH treatment, Clarifying depth filtration and nanofiltration. In summary, a sufficient safety margin with respect to HIV, HBV, HCV, HAV and B19V, has been adequately demonstrated. Therefore the recommendations for the text in Section 4.4 SPC according to note for guidance on the warning on transmissible agents in SPCs and package leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03) are considered acceptable.

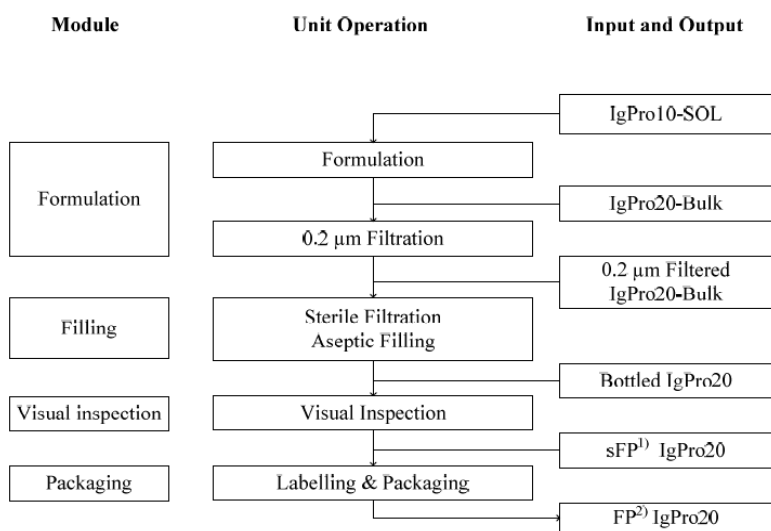
The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus (liver inflammation), and for the non-enveloped hepatitis A virus and B19V (Sticker's disease).

Immunoglobulins have not been associated with hepatitis A or B19V infections, possible because the antibodies against these infections, which are contained in the product, are protective.

In summary compliance with the requirements on virus safety as outlined in Guideline CPMP/BWP/269/95 has been demonstrated.

**Manufacture**

The manufacturing process of the final product is performed at CSL Behring AG, Bern Switzerland. The manufacturing process starts with the isolated drug substance solution (IgPro10-SOL) and ends with the labelling & packaging step leading to the IgPro20 final product. The manufacturing steps downstream from IgPro10-SOL consist of protein concentration and formulation 0.2µm bulk filtration and storage, sterile filtration, aseptic filling visual inspection and labelling & packaging.



**Process Validation and/or Evaluation:**

The processing steps bulk storage and sterile filtration, aseptic filling into final containers, and sterile filter validation were initially classified as critical and discussed in the Risk Analysis. These processing steps have been validated in process validation studies.

The manufacturing of the IgPro20bulk from precipitate A and fraction II+III was validated in three campaigns with 3 bulk lots each.

- 1) IgPro20 bulk manufacturing process using Precipitate A and Fraction II+III Precipitate
- 2) IgPro20 bulk manufacturing process using alternative filter aids, use of Precipitate A as starting material manufactured with an alternative filter aid and use of Fraction II+III manufactured with increased pool size, reduced Fraction I post-wash and increased ethanol addition rate
- 3) use of Fraction II+III Precipitate manufactured with prothrombin adsorption

In summary, all results of these three process validation activities met the acceptance criteria or complied following resolution of deviations. Comparability reports demonstrate that the stability of the final product IgPro10 as well as IgPro10 process parameters and IgPro20 impurity profiles are

comparable for the products manufactured from either intermediates Precipitate A or Fraction II+III Precipitate, or the alternative filter aids or the prothrombin adsorption. So far, the validation of the combination of all three options (1-3) demonstrating consistency was missing at the time of the opinion. The applicant has committed not to use alternative filter aids with and without prothrombin adsorbed, modified II+III PPT until process validation data is submitted. This combination occurs rarely. These data should be submitted as follow up measure. Depending on the data necessary corrective actions, a variation might be requested in order to adapt the manufacturing process accordingly.

The aseptic filling process validation was limited to the IgPro20 bulk storage, sterile filtration and aseptic filling. The formulated bulk (IgPro20-BLK) is stored in a 300 L mobile tank. Bulk stability in stainless steel containers was demonstrated by limited stability studies and bulk storage was validated by media holds in the tank and process validations.

**Batch Analysis:** Bulk lots as well as their associated filling lots have been manufactured from Precipitate A and Fraction II+III Precipitate for the purposes of clinical testing, process validation and stability testing. The data were provided. IPCs of all batches manufactured demonstrate excellent lot-to-lot consistency for microbiological attributes and for protein content.

#### ***Control of excipients***

Excipients are L-proline, polysorbate 80 and Water for Injections. All excipients are tested according to the methods described in the actual monographs. No novel excipients, no excipients of human or animal origin are used in the formulation of IgPro20. Non-compendial excipients are not present in IgPro20.

#### ***Control of Drug Product***

The proposed specifications for the drug product are in compliance with the requirements laid down in the Ph. Eur. Monograph "Human normal immunoglobulin"; except for the parameters pH and total protein. The Expert Group 6B (European Pharmacopoeia Commission) decided to revise the upper limit for total protein and the pH range in the monograph as soon as licensing of Hizentra is complete. Due to the subcutaneous route of administration a higher protein content than the maximum of 180g/l is acceptable. In order to reach stability of this high protein solution it was also necessary to go below the lower pH limit of 5.0. These deviations from the "Human Normal Immunoglobulin" 0338 monograph are acceptable and justified already with the nature of this product. The applicant decided to use the bacterial endotoxin test instead the rabbit pyrogen test. This can be accepted according to the revised monograph 01/2010: 0338 if a justification is provided.

Descriptions of the different analytical methods are presented in a condensed form. The methods described have been validated according to ICH and pharmacopoeial guidelines with the exception of the test for appearance. All analytical methods met the acceptance criteria of the validation and are suitable for the intended use.

Batch analysis data were presented. Batch data, which are clearly inside the specification-range, demonstrate uniformity of the product and show consistency of the manufacturing process.

In very detailed impurity profile reports the characterization of impurities of Hizentra produced from precipitate A, Fraction II+III precipitate, Beriplex-adsorbed Fraction II+III precipitate and IgPro20 manufactured using alternative filter aids were presented. No relevant differences between the investigated lots were detected. All impurities were either depleted to levels near or below the

quantification limits or were at least drastically reduced. All measured parameters included in the specification were within the specified limits.

#### ***Reference Standards or Materials***

The applicant uses different in-house standard materials calibrated against international standards for drug product testing.

#### ***Container Closure System***

The IgPro20 final product is aseptically filled into 6R, 10R, 15R, and 20R Type I glass containers. Tubular glass injection vials with high hydrolytic resistance. The filling volumes are 5 ml, 10 ml, 15 ml and 20 ml, respectively.

The vials can be closed with a ready-to-sterilize stopper. The stopper is similar to the CSL Product Privigen (formulation and coating) but 20 mm design instead of 32 mm. The rubber formulation complies with the Type I requirements of Ph. Eur. and USP and is free of latex: The stopper is secured by crimp caps consisting of an aluminium hole-bordered cap with a polypropylene plastic disc.

Furthermore container closure integrity has been validated through a program of microbial container closure integrity tests.

#### ***Stability***

The presented stability program is acceptable. The stability studies, including the selection of test parameters and test intervals, were performed according to ICH guidelines Q1A (R2) and Q5C. The stability studies apply a bracketing design according to ICH guideline Q1D by using the smallest (5mL) and the largest (20mL) filling sizes. A Post-approval Stability Protocol and Stability Commitment were provided.

To demonstrate the long-term stability of the drug product (24 months at 5 / 25°C) the applicant has performed adequate stability studies for the drug product derived from intermediate Precipitate A and fraction II+III for the filling sizes 5 and 20 ml using glass type I vials. The reports provide 24 months real time data of three IgPro20 process validation bulk lots. An extensive comparability report compares real time data of 24 months (25°C). The presented data demonstrate that the stability is comparable. For the main changes during the development of the manufacturing process 18 month real time data are presented. The resulting measured stability data are acceptable for the parameters analyzed.

In accordance with EU GMP guidelines<sup>1</sup>, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

### **2.2.4. Discussion on chemical, pharmaceutical and biological aspects**

The manufacturing process of the subcutaneous immunoglobulin (SCIG) solution Hizentra is based on the IgPro10 (Privigen: EMEA/H/C/831) process except for formulation and final protein concentration. The manufacturing of the drug substance IgPro10-SOL is congruent with Privigen. Up to this point the process validation of IgPro10-SOL was described and already assessed with the marketing authorisation application or variations applications for Privigen. In response to the day 120 LOQ a tabulated overview was provided with Privigen questions/responses made during the review in 2007 and the following variations. It was indicated how they relate to Hizentra. The same commercial plant

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<sup>1</sup> 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

is used for both PRIVIGEN and HIZENTRA. Both products are alternatively produced at the same manufacturing lines.

A description of the manufacturing process and in-process controls is provided. However, in comparison to PRIVIGEN, there is an additional concentration step. This process step formulation was now described in more detail and the corresponding section of the Dossier was updated.

The development of the product Hizentra was described in detail and the process validation reports demonstrate that the entire manufacturing process is robust, reliable and high yielding. Different filter aids and the three plasma treatments on cryo-poor plasma might be used alternatively. So far the filter aids and the plasma adsorption steps itself were validated. The applicant has committed not to use alternative filter aids with and without prothrombin adsorbed, modified II+III PPT until process validation data is submitted. The very detailed impurity profile reports together with the presented batch analysis data demonstrate that Hizentra is a highly purified IgG solution ( $\geq 98\%$  purity) which is clearly inside the specification-range. Uniformity of the product and consistency of the manufacturing process was demonstrated. More than 90% of the IgG consists of monomers and dimers. IgG function (Fc and Fab mediated activity) is retained. Subclass distribution and antigenic reactivity is discussed in detail and it is demonstrated that the reactivity to a variety of investigated antigens has been retained in the final product.

The applicant specifies that no IPC's regarding the filled volume or extractable volume are set for the filled vials. Since Hizentra is a high concentrated IgG solution, the viscosity of the solution can have an influence on the extractable volume of the filled vials. However, the weight check performed during filling and the validation of the extractable volume justify the lack of the extractable volume as an IPC.

The formulation of Hizentra (20% IgG, 250 mmol/L L-proline, 20  $\mu\text{g}/\text{mL}$  polysorbate 80, pH 4.8) is based on the IgPro10 (Privigen) formulation and was then further developed in order to address typical features of very highly concentrated IgG solutions. The Company claims that the formulation is based on the prior knowledge acquired with PRIVIGEN, particularly with regards to the selection of pH and proline. Polysorbate 80 was mainly tested with regards to appearance of HIZENTRA.

The proposed specifications for the drug product are in compliance with the requirements laid down in the Ph. Eur. Monograph "Human normal immunoglobulin"; except for the parameters pH and total protein. The Group of Experts No 6B (European Pharmacopeia Commission) decided to revise the upper limit for total protein and the pH range in the monograph as soon as licensing of Hizentra is complete. Due to route of administration "subcutaneous" a higher protein content than the maximum of 180g/l is acceptable. In order to reach stability of this high protein solution it was also necessary to go below the lower pH limit of 5.0 as defined in the "Human Normal Immunoglobulin" 0338 monograph. These discrepancies are acceptable and justified by the nature of this product.

The applicant decided to use the bacterial endotoxin test instead the rabbit pyrogen test. This can be accepted according to the revised monograph 01/2010: 0338 if a justification is provided. The applicant presented sufficient data of 67 IgPro20 lots tested for both Pyrogen and Endotoxins, 66 lots passed the initial Rabbit Pyrogen Test. In one case, additional Rabbit Pyrogen testing was necessary but also passed the test. This result is reflected in the Endotoxins test results where all results are below quantitation limit. The applicant laid down also the principle of process controls and quality assurance program in order to assure the microbiological control. The use of the Bacterial Endotoxin test is so far justified. The applicant addressed the point "presence of non-endotoxin pyrogenic substances" in relation to cytokines with the temperature profiles observed in the rabbit pyrogen test but not with an additional alternative test. Process related considerations were not addressed (guideline on the replacement of rabbit pyrogen testing by an alternative test for plasma derived medical products EMEA/CHMP/BWP/452081/2007).

The results of 38 final drug products lots show that Polymers + aggregates were below 0.1% for all batches, except one batch with a 0.2% value. The applicant tightened the final specifications at release for the parameter Polymer + Aggregates to  $\leq 4\%$ . The limit of  $\leq 10.0\%$  for Polymers + Aggregates at end of shelf life is set according to the Ph.Eur. However, the results of the stability studies which are currently available show that Polymers + Aggregates were  $\leq 0.4\%$  after 18 months at  $+25^{\circ}\text{C}$  and  $\leq 0.5\%$  after 24 months at  $+25^{\circ}\text{C}$ , depending on the alternate manufacturing processes.

The preapproval testing revealed that all tested samples complied with the specifications. The consistency of the lots produced is considered acceptable.

The chosen formulation presents Hizentra as a stable, clear and almost colourless immunoglobulin solution for the long-term stability of the drug product at 5 /  $25^{\circ}\text{C}$ . Therefore the applicant proposes storage of 24 months between 5  $^{\circ}\text{C}$  and 25  $^{\circ}\text{C}$  of Hizentra. In summary the presented data show that after storage for 24 months at 5  $^{\circ}\text{C}$  or 25  $^{\circ}\text{C}$  all parameters remain within the specified ranges. In order to demonstrate stability during temperature shifts the applicant presented new 12 months stability data with four temperature cycling steps between  $-5^{\circ}\text{C}$  and  $30^{\circ}\text{C}$  in the beginning of the study. The selected stability parameters required remain stable if exposed to varying temperature conditions. No additional wording in the SPC is necessary.

In summary compliance with the requirements on virus safety as outlined in Guideline CPMP/BWP/269/95 has been demonstrated.

Finally no major points are identified during the assessment of the Quality part of Hizentra, the points for clarification were answered by the applicant. Five remaining issue for clarification should be addressed by the applicant

### **2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The marketing authorisation application for Hizentra is recommended for approval based on quality grounds.

## **2.3. Non-clinical aspects**

### **2.3.1. Introduction**

Human immunoglobulins are naturally occurring proteins with well-established safety and tolerability record. It is generally acknowledged that testing of human immunoglobulin preparations in animal models is of limited value and these limitations are also discussed in the ICH S6 (Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals CPMP/ICH/302/95, which are applicable to plasma derived products). Therefore, several nonclinical studies are not required for IgPro20.

For IgPro20 the Applicant has performed pharmacodynamic, safety pharmacology, pharmacokinetic and antigenicity studies in rats, and pharmacokinetic and local tolerance studies in rabbits. Local tolerance studies were performed according to GLP.

In addition, several non-clinical studies have been performed for the excipient L-proline.

## **2.3.2. Pharmacology**

### ***Primary pharmacodynamic studies***

Primary pharmacodynamic evaluation with six antibody specificities (Fab-function) and two Fc-function in vitro assays (one measuring complement activation by complexed IgG, the other Fc $\gamma$ -receptor interaction of complexed IgG) showed proper Fab- and Fc-function of IgPro20. The Fc-function of IgPro20 was tested and compared well with licensed IVIG products. The efficacy of subcutaneous immunoglobulin IgPro20 has been demonstrated in experimental allergic encephalomyelitis (EAE) in rats, a preclinical model of human multiple sclerosis and was comparable to the intravenous immunoglobulin treatment (study EAR03/06 Treatment of EAE with IgPro20). For a human immunoglobulin preparation with its various non-relevant interactions within the animal models the approach is considered sufficient.

### ***Secondary pharmacodynamic studies***

Secondary pharmacodynamic studies have not been performed with IgPro20, which is acceptable given the knowledge about human normal immunoglobulins.

### ***Safety pharmacology programme***

Study HYR 01/06 Effects of IgPro20 on Blood Pressure was conducted in anaesthetized rat model for characterizing the vasoactivity of IgPro20. It measured hypotensive effects of IgPro20 after i.v. bolus administration. IgPro20 was well tolerated and the changes in blood pressure were only moderate (short drop of mean arterial blood pressure to 65-73% of control 9-20 min after i.v. bolus), and the extent of change was similar as with other marketed products. These results do not raise any concerns. Further safety pharmacology studies with IgPro20 are not necessary because of the well-established history of safety and efficacy of IVIGs in humans.

Safety pharmacology studies with L-proline revealed no clinical signs of neurotoxicity, and no relevant modifications of behaviour were seen with L-proline in rats (Study 1657/ZLB/02 Irwin Test with L-Proline, Study PSR 08/06 Pharmacokinetics of L-Proline in Rats following a single s.c. or i.p. Injection).

### ***Pharmacodynamic drug interactions***

Nonclinical pharmacodynamic drug interaction studies have not been performed with IgPro20. Human IgG products have been used in clinical practice for over 50 years and as significant adverse drug interactions have not been reported with them, therefore it is acceptable not to conduct pharmacodynamic drug interaction studies for this product.

Due to the biotransformation routes of L-proline no pharmacodynamic interactions are to be expected with this excipient.

Polysorbate 80 is a well-known and widely used non-ionic surfactant which is used at low concentration in marketed SCIG and IVIG products, and has been applied in such products at doses higher than in IgPro20. Because of the low dose of polysorbate 80 applied with IgPro20 ( $\leq 0.06$  mg/kg bw) and the experience with IVIGs pharmacodynamic drug interactions are not expected with polysorbate 80.



### 2.3.3. Pharmacokinetics

Pharmacokinetic studies were performed in rabbits and rats. An ELISA method was used for the determination of human IgG in plasma samples from rats and rabbits. These analytical methods were validated according to the validation reports of analytical methods submitted by the Applicant.

In a single dose pharmacokinetic study PSK 01/05 in rabbits (10/group) the bioavailability of IgPro20 after subcutaneous (s.c.) administration at dose of 400 mg/kg was compared to Vivaglobin and IgPro16. The differences between the three products were not significant.

In a second single dose pharmacokinetic study PSK 04/05 in rabbits (20/group) s.c. administration by single injection of IgPro20 at dose of 400 mg IgG/kg was compared to IgPro16. The investigated products showed a similar absorption rate and bioavailability.

Repeat-dose studies were performed in rats for 5 (Study PSR 02/06) and 28 days (Study PSR 09/08). In study PSR 02/06 IgPro20 was injected s.c. on five consecutive days and relative bioavailability was assessed in comparison to IgPro10 administered intravenously. The overall bioavailability was 57% with 90% confidence interval of 49-67%. AUC values increased for both application routes with increasing doses. The AUC was clearly larger in the higher dose group. While the elimination-related half-lives showed no significant differences between the dose groups, the absorption half-life in the s.c. groups was clearly shorter in the high dose group. After s.c. administration the two doses showed similar rates of elimination but a four times more rapid rate of absorption in the higher dose group. The reason for this finding is not clear, but the higher application volume might explain a faster absorption from the injection site. It was concluded that the bioavailability of s.c. administered IgPro20 is about 60 % of the i.v. administered IgPro10 and that the AUC increased with increasing doses of immunoglobulin.

In study PSR 09/08 IgPro20 was administered s.c. in rats at doses of either 200 mg or 800 mg IgPro20/kg bw once daily every other day for 28 days. Both groups showed increasing serum levels of human IgG up to day 21. During the last week of treatment steady state concentrations were reached. All animals tolerated the repeated s.c. application of IgPro20 without adverse effects or notable clinical signs.

Distribution studies of IgPro20 have not been performed, which is considered acceptable.

Pharmacokinetic studies with the excipient L-proline were performed in the rat and the dog (Study PSR 08/06: Safety Pharmacology and Pharmacokinetics exploratory study, 925/034: Repeat-dose toxicity, 925/035, 668316, 668321, AA30034: Reproduction toxicity Segment II, PSR 03/07: Pharmacokinetics in juvenile animals). The metabolism of L-proline is sufficiently described in the literature. Data of the toxicity studies in dogs demonstrate that the urinary excretion is in line with human data showing that L-proline is reabsorbed in renal tubules.

No further pharmacokinetic studies are required.

### 2.3.4. Toxicology

#### *Single dose toxicity*

No single dose toxicity studies were performed, which is considered justified.

### ***Repeat dose toxicity***

No repeat dose toxicity studies were performed with IgPro20. This is acceptable since administration of Human normal immunoglobulin to animals can be expected to initiate the immunological response, which would interfere with the toxicity evaluation.

### ***Genotoxicity***

No studies on genotoxicity were performed with IgPro20, which is in accordance with Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6). Human immunoglobulins are not expected to directly interact with DNA or other chromosomal material.

### ***Carcinogenicity***

No studies on carcinogenicity were performed, which is in accordance with Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95, ICH S 6). Human immunoglobulins are endogenous materials for which carcinogenicity studies are inappropriate.

### ***Reproduction Toxicity***

Human IgGs cannot interact directly with DNA or chromosomes in intact human cells. Genotoxicity testing of IgPro20 is therefore not appropriate.

### ***Toxicokinetic data***

Toxicokinetic data has not been generated and are not considered necessary.

### ***Local Tolerance***

Local tolerance of IgPro20 was evaluated in rabbits.

Study 143-143-552 (Local tolerance testing of ready-to-use protein solutions in the rabbit) was designed to determine the local tolerance of four different formulations of the same test article IgPro in comparison to the excipient solution, a control protein and 0.9% saline in male and female rabbits. All were applied both as a s.c. bolus injection and as a s.c. infusion, and observation was performed for 96 hours IgPro20 was in the same range of tolerability when compared to the reference product (Beriglobin P). No differences could be identified between genders and no statistically significant difference was observed between s.c. bolus injection and s.c. infusion.

Study 143-140-883 (Local tolerance testing of IgPro20 vs. saline 0.9% in the rabbits) tested local tolerance of IgPro20 in a concentration of 200 mg/ml in comparison to saline in 6 male and 3 female New Zealand White rabbits after a single intravenous, intra-arterial and paravenous administration of a volume of 0.5 ml. IgPro20 was well tolerated after intravenous and intra-arterial application.

IgPro20 was locally well tolerated in rabbits. Erythema and oedema formation induced by IgPro20 were fully reversible and suggested to be a protein-dose dependent effect.

### ***Other toxicity studies***

Immunotoxicity study was performed in rats (Study PSR0908 Anti-human IgG Antibody detection in rat serum after repeated dosing of IgPro20). Rats were treated with either 200 mg/kg or 800 mg/kg

IgPro20 via the subcutaneous route. IgPro20 was given every other day, starting at day 0 and ending at day 28. Plasma samples for rat IgG/IgM antibody detection were drawn at day 0, 6, 14, 21 and 28 before IgPro20 administration. Repeat subcutaneous IgPro 20 application induces a rapid human IgG/M antibody formation in the rat.

### ***Toxicity studies with the excipient L-proline***

Several toxicity studies have been conducted for the excipient L-proline.

The assessment of high doses of L-proline alone in 5-day and 28-day repeat-dose studies in rats (Applicant Study No. 02\_046, Test Facility Study No. 925/034 L-proline- 5 day intermittent intravenous infusion dose range-finding study in the rat and Applicant Study No. ZLB 03\_037, Test Facility Study No. 925/035 L-proline- 4 week daily 7-hour intravenous infusion toxicity study in the rat followed by a 2-week treatment-free period) did not reveal signs of toxicity except for reductions in the body weight gain and food consumption in some groups of animals in the 28-day toxicity study, mainly during the first two weeks of treatment. For L-proline, a NOAEL of 1449 mg/kg bw/day, the highest dose assessed, was defined for rats. Thus a safety margin of 25 was obtained compared to the L-proline dose of 58 mg/kg administered once a week with IgPro20 at 400 mg IgG/kg bw in clinical studies.

In the 7-day and 28-day repeat-dose toxicity studies in dogs, daily intravenous L-proline doses of up to 4350 mg/kg bw showed no overt toxicity (Study ZLB 06\_009, 668316 L-proline preliminary 7-day dose range finding intravenous (7 h) infusion study in beagle dogs and Study CSL 07\_002, 668321 28 Day Intravenous (7 h) Infusion Toxicity Study in the Beagle Dog with a 14 Day Recovery Period). The NOAEL was considered to be 4350 mg/kg. Thus, a safety margin of 75 relative to the maximum human dose used in clinical trials with IgPro20 could be established.

For excipient L-proline no genotoxic effects were shown in results from in vitro and in vivo genotoxicity/clastogenicity assays in combination with L-isoleucine and nicotinamide (Study 22196 Salmonella thyphimurium/ mammalian microsome plate incorporation assay (Ames Test), Study 49196 Bacterial reverse mutation test (Ames Test) using the pre-incubation method, Study CLE 1554-3-D5140 Induction of chromosome aberration in cultured Chinese Hamster Ovary (CHO) cells, Study Zen-0995 Pro-Tox (C): Bacterial Stress Gene Assay (16 constructs) with solutions containing nicotinamide, proline, leucine, and isoleucine). Considering the known metabolism of the three excipients, which suggest a low interaction between the compounds, these studies are considered relevant for L-proline as a single excipient as well.

For L-proline segments I (fertility and early embryonic development) and III (pre- and post-natal development, including maternal function) of reproductive toxicity data have not been generated. Teratogenicity (segment II) data were generated in rats for L-proline (Study AA30034 Embryo Toxicity study). As result 1449 mg/kg/day L-proline administered 7-hour daily by intravenous infusion can be considered as No Observed Effect Level.

No significant memory-impairing effects of L-Proline pre-treatment was found on Morris Water Maze Performance in rats (Study PSR 0107 Effects of early L-proline or glycine administration on Morris Water Maze Performance in rats, Study ZLB06-006 Effects of L-proline or glycine administration on Morris Water Maze Performance in rats).

The efficiency of clearance of L-proline by young as compared to adult rats was less after a single s.c. administration (Study PSR0307 Pharmacokinetics of L-proline or glycine following a single s.c. administration in young rats). This pharmacokinetic observation was expected from literature.

### **2.3.5. Ecotoxicity/environmental risk assessment**

The Guideline on the Environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00) states that "aminoacids and proteins [...] are exempted [*of environmental risk assessment*] because they are unlikely to result in significant risk to the environment".

IgPro20 contains human immunoglobulins as the active substance and also L-proline as an excipient. Therefore, environmental risk assessment is not required.

### **2.3.6. Discussion on non-clinical aspects**

Pre-clinical studies performed with IgPro20 show results that are expected for human normal immunoglobulin product and do not raise any concerns.

L-proline is used as a stabilizer and is already approved as stabilizer in marketed IgG products and as active ingredient in medicinal products for parenteral nutrition (at daily doses of up to 245 mg/kg/day up to several months), which are well tolerated. L-proline as an amino acid is part of proteins and normal diet with normal daily intake of approximately 5.2 g. In conclusion, the results from a battery of in vivo and in vitro toxicology, genotoxicity and teratotoxicity studies the excipient L-proline can be considered as safe at the proposed doses of up to 58 mg L-proline/kg bw.

Considering the purity and stability characteristics of IgPro20, not conducting pharmacodynamic and pharmacokinetic interaction studies for substance related impurities is acceptable. During the production process the ethanol which is added for fractionation of human plasma as well the octanoic acid which is used in a precipitation step are eliminated.

### **2.3.7. Conclusion on the non-clinical aspects**

Several non-clinical studies are not required for IgPro20. The pre-clinical studies performed by the Applicant are deemed sufficient and do not raise any concerns.

Overall, the safety pharmacology and toxicology studies reveal no special risk for humans. This information has been included in the SPC.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

IgPro20 is a Human Normal Immunoglobulin product that has been developed for subcutaneous administration. The product has 20% IgG concentration, which is higher than for currently marketed products and aimed at decreasing administered volume in s.c. infusions. The clinical development programme has been developed in line with requirements of Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use (CPMP/BPWG/283/00). In the development programme treatment with IgPro20 has been compared to current immunoglobulin replacement therapy (mainly intravenous therapy with 'parent' product of IgPro20 – Privigen).

### **GCP**

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

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

**Table. Overview of clinical studies**

<b>Type of study</b>	<b>Study identifier</b>	<b>Description of the study</b>
Phase III (Europe)	ZLB06_001CR	Pivotal study in subjects with PID to assess efficacy, safety, tolerability, PK, and HRQL of IgPro20
Phase III (USA)	ZLB04_009CR	Supportive study in subjects with PID to assess efficacy, safety, tolerability, and PK of IgPro20
Phase I	ZLB04_008CR	Supportive study in healthy subjects to assess safety and local tolerability of IgPro16 and IgPro20 in comparison to Vivaglobin
Phase I	ZLB06_003CR	Supportive study in healthy subjects to compare safety and tolerability of IV administration of IgPro20 (at the SC dose) in comparison to Privigen

HRQL = Health-related quality of life; IV = Intravenous; PID = Primary immunodeficiency; PK = Pharmacokinetic(s); SC = Subcutaneous; USA = United States.

### 2.4.2. Pharmacokinetics

The data on pharmacokinetic properties was derived from 2 sub-studies in multi-centre, single-arm, prospective, open-label, Phase III studies in PID adults and children:

- Study ZLB06\_001CR (Europe: 23 out of 51 patients in PK substudy)
- Study ZLB04\_009CR (USA: 21 out of 49 patients in PK substudy)

In both studies the patients had been on previous IVIG treatment (either at 4-weekly or 3-weekly dosing intervals). After a 12 week wash-in/wash-out period, the patients' PK parameters for total IgG (AUC, C<sub>max</sub>, C<sub>min</sub>, T<sub>max</sub>) were derived by non-compartmental analysis in steady state at Week 28 ± 1. Furthermore, descriptive statistics were derived for concentrations of IgG subclasses, specific IgGs (anti-measles, anti-CMV, anti-Haemophilus influenzae, anti-tetanus, and anti-Streptococcus pneumoniae), and L-proline. The main difference between the two studies was in the dosing. For 23 PID patients in the PK sub-study ZLB06\_001CR the mean IgPro20 dose per week (118.7 mg/kg) was comparable to the weekly equivalent of mean previous IGSC or IGIV doses. In the Study ZLB04\_009CR the mean dose per week during the wash-in/wash-out period ranged from 193.8 - 205.4 mg/kg. (1.3 times the mean weekly equivalent dose of the former IVIG which was 156.1 mg/kg). To attain C<sub>target</sub> (15.00 g/L) a dose adjustment coefficient (DAC) for IgPro20 treatment was calculated as 1.53 (range: 1.26 to 1.87), therefore for the second part of the study this resulted in a mean IgPro20 dose of 234 mg/kg. Please refer to Clinical efficacy section for more detailed information on dosing.

### ***Absorption, Distribution and Elimination***

#### **ZLB06\_001CR**

At steady state (Week 28 ± 1) the mean C<sub>max</sub> was 8.26 g/L, T<sub>max</sub> 2 days, AUC 53.6 g/L\*day and the mean total serum IgG concentrations in range between 7.44 and 7.98 g/L. The mean C<sub>min</sub> (C<sub>trough</sub>) measured prior to the next SCIG administration was 7.54 g/L. The distribution of IgG subclasses at steady state corresponded to the naturally occurring distribution. The data submitted on the specific IgGs at Week 28 indicate good protection from selected pathogens relevant for immunodeficiency patients. The T<sub>max</sub> for IgPro20 in study ZLB06\_001CR is similar or shorter than for currently marketed SCIGs (2 days vs. 2 to 6 days).

For the excipient L-Proline 3 out of 23 patients had L-proline levels above the upper limit of the normal range of 450 µmol/L (max 662 µmol/L).

### ZLB04\_009CR

At steady-state (Week 28 ± 1) the resultant C<sub>max</sub> was 16.16 g/L, T<sub>max</sub> 2-4 days, C<sub>trough</sub> was 14.48 g/L and standardised AUCs was 105 day × g/L the mean total serum IgG concentrations ranged between 13.83 and 15.58 g/L. The mean trough levels were 29% higher than the former Privigen trough levels (11.27 g/L).

For L-proline no accumulation could be seen when measured at steady state during one dosing interval. The maximum reached individual value was 789.0 µmol/L. One day post-infusion the mean levels returned to the level prior to the infusion (~220 µmol/L).

### *Dose proportionality and time dependencies*

In study ZLB04\_009CR comparison of the geometric mean ratios of the AUCs revealed that exposure under IgPro20 was non-inferior to Privigen, thereby fulfilling the aim of the second part of the study. The trough level ratios (TLR) of SCIG vs. IVIG at steady-state was 1.29, i.e. matching AUCs are associated with IgG C<sub>trough</sub> values during SCIG treatment that are 1.29 times higher than the preceding IgG C<sub>trough</sub> values during IVIG treatment with Privigen. As expected, the total serum IgG concentrations were higher in study ZLB04\_009CR where almost double doses of IgPro20 were used.

### *Special populations*

The proportion of children 2 to < 12 years of age included in the PK assessments was considerably higher in study ZLB06\_001CR compared to study ZLB04\_009CR (39.1% vs. 5.6%). In study ZLB06\_001CR in children 2 to < 12 years of age, slightly lower mean values compared to adults 16 to < 65 years of age were observed for C<sub>max</sub> (8.09 vs. 8.31 g/L), AUC<sub>last</sub> (52.30 vs. 54.52 day × g/L), and AUC<sub>τ</sub> (48.18 vs. 56.26 day × g/L). However, overall there were no clinically relevant differences between children and adults in the PK of total IgG, IgG subclasses, specific IgGs, and L-proline after IgPro20 administration, as indicated by subgroup analyses by age class in study ZLB06\_001CR.

**Table. Steady-state pharmacokinetics, additional analysis by age groups in study ZLB06\_001CR**

Parameter	Mean (SD); T <sub>max</sub> : median (range)			
	Total (N=23)	Age class		
		2 to < 12 years (N=9)	12 to < 16 years (N=3)	16 to < 65 years (N=11)
C <sub>max</sub> (g/L)	8.26 (1.255)	8.09 (1.492)	8.60 (1.443)	8.31 (1.096)
T <sub>max</sub> (day)	2.06 (0.94-6.92)	2.06 (0.94-6.92)	1.98 (1.93-2.94)	2.07 (0.95-3.98)
AUC <sub>last</sub> (day × g/L)	53.70 (9.161)	52.30 (9.987)	54.91 (11.548)	54.52 (8.672)
AUC <sub>τ</sub> (day × g/L)	53.61 (9.984)	48.18 (10.044)	55.59 (12.335)	56.26 (9.040)

AUC<sub>last</sub> = Area under the concentration-time curve until last measured concentration; AUC<sub>τ</sub> = Area under the concentration-time curve during regular dosing interval; C<sub>max</sub> = Maximum concentration; N = Total number of subjects in population or subgroup; SD = Standard deviation; T<sub>max</sub> = Timepoint of maximum concentration.

### ***Pharmacokinetic interaction studies***

No pharmacokinetic interaction studies have been conducted, which is acceptable for human normal immunoglobulin product.

### ***Pharmacokinetics using human biomaterials***

No pharmacokinetic studies using human biomaterials have been conducted, which is acceptable for human normal immunoglobulin product.

#### **2.4.3. Pharmacodynamics**

Pharmacodynamic studies are not requested by the relevant Guideline (CPMP/BPWG/283/00). The text of the core SPC has been adopted by the Applicant and reflects the pharmacodynamic properties of human normal immunoglobulin:

*"Human normal Immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.*

*Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1,000 donors. 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."*

#### **2.4.4. Discussion on clinical pharmacology**

For the entire assessment of human normal immunoglobulin for subcutaneous administration (pharmacokinetics, efficacy and safety) the relevant Guideline (CPMP/BPWG/283/00) requests data from at least 30 patients (15 subjects for pharmacokinetics – no children required), for time period of 12 – 24 weeks. Therefore, the submitted data set of 100 patients with primary humoral immunodeficiency (44 of them in pharmacokinetic study, 16 children) followed for up to 12 months meets these requirements.

According to the inclusion criteria for the ZLB04\_009CR pharmacokinetic substudy, subjects should have received IGIV therapy with Privigen at regular 3- or 4-week intervals for at least 3 months prior to receiving IgPro20. These subjects were previously enrolled in the preceding studies with Privigen ZLB03\_002CR (11 out of the 18 patients assessed for PK) and/or its extension ZLB05\_006CR. (7 out of the 13 patients assessed for PK).

Both studies meet the criteria of two different approaches (Europe, USA) for the investigation of pharmacokinetics of a subcutaneous immunoglobulin product. The switch of dosing from IVIG to SCIG in the study ZLB06\_001CR was a simple calculation (namely dividing the former IVIG dose by 3 or 4) and leaving the finer adjustments up to the treating physician with the aim of maintaining sufficient trough levels. In the study ZLB04\_009CR an algorithm was developed to ensure similar AUCs between former IVIG and current SCIG and to provide the physician with a tool for calculation of individual trough level ratios. The resulting mean IgPro20 dose was approximately 50% higher in the study conducted in the USA than in the pivotal study conducted in Europe, which resulted in higher C<sub>max</sub> and AUC values at steady-state. However, in the Core SPC for SCIGs (CPMP/BPWG/282/00) no specific target trough levels are defined, rather it is stated that ... "the subcutaneous route should achieve a sustained level of IVIG". Additionally, in the revised IVIG Core SPC protective trough levels are considered to be 5-6 g/L, whereby individual tailoring maybe necessary if further SBIs occur, when levels may have to be raised to >6-9 g/L. Such values have been achieved also with the lower dosage

levels applied in the study conducted in Europe. Thus, the dosage strategy applied in the study conducted in Europe and proposed for IgPro20 is acceptable and it is the individual patient's clinical response that plays the major role in any dose adjustment.

Upon request by the CHMP the applicant provided the data regarding the terminal half-life. However, the values obtained were not reliable due to the short observation period of 7 days for PK measurements. Nevertheless, given the established efficacy of IgPro20, this unsolved issue is of a limited impact and does not justify further requests.

For the excipient L-Proline in the study ZLB04\_001CR 3 out of 23 patients had L-proline levels above the upper limit of the normal range of 450 µmol/L (max 662 µmol/L). In study ZLB04\_009CR maximal level of 789 µmol/L was reached. However, this is considerably lower than in the studies with "parent" product Privigen, where maximal levels of 1927 µmol/L (in PID study) and 2951 µmol/L (in ITP study) were reached and more than 90% were eliminated within 24 hours. The safety issues of possible hyperprolinaemia were fully discussed at the time of granting the marketing authorisation for Privigen. From the preclinical evaluation derived from a battery of in vivo and in vitro toxicology, genotoxicity and teratotoxicity studies L-proline can be considered to be safe at the proposed dose of up to 58 mg L-proline/kg. No additional concerns with regard to L-proline are raised by these studies.

#### **2.4.5. Conclusions on clinical pharmacology**

Due to differences in study design between the two studies, the mean of individual median IgPro20 doses were approximately 50% lower in study ZLB06\_001CR compared to study ZLB04\_009CR, accordingly the C<sub>max</sub> and AUC values were also lower.

Although no specific target values are set in the core SPC or Guideline for SCIG, mean C<sub>max</sub> (8.26 g/L), T<sub>max</sub> (2 d) and AUC (53.6 g/l\* d) and C<sub>trough</sub> (7.54 g/L) obtained in the study ZLB06\_001CR are in line with data from other licensed SCIGs. The C<sub>max</sub> and AUC results are minimally lower in children, but this is not considered to be clinically relevant and does not warrant any different wording in the SPC.

### **2.5. Clinical efficacy**

In s.c. regimens smaller doses are given more frequently (weekly) as compared to the large boluses of IV infusions every 3 or 4 weeks. The European Note for Guidance on the Clinical Investigation of SCIG (CPMP/BPWG/283/00) request the demonstration of sustained IgG C<sub>trough</sub> values that are comparable to the previous IGIV treatment and provide adequate protection from infections at the same weekly equivalent dosing as for IGIV for IGSC therapy.

#### **2.5.1. Dose response studies**

A formal dose finding study was not conducted for IgPro20. Dosage in main studies was adjusted according to clinical practice and obtained C<sub>trough</sub> levels.

#### **2.5.2. Main study**

A multicentre, single-arm, prospective, open-label, phase III study was performed for the evaluation of clinical efficacy in subjects with a diagnosis of primary humoral immunodeficiency (PID).

#### **Study ZLB06\_001CR**



## **Methods**

### **Study Participants**

Male or female subjects > 2 to ≤ 65 years of age (for sites in the UK: 16 to 65 years of age) with a diagnosis of primary humoral immunodeficiency (common variable immunodeficiency [CVID], x-linked agammaglobulinemia [XLA] or autosomal recessive agammaglobulinaemia [ARAG]) and who have received IGIV therapy at regular 3- or 4-week intervals or IGSC therapy at regular weekly intervals at a stable dose for at least 6 months prior to receiving IgPro20 and had at least 3 documented IgG Ctrough values ≥ 5 g/L during 3 months on IGIV or IGSC replacement therapy prior to receiving IgPro20.

### **Treatments**

Subjects were treated with weekly SC IgPro20 infusions for a 12-week wash-in/wash-out period (Infusions 1 to 12) followed by a 28-week efficacy period (Infusions 13 to 40 including 1 week of follow-up) at doses that were generally equal to the weekly equivalent doses of the subjects' previous IVIG or SCIG therapy. In total, each subject was to receive 40 infusions.

IgPro20 was administered s.c. using infusion pumps. The number of injection sites depended on the volume of the total dose, the maximum volume per injection site ranging from 15 mL (initially) to 25 mL and maximum total infusion flow rate ranging from 25 mL/h (during the wash-in/wash-out period) to 35 mL/h (during efficacy period), depending on tolerability. Treatment with IgPro20 was predominantly home-based and performed by the subject (or parent or guardian) after a training period at the study site.

For subjects previously treated with IGIV, the initial weekly dose of IgPro20 during the wash-in/wash-out period was one third (previous 3-weekly schedule) or one fourth (previous 4-weekly schedule) of the previous IGIV dose. For subjects already on IGSC therapy, the initial weekly dose of IgPro20 during the wash-in/wash-out period was the same dose as previously.

If necessary or medically indicated, the weekly dose of IgPro20 was adjusted at the investigator's discretion during the wash-in/wash-out period to attain IgG Ctrough values of at least 5 g/L. Except for adjustments due to changes in body weight, no further dose adjustments were to be performed during the efficacy period, unless medically indicated. Subjects with 2 consecutive IgG Ctrough values of < 5 g/L during the efficacy period were to be discontinued from the study.

Other immunoglobulins, steroids (except in small doses) or other immunosuppressive drugs were prohibited during the study. Any medication that was not intended for the primary purpose of masking signs of adverse reactions to the infusions, and which was taken by the subject on a regular basis, could be continued.

### **Objectives**

The overall objective of this study was to investigate the efficacy, tolerability, safety, and pharmacokinetics of IgPro20 in subjects with PID. A further objective was to investigate the HRQL associated with IgPro20 treatment.

## Outcomes/endpoints

The primary endpoint was evaluated by a descriptive comparison of 3 Ctrough values measured during previous treatment prior to the study with 6 consecutive Ctrough values measured at a steady-state period within the study.

The secondary endpoints were consistent with those required in the Note for Guidance CPMP/BWPG/283/00 (e.g infection rate, use of antibiotics). Quality of life of patients was specifically followed considering the wide use of SCIG as self-administration at home and the intended reduction of infusion volume and duration of infusion of IgPro20 (20% IgG solution) compared to 10% and 16% IGSC preparations used in Europe and elsewhere in the world for replacement therapy. HRQL instruments included Short Form-36 (SF-36) Health Survey, Child Health Questionnaire-Parent Form 50, Treatment Satisfaction Questionnaire for Medication, Questionnaire on the IgG Therapy, Life Quality Index and a health status rating scale.

## Sample size

There was no formal sample size calculation, which is appropriate for performing descriptive comparison of primary endpoint. Sample size was chosen in order to fulfil the recommendations of the Guideline CPMP/BWPG/283/00.

## Randomisation

Not applicable (single-arm study).

## Blinding (masking)

Not applicable (open-label study).

## Statistical methods

The primary analysis was a descriptive comparison of 6 consecutive IgPro20 IgG Ctrough values per subject (before Infusions 12 to 17) with IgG Ctrough values obtained prior to the first IgPro20 infusion. Further efficacy and safety data were analysed descriptively. Changes in HRQL scores compared to baseline were analysed descriptively, including median changes and confidence intervals.

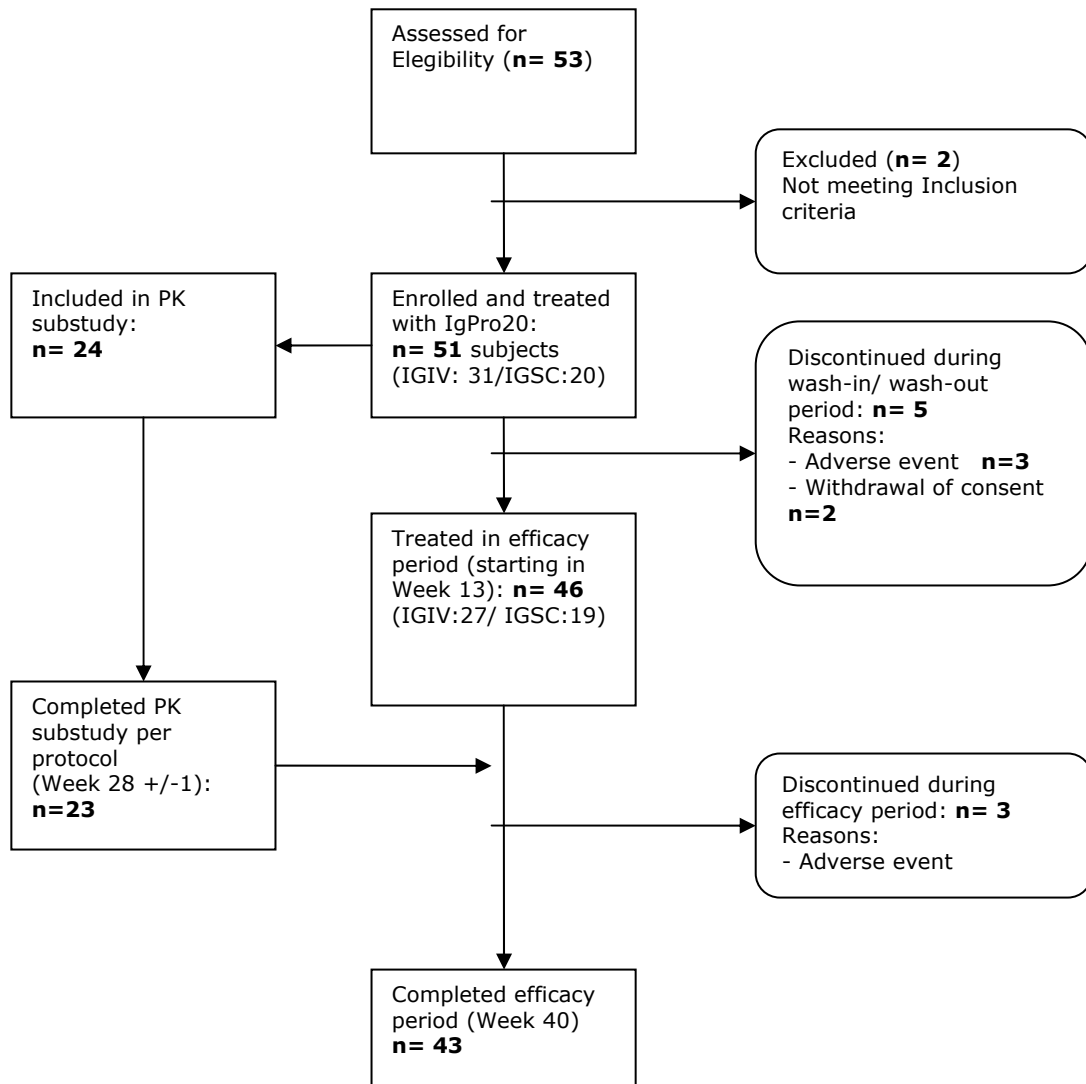
All efficacy endpoints were evaluated in the ITT population (all subjects who had the disease under study and were treated with IgPro20 during the efficacy period starting with Week 13), except for an additional analysis of both the primary efficacy endpoint and the secondary efficacy endpoint of SBIs in the PPE population (all subjects who completed the 28-week efficacy period according to protocol). Subgroup analyses of efficacy endpoints were performed in ITT population. The PPK population comprised subjects included in PK substudy. The Full HRQL population comprised subjects who completed the baseline and at least 1 follow-up HRQL assessment.

No data imputation was made. For primary efficacy endpoint, patients with missing or unsuitable baseline value were not excluded from the analysis, but all available and adequate values were taken into account. For the calculation of annual rates periods of days for which the data was missing were not taken into account.

## Results

### Participant flow

Figure. Participant flow in study ZLB06\_001CR



### Recruitment

A total of 53 subjects were screened, and 51 subjects were enrolled into the study and treated.

### Conduct of the study

During the 28-week efficacy period, subjects visited the study site at least every 4 weeks for the efficacy and safety evaluations. In addition, subjects recorded in a diary details regarding the dose of IgPro20 administered and certain aspects of the efficacy and safety of IgPro20.

There were 3 amendments to the original study protocol, including deletion of one secondary objective (change in viral safety markers, which were measured only at screening), change in inclusion criteria (addition of ARAG) and definition of minimum number of subjects per subgroup for subgroup analysis.

## **Baseline data**

In the ITT population, 15 subjects (32.6%) were female and 31 subjects (67.4%) were male. Seventeen subjects had XLA, while gender distribution was balanced amongst subjects with other PIDs. There were no statistically significant differences in the demographic characteristics of the ITT and PPK population, and the demographic characteristics of the AT and PPE populations were generally similar to those of the ITT population.

**Table. Demographic characteristics of subjects in study ZLB06\_001CR**

Parameter	ITT population (N=46)	PPK population (N=23)	Difference <sup>a</sup>
Sex, n (%)			p = 0.8240
Female	15 (32.6)	8 (34.8)	
Male	31 (67.4)	15 (65.2)	
Age (years)			
Mean (SD)	21.5 (15.60)	20.6 (14.10)	p = 0.7646
Median (range)	16.5 (3-60)	15.0 (6-49)	ND
Age group, n (%)			p = 0.8991
2 - < 12 years	17 (37.0)	9 (39.1)	
12 - < 16 years	5 (10.9)	3 (13.0)	
16 - < 65 years	24 (52.2)	11 (47.8)	
Race, n (%)			NA
White	46 (100)	23 (100)	
Body weight (kg) by age group, mean (SD); median (range)			
Total	52.1 (24.75); 55.0 (13-96)	51.4 (20.92); 56.0 (20-77)	p = 0.8685
2 - < 12 years	25.4 (11.20); 22.0 (13-56)	30.8 (12.26); 27.0 (20-56)	ND
12 - < 16 years	57.1 (15.84); 53.3 (36-77)	60.3 (21.47); 68.2 (36-77)	ND
16 - < 65 years	69.9 (14.28); 72.8 (41-96)	65.8 (10.86); 70.4 (41-74)	ND
BMI (kg/m <sup>2</sup> ) by age group, mean (SD); median (range)			
Total	20.6 (4.90); 20.1 (12-32)	20.3 (3.84); 20.7 (14-27)	p = 0.7185
2 - < 12 years	16.3 (2.89); 15.3 (12-24)	17.4 (3.27); 16.5 (14-24)	ND
12 - < 16 years	20.6 (2.29); 20.1 (18-23)	21.3 (2.96); 22.9 (18-23)	ND
16 - < 65 years	23.6 (4.16); 23.5 (16-32)	22.4 (3.10); 22.7 (16-27)	ND

BMI = Body mass index; ITT = Intention-to-treat; N = Total number of subjects in the population; n = Number of subjects; NA = Not applicable; ND = Not determined; PPK = Per-protocol pharmacokinetic; SD = Standard deviation.

<sup>a</sup> Differences between the observed values in the PPK population and the mean values in the ITT population (i.e., the assumed known values for the target population) were analysed by Chi-Square Goodness of Fit test for the categorical variables sex and age group, and by 1-sample t-test for the continuous variables age, body weight, and BMI.

## Numbers analysed

The AT population consisted of 51 subjects, the ITT population of 46 subjects, and the PPE population of 34 subjects. The PPK population comprised 23 subjects. The Full HRQL population comprised 48 subjects.

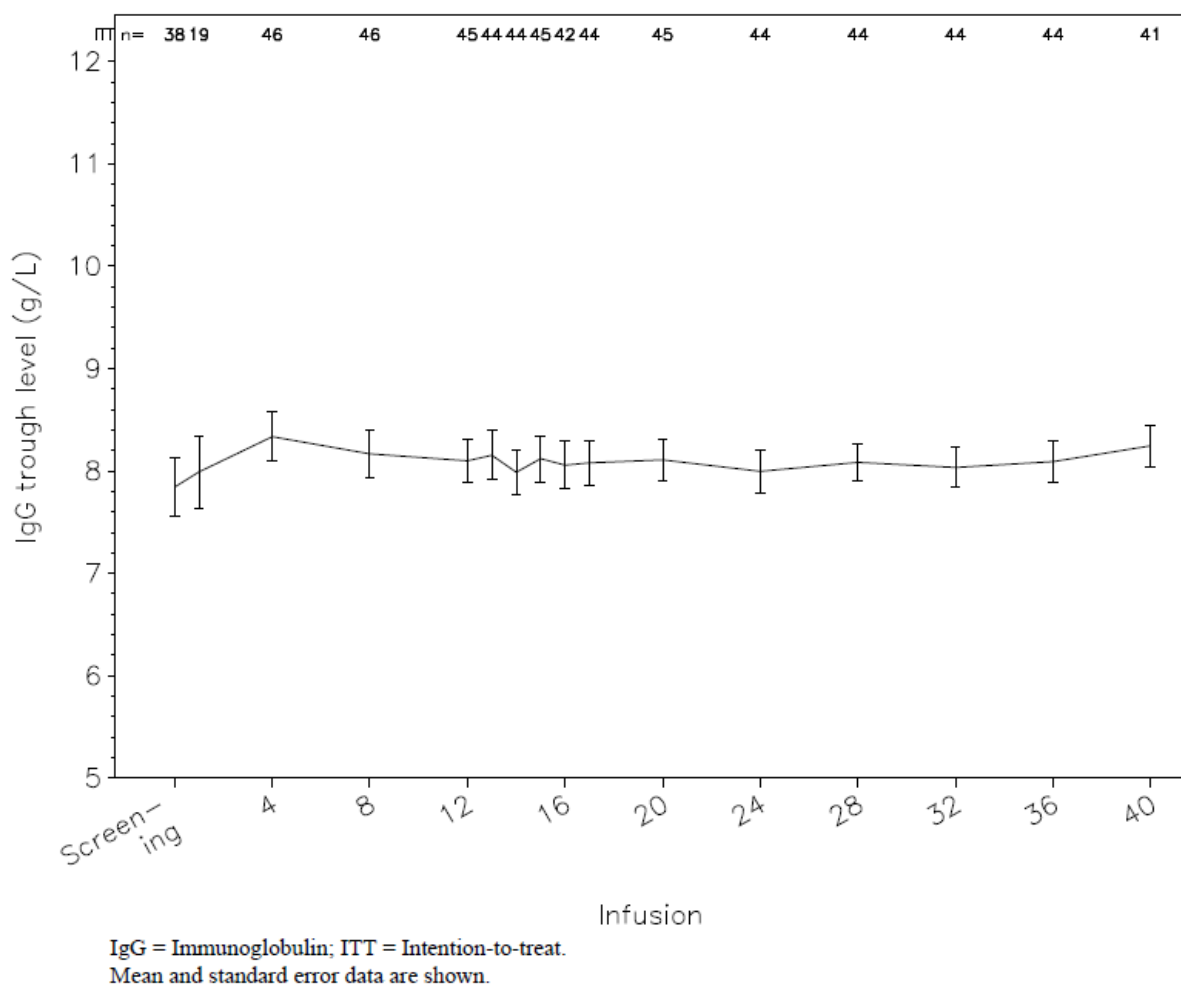
A total of 43 subjects completed the efficacy period (full treatment period of 40 weeks) out of 46 patients in the ITT population.

## Outcomes and estimation

During the last 9 months before enrolment into the study, the mean of the individual median weekly equivalent IGIV or IGSC doses administered before the start of the study was 118.4 mg/kg (for the 28 IVIG subjects (60.9%) the dose was 131.5 mg/kg, and for the 18 SCIG subjects (39.1%) it was 107.0 mg/kg). This is comparable to the doses during the study: 120.0 mg/kg, with a similar mean value during the wash-in/wash-out and the efficacy periods. Overall, the individual median doses (120 mg/kg i.e. around 0.4 g/kg monthly), and the median treatment interval (7 days) concurred with the posology claimed in the proposed SPC.

Mean IgG Ctrough values were generally stable during the efficacy period, ranging between 7.99 and 8.25 g/L with a mean of individual median IgG Ctrough value of 8.10 g/L. This equates an increase of 8.1%.

**Figure. Mean serum IgG Ctrough levels in ITT population (study ZLB06\_001CR)**



**Table. Median serum IgG Ctrough levels in ITT population (study ZLB06\_001CR)**

Period	IgG trough level in g/L (N=46)	
	Mean (SD)	Median (range)
Pre-study <sup>a</sup>	7.49 (1.570)	7.02 (5.3-11.7)
Infusions 12 to 17	8.10 (1.443)	7.99 (5.1-12.4)
Infusions 12 to 41	8.10 (1.340)	8.09 (5.2-11.2)

IgG = Immunoglobulin G; N = Total number of subjects in the population; SD = Standard deviation.  
Each subject's values were first aggregated to the median and then median values were analysed.

<sup>a</sup> Data for 2 subjects were missing.

Clinical data regarding the number of serious bacterial infection (SBIs), infection rate, days out of school/work, days of hospitalization and use of antibiotics have been evaluated as secondary objectives.

During the wash-in/wash-out period, 1 subject had an SBI (as defined in the FDA Guidance for Industry) of pneumonia, resulting in an annual rate for the full evaluation period of respectively 0.03 SBIs/subject/year (ITT) and 0.04 SBIs/subject/year (PPE).

During the efficacy period there was no case of SBI, therefore the annual rate of SBIs per subject was 0, with upper 99% confidence limits of 0.192 for the ITT population and 0.250 for the PPE population.

Other infections, mainly cough, upper respiratory tract infection and bronchitis, resulted in a total annual rate of 5.18 infections/subject/year (95% confidence limits: 4.305; 6.171).

20 subjects in the ITT population (43.5%) missed work/school/kindergarten/day care or were unable to perform normal activities due to infections on a total of 198 days during the efficacy period, which amounted to an annual rate of 8.00 days/subject/year. 4 subjects (8.7%) were hospitalized due to infections during the efficacy period for a total of 86 days, which is in accordance with an annual rate of 3.48 days/subject/year. Overall, 32 subjects (69.6%) were treated with antibiotics on 1743 days during the efficacy period, mainly for treatment of an AE (63%) which resulted in an annual rate of 72.75 days/subject/year and equates a median duration of 23.0 days (range: 4 to 197 days).

**Table. Results for secondary efficacy endpoints (study ZLB06\_001CR)**

Secondary efficacy endpoint	Efficacy period		Full evaluation period	
	Number (%) of subjects	Number (annual rate) of events/days	Number (%) of subjects	Number (annual rate) of events/days
	(N=34)	(N=6729)	(N=34)	(N=9581)
Serious bacterial infections (PPE)	0	0	1 (2.9)	1 (0.04)
	(N=46)	(N=8745)	(N=46)	(N=12606)
Serious bacterial infections (ITT)	0	0	1 (2.2)	1 (0.03)
Infection episodes	36 (78.3)	124 (5.18)	41 (89.1)	181 (5.24)
Days with antibiotics for infection prophylaxis or treatment	32 (69.6)	1743 (72.75)	37 (80.4)	2464 (71.34)
	(N=46)	(N=9033) <sup>b</sup>	(N=46)	(N=12576) <sup>b</sup>
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections <sup>a</sup>	20 (43.5)	198 (8.00)	31 (67.4)	322 (9.35)
Days hospitalized due to infections <sup>a</sup>	4 (8.7)	86 (3.48)	4 (8.7)	105 (3.05)

ITT = Intention-to-treat; N = Total number of subjects in the population or total number of days; PPE = Per-protocol efficacy.

<sup>a</sup> Including data obtained at Week 12.

<sup>b</sup> Total number of diary days.

The improvement of quality of life was not evidenced through the analysis of HRQL instruments, neither when patients switched from IgIV to SCIG nor when they switched from "less concentrated" SCIG to IgPro20. Out of 43 patients who completed the efficacy period 39 patients received IgPro20 at home at Week 40.

## Ancillary analyses

For the primary endpoint, similar results were observed in ITT and PPE populations. The mean of individual median IgG Ctrough values during efficacy period were respectively 8.10 g/L (ITT) and 8.25 g/L (PPE). Compared to IgG Ctrough values during the pre-study IGIV or IGSC treatment, the mean of individual median IgG Ctrough values increased respectively by 8.1% (ITT) and 7.4% (PPE).

Subgroup analysis by age class, disease type, gender and previous replacement therapy brought up neither clinically relevant differences nor consistent trends. However, it should be taken into account that number of subjects in most of the subgroups was low.

Due to the small number of participants, some parameters in study ZLB06\_001CR have been influenced by the course of the disease of a 5-year old female subject 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 and had an SBI (pneumonia) in the wash-in/wash out phase. Although the actual rate of infections would not be influenced, the parameter "days missed from school" and "days spent in hospital" would be considerably decreased if this patient was omitted in the analysis.



## Summary of the main study

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

**Table. Summary of Efficacy for trial ZLB06\_001CR**

<b>Title:</b> A multicentre study of the efficacy, tolerability, safety, and pharmacokinetics of Immune Globulin Subcutaneous (Human) IgPro20 in subjects with primary immunodeficiency			
Study identifier	Protocol: ZLB06_001CR		
Design	Prospective, uncontrolled, open-label, multicentre, single-arm, Phase III study of IgPro20 in subjects with primary immunodeficiency (PID) previously treated with IVIG or SCIG for at least 6 months.		
	Duration of main phase:	28 weeks	
	Duration of wash-in/ wash-out period:	12 weeks	
	Duration of Extension phase:	N/A	
Hypothesis	N/A (descriptive comparison)		
Treatments groups	Pre-study	Treatment: IVIG or SCIG Duration: for 3 to 6 months prior to the study Number of subjects: 46	
	Infusions 12 to 17	Treatment: IgPro20 dose generally equal to previous weekly equivalent IVIG or SCIG dose; weekly infusion; s.c. Duration: Infusions 12 to 17 Number of subjects: 46	
	Infusions 12 to 41	Treatment: IgPro20 dose generally equal to previous weekly equivalent IVIG or SCIG dose; weekly infusion; s.c. Duration: Infusions 12 to 41 Number of subjects: 46	
	Efficacy period	Treatment: IgPro20 dose generally equal to previous weekly equivalent IVIG or SCIG dose; weekly infusion; s.c. Duration: Infusions 13 to 41, 28 weeks Number of subjects: 46	
	Full evaluation period	Treatment: IVIG or SCIG weekly and then after IgPro20; weekly infusion; s.c. Duration: wash-in/ wash-out and efficacy period, infusions 1 to 41 Number of subjects: 46	
Endpoints and definitions	Primary endpoint	Total serum IgG C <sub>trough</sub> values	Six total serum C <sub>trough</sub> values before Infusions 12 to 17 were descriptively compared to three C <sub>trough</sub> values obtained during the previous IGIV or IGSC treatment.
	Secondary endpoint	SBI	Rate of clinically documented serious bacterial infections (SBIs defined according to Food and Drug Administration guidance)
	Secondary endpoint	Infections	Number of infection episodes
	Secondary endpoint	Days out	Number of days out of work/ school/ kindergarten/ day care or unable to perform normal activities due to infections

	Secondary endpoint	Hospitalization days	Number of days of hospitalization due to infections	
	Secondary endpoint	Antibiotics use	Use of antibiotics for infections, prophylaxis and treatment	
<b>Results and Analysis</b>				
<b>Analysis description</b>	<b>Primary Analysis</b>			
Analysis population and time point description	Intent to treat: 46 subjects comprised all subjects who had the disease under study and were treated with IgPro20 during the efficacy period (starting with Week 13)			
Descriptive statistics and estimate variability	<b>Treatment group</b>	<b>Pre-study</b>	<b>Infusions 12 to 17</b>	<b>Infusions 12 to 41</b>
	Mean total serum IgG C <sub>trough</sub> (SD)	7.49 (1.570)	8.10 (1.443)	8.10 (1.340)
	Median total serum IgG C <sub>trough</sub> (range)	7.02 (5.3-11.7)	7.99 (5.1-12.4)	8.09 (5.2-11.2)
	<b>Treatment group</b>	<b>Efficacy period</b>		<b>Full evaluation period</b>
	Number of subjects	46		46
	Annual Rate of SBI (upper 99% confidence limit)	0 SBIs/subject/year (0.192)		0,03 SBIs/subject/year (0.192)
	Annual rate of Infections	5.18 infections/subject/year		5.24 days/subject/year
	Annual rate of Days out	8.00 days/subject/year		9.35 days/subject/year
	Annual rate of Hospitalization days	3.48 days/subject/year		3.05 days/subject/year
	Annual rate of Antibiotics use	72.75 days/subject/year		71.34 days/subject/year
Effect estimate per comparison	Primary endpoint: Total serum IgG C <sub>trough</sub> values	Comparison groups ----- Mean of individual median IgG C <sub>trough</sub> values		Pre-study vs Infusions 12 to 17 ----- Increased by 8.1%

## Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

## Clinical studies in special populations

According to the recommendations of the CPMP "Note for guidance on the clinical investigation of human normal immunoglobulin for subcutaneous and intramuscular use" clinical efficacy data for children have been provided within the scope of studies ZLB06\_001CR and ZLB04\_009CR.

Subgroup analysis by age class as well as by disease type, gender and previous replacement therapy brought up neither clinically relevant differences nor consistent trends.

## Supportive study

### Study ZLB04\_009CR

Study ZLB04\_009CR was multicentre, single-arm, prospective, open-label, phase III study for the evaluation of clinical efficacy in subjects with a diagnosis of primary humoral immunodeficiency (PID). It was designed according to the FDA Guidance for Industry for developing IVIG products and suggestions by the FDA.

### *Methods*

Contrary to the study ZLB06\_001CR, patients could be aged more than 65 years and were previously treated by IVIG only (for a majority with the parent product of IgPro20, Privigen). The exclusion criteria were the same as in the trial ZLB06\_001CR. The efficacy period was longer (12 months) than in study ZLB06\_001CR (28 weeks).

### Study Participants

Male or female subjects 2 to 75 years of age with a diagnosis of primary humoral immunodeficiency (common variable immunodeficiency [CVID], X-linked agammaglobulinaemia [XLA]), who had received an IGIV therapy at regular 3- or 4-weekly intervals for at least 3 months prior to receiving IgPro20 and had previous documented serum IgG Ctrough values of  $\geq 5$  g/L.

### Treatments

IgPro20 was administered SC infusion pumps. The number of injection sites depended on the volume of the total dose. Depending on stage of the study and tolerability the maximum volume per injection site ranged at different from 15 mL to 25 mL per site and maximum total infusion flow rate – from 15 mL/h to 50 mL/h. The number of injection sites was not supposed to exceed 4, though in practice more than 4 injection sites could be used consecutively during the same infusion.

The initial weekly dose of IgPro20 during the wash-in/wash-out period was the equivalent of previous weekly dose times 1.30 (130%). The weekly s.c. dose of IgPro20 was adjusted individually at the end of the wash-in/wash-out period. For subjects in the PK substudy, the individual adjustment was based on 4 IgG Ctrough values measured at Weeks 9 to 12 (at the end of the wash-in/washout period) of s.c. dosing). Subjects not participating in the PK substudy had their IgPro20 doses adjusted by applying the mean dose adjustment coefficient from the PK substudy population with evaluable data for Part I, which was 1.53 times the subjects' preceding IGIV dose.

Other immunoglobulins (i.e., SCIGs or IVIGs) or systemic immunosuppressive drugs (except steroids in limited doses) were prohibited during the study.

### Objectives

The overall objective of this study was to investigate the efficacy, safety, and tolerability of IgPro20 in subjects with PID. The primary objective of this study was to evaluate whether the annual rate of SBIs per subject was less than one.

### Outcomes/endpoints

Primary endpoint was annual rate of SBIs per subject.

Secondary endpoints were:

- Rate of SBIs in the PPE and ITT populations
- Number of infection episodes
- Number of days out of work/school/kindergarten/day care or unable to perform normal daily activities due to infections
- Number of days hospitalized due to infections
- Number of days with antibiotics for infection prophylaxis or treatment
- Trough levels of total IgG serum concentrations

## **Sample size**

Sample size calculation was done in order to assess whether the infection rate per subject per year was less than 1. It was calculated that with 32 patients and a yearly infection rate of 0.5 infections per subject a one-sided test with type I error 0.01 would have about 80% power to detect a risk decrease (i.e. an infection rate < 1 infections per year per subject). In order to account for subject withdrawal 50 subjects were planned to be enrolled.

## **Randomisation**

Not applicable (single-arm study).

## **Blinding (masking)**

Not applicable (open-label study).

## **Statistical methods**

For the primary efficacy endpoint (annual rate of clinically documented SBIs during the efficacy period) the upper 1-sided 99% confidence limit upper limit was calculated (assuming Poisson distributed data). In case this limit was below 1, it was concluded that the annual rate of clinically documented SBIs is less 1. Secondary efficacy endpoints and safety variables were analysed descriptively.

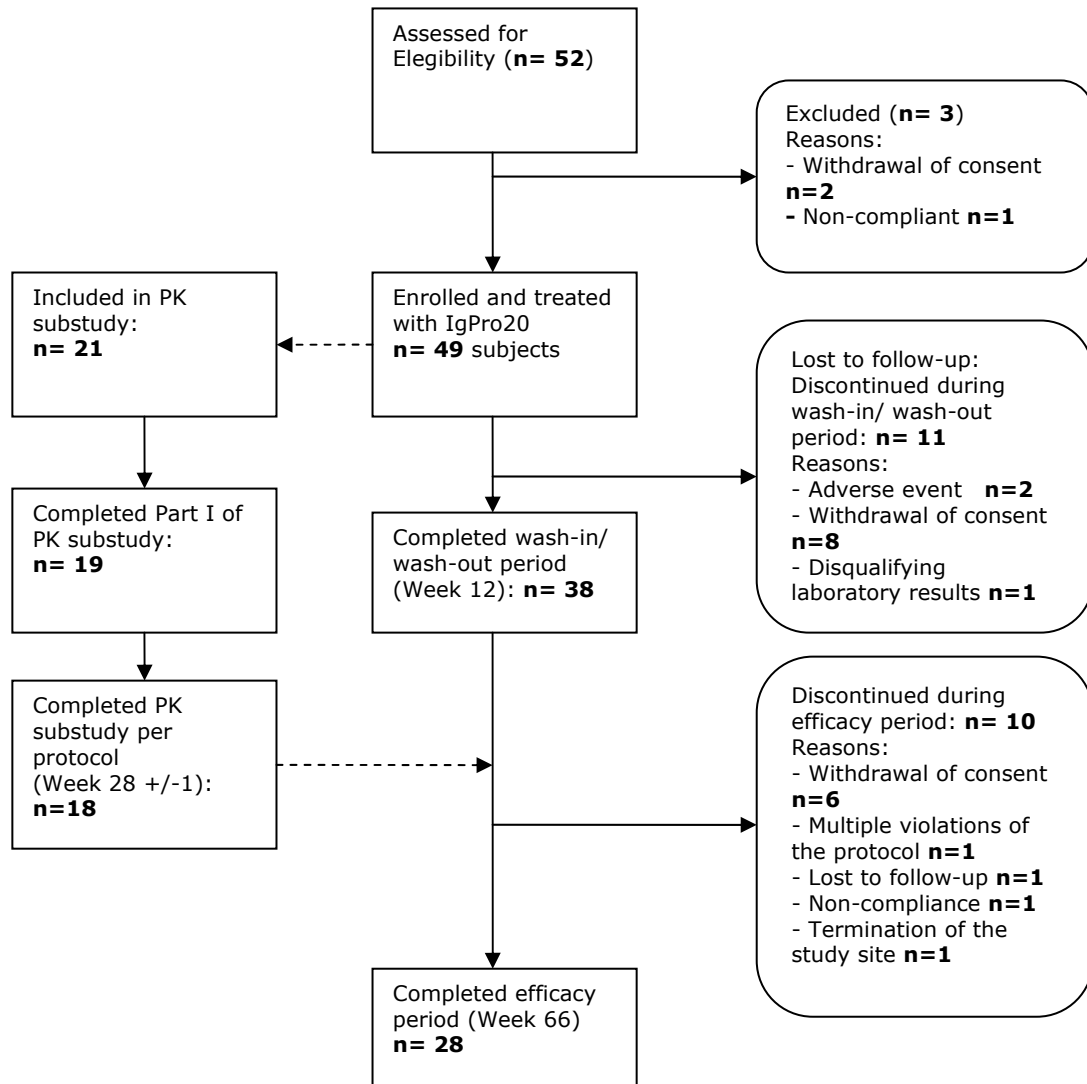
All efficacy endpoints were evaluated for the MITT population (subjects treated with IgPro20 during the efficacy period, i.e. after Week 12), except for the secondary efficacy endpoint of SBIs in the ITT (all subjects treated with IgPro20) and PPE (subjects who completed the efficacy period with no major protocol deviations) populations. Subgroup analyses of efficacy endpoints were based on the PPE population.

For subjects discontinued from the study 5 different data imputation methods were applied in additional exploratory analyses in order to evaluate the robustness of the result of the primary analysis, but no data imputation was made in the primary analysis.

## **Results**

## Participant flow

Figure. Participant flow in study ZLB04\_009CR



## Recruitment

This multicenter study was conducted at 12 sites in the USA. A total of 52 subjects were screened and 49 subjects were enrolled into the study.

## Conduct of the study

During the 12-month efficacy period, subjects visited the study site at 4-week intervals for the efficacy and safety evaluations. In addition, subjects were issued a diary into which details regarding the dose of IgPro20 administered and certain aspects of the efficacy and safety of IgPro20 were entered.

There were 4 amendments to the original study protocol, including incorporation of health-related quality of life assessment and definition of maximum number of injection sites and maximum total flow of study drug.

## Baseline data

The demographic characteristics of the ITT and PPE populations were similar to those of the MITT population. The demographic characteristics of the 19 PK subjects were similar to those of the ITT population, and approximately 40% of the ITT population were PK subjects, indicating that there was no great difference between the demographics of PK subjects and non-PK subjects.

## Numbers analysed

A total of 49 subjects were treated with IgPro20 and comprised the ITT population that was evaluated for safety. 11 subjects in the ITT population were excluded from the MITT population. Thus, the MITT population consisted of 38 subjects who were evaluated for efficacy. The PPE population consisted of 25 subjects.

## Outcomes and estimation

The individual median IgPro20 doses administered for MITT population was 181.4 mg/kg during the wash-in/wash-out period, corresponding to 1.27 times the previous IGIV dose and 213.2 mg/kg, during the efficacy period, corresponding to 1.49 times the IGIV dose. Furthermore, these median doses were considerably higher than in study ZLB06\_001CR (1.62 and 1.87 times respectively). This was expected considering that a Dose Adjustment Coefficient of 1.5 was applied when switching from IGIV treatment to IgPro20 to ensure comparable systemic IgG exposure.

The annual SBI rate per subject was zero (upper 99% confidence limit: 0.132). Thus, the goal set by the protocol was achieved and is considered clinically relevant.

The total number of subjects who had a non-serious infection in the efficacy period was 31/38, namely (81.6%). Nevertheless, the total rate of infection was 2.76 infections/subject/year (95% CI: 2.235; 3.370) whereby the majority affected the upper respiratory tract.

12 subjects (31.6%) missed work/ school/kindergarten/day care or were unable to perform normal activities due to infections on 71 days during the efficacy period, which amounted to an annual rate of 2.06 days/subject/ year. Only one subject was hospitalized during the efficacy period for 7 days due to infections, which amounted to an annual rate of 0.20 days/subject year. Overall, 27 subjects (71.1%) were treated with antibiotics on 1688 days during the efficacy period, mainly for treatment of an AE (65,8%) which amounted to an annual rate of 48.5 days/subject/year.

**Table. Results for secondary efficacy endpoints in MITT population (study ZLB04\_009CR)**

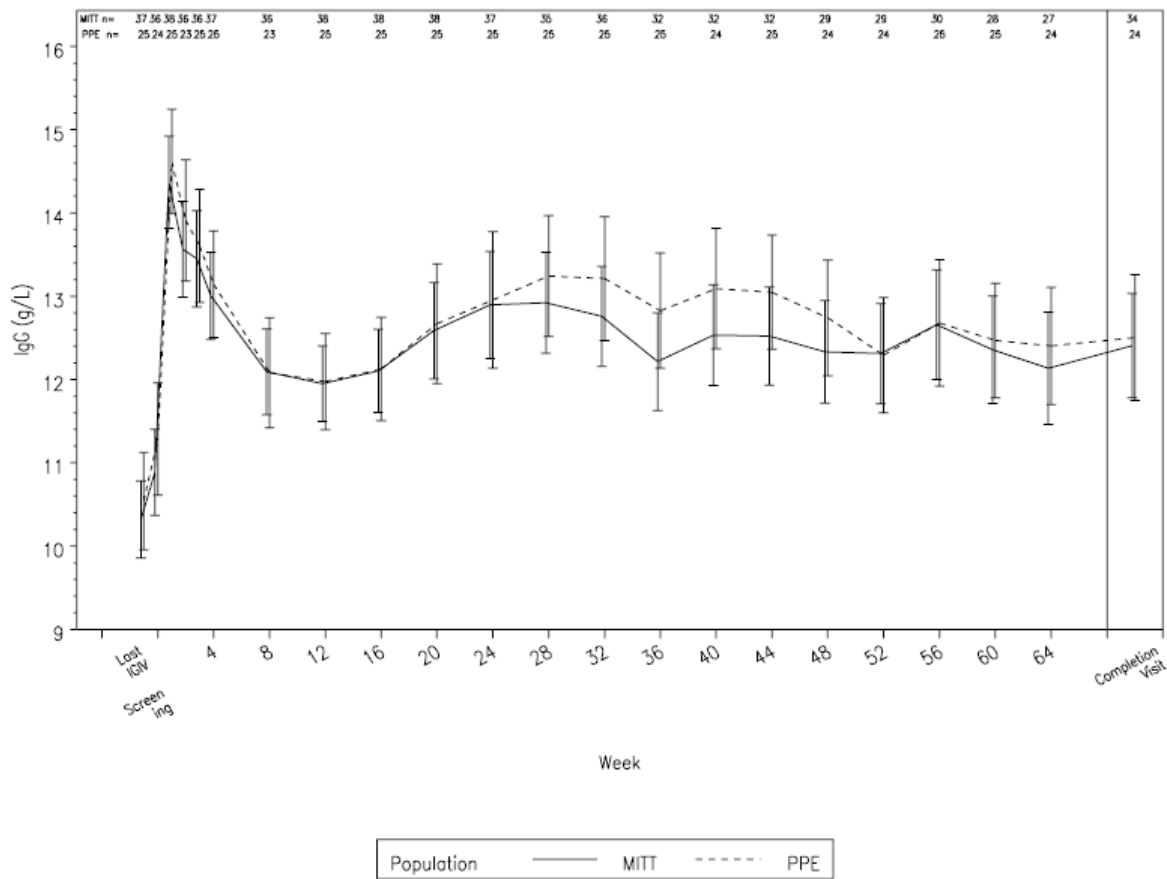
Secondary efficacy endpoint	Number (%) of subjects	Number (annual rate) of events/days
	(N=38)	(N=12697)
Infection episodes (serious <sup>a</sup> and non-serious)	31 (81.6)	96 (2.76)
	(N=38)	(N=12605)
Days out of work/school/kindergarten/day care or unable to perform normal activities due to infections	12 (31.6)	71 (2.06)
	(N=38)	(N=12605)
Days hospitalized due to infections	1 (2.6)	7 (0.2)
	(N=38)	(N=12697)
Days with antibiotics for infection prophylaxis or treatment	27 (71.1)	1688 (48.5)

N = Total number of subjects in the population or total number of days.

<sup>a</sup> There were no serious infections during the study.

Mean IgG Ctrough values were generally stable and reached 12.53 g/L (SD: 3.21 g/L) during the efficacy period. Compared to the last 3 months of IGIV treatment before the start of IgPro20 treatment in the current study, the mean IgG Ctrough increased by 2.44 g/L (24.2%) with IgPro20.

**Figure. Mean IgG Ctrough levels (study ZLB04\_009CR)**



IgG = Immunoglobulin G; IGIV = Immune Globulin Intravenous (Human); MITT = Modified intention-to-treat; n = Number of subjects with available data; PPE = Per-protocol efficacy.

Mean and standard error data are shown.

Only the first reported value per visit was taken into account.

### 2.5.3. Discussion on clinical efficacy

#### Design and conduct of clinical studies

The study design of the pivotal study complies with the current standards requested by the Guideline (CPMP/PWG/283/00).

In both studies, only the diagnostic criteria for serious bacterial infections were uniformly defined in the protocols. Diagnosis of all other infections was at investigator’s discretion and according to the national standard of medical practice. This situation may reflect different diagnostic approaches to infections in various countries. The efficacy period of study ZLB04\_009CR lasted 12 months, thereby excluding a seasonal bias, contrary to study ZLB06\_001CR. The differences in study design between the two phase III studies may have led to differences in some of the results.

#### Efficacy data and additional analyses

The pivotal study ZLB06\_001CR demonstrated that the sustained IgG Ctrough levels measured at steady-state during IgPro20 treatment were comparable to those measured during the subject’s previous treatment. The supportive study ZLB04\_009CR demonstrated that no SBI occurred during the study. For both studies the primary endpoint was thus clearly met.



The doses in study ZLB06\_001CR were approximately 50% lower than in study ZLB04\_009CR. In addition, one or more infusion site could be used in study ZLB06\_001CR and the mean infusion rates were 25.3 mL/h, whereas up to 4 injection sites could be used in study ZLB04\_009CR and the mean infusion rates were 39.1 mL/h.

The mean of the weekly equivalent median doses of previous therapy were comparable between the studies (144.4 mg/kg in study ZLB04\_009CR and 131.5 mg/kg in study ZLB06\_001CR). The individual median serum IgG Ctrough values were higher in study ZLB04\_009CR (10.09 g/L) than in the pivotal study ZLB06\_001CR (6.78 g/L). Each study then followed its own dosing regimen which resulted in different mean values of the individual median IgG Ctrough values (12.53 g/L in study ZLB04\_009CR and 8.10 g/L in study ZLB06\_001CR).

The total annual rate of infections reported in study ZLB06\_001CR was 5.18 infections/subject/year for the efficacy period. This rate appears quite high compared to that of study ZLB04\_009CR (2.76 infections/subject/year). In the discussion of this difference in the annual rate of infections between the two studies the Applicant highlighted that a major impact was made by 8 study ZLB06\_001CR subjects with individual annualized infection rate between 10.139 and 17.743 for the full study duration. The highest incidence by type of infection in study ZLB06\_001CR was for upper respiratory tract infections and bronchitis (> 20% of patients for each) and it was for sinusitis (39.5% of subjects) and nasopharyngitis (15.8%). Interestingly, only 1 case of cough (=annual rate of 0.029) was reported as an infection in study ZLB04\_009CR, whereas 23 episodes (=0.960) were reported in study ZLB06\_001CR. Other infections (i.e. non-respiratory) showed no imbalance between the studies. So although it cannot be ruled out that the higher IgPro20 doses administered in study ZLB04\_009CR (up to 1.87 times) and subsequent higher mean IgG Ctrough values may lead to lower annual rate of infections when compared to study ZLB06\_001CR, it may also be influenced by reporting practices (e.g. registering cough as an infection or not).

The rate of infections per subject per year in both IgPro20 studies is within the reported range from the studies of other immunoglobulins (Lucas, 2010 – a longitudinal study in 90 COVID patients over 22 years receiving either IVIG or SCIG showed an annual rate of infections of 4.7).

14 subjects withdrew consent in study ZLB04\_009CR compared to 2 in study ZLB06\_001CR. 60.5% of subjects received the stipulated infusions (54) in study ZLB04\_009CR compared to 80.4% in study ZLB06\_001CR. This questions the compliance of the subjects in study ZLB04\_009CR, in particular considering high doses. The lower compliance may have resulted from patients' discomfort. Overall, the reasons of withdrawal of consent in study ZLB04\_009CR seem to be related to patients' discomfort, especially when compared to study ZLB06\_001CR. As a result the EU SPC has adopted the lower infusion rate (initial infusion rate should not exceed 15 ml/hour/site; maximum: 25 ml/hour/site) and limited the infusion sites to 4, provided that the maximum infusion rate for all sites combined does not exceed 50 mL/hour.

In addition, as the compliance to the home treatment is a criterion of success for a SCIG, the data from currently ongoing extension study ZLB07\_002CR will be of interest.

In the subgroup analyses in study ZLB06\_001CR, analysing the previous replacement therapy/trough levels and infection rates did not reveal a distinct linear relationship between trough level and infection rate. The mean of individual median IgG Ctrough values was higher in subjects previously treated with SCIG (8.43 g/L) compared to subjects previously treated with IVIG (6.78 g/L); following IgPro20 treatment the levels then decreased in the former SCIG group by 1.9% and increased in the former IVIG group by 17.7%. A higher annual rate of infections was observed in former SCIG group (7.48 infections/subject/year) compared to the former IVIG group (3.44 infections/subject/year), probably due to a small number of individuals who experience multiple infectious events. The higher annual rate

of infections in subjects previously treated with SCIG was reflected in a higher incidence of subjects missing work/school/kindergarten/day care or unable to perform normal activities due to infections.

The company provided an additional event analysis concerning the per subject annual rate of infections, days out of work, days of hospitalization and use of antibiotics which excluded the data from a 5-year old female subject with a history of «chronic pneumonia» (in order to prevent a bias caused by the chronic nature of this participants' pneumonic disease). For both the main and full evaluation periods the actual rate of infections was not influenced by including or omitting this patient, however given the chronic nature of her severe infection the days missed from school and days spent in hospital were considerably decreased by the omission of this patient.

#### **2.5.4. Conclusions on the clinical efficacy**

For both efficacy studies the primary endpoints (sustained IgG trough levels and SBI < 1/subject/year, respectively) were clearly met.

IgG Ctrough levels were comparable to those measured during the subject's previous treatment. In study ZLB04\_009CR and study ZLB06\_001CR during the efficacy period there was no case of serious bacterial infections (SBI). However, in the wash-in/wash-out period in study ZLB06\_001CR there was 1 SBI (pneumonia), resulting in an annual rate of respectively 0.03 SBIs/subject/year, which is below the accepted threshold of 1 SBI/subject/year.

The 1.87 times higher IgPro20 doses administered in study ZLB04\_009CR led to higher mean IgG Ctrough levels; this may be the cause of the lower annual rate of infections compared to study ZLB06\_001CR (~2.5 vs ~5 infections/patient /year). However, this should be viewed with caution as a) the diagnosis of "other infections" (i.e. not SBI) was at investigator's discretion and according to the national standard of medical practice and therefore not easily comparable and b) a clear linear dose-Ctrough-response correlation did not result from the subgroup analysis in study ZLB06\_001CR of previous treatments, the resulting trough levels and the infections rates when compared to the current treatment.

The compliance of patients in study ZLB06\_001CR seemed to be higher than in study ZLB04\_009CR, supporting the dosage regime used in study ZLB06\_001CR.

### **2.6. Clinical safety**

#### **Patient exposure**

The applicant presented data of two completed Phase III studies (ZLB06\_001CR, ZLB04\_009CR) and two completed Phase I studies (ZLB04\_008CR, ZLB06\_003CR). In these four studies a total of 148 patients were treated, 115 adults (age: 16 - < 65 years) and 33 children (age: 2 - < 16 years, whereby more patients from 2 to < 12 years group were included in Study ZLB06\_001CR than in Study ZLB04\_009CR (respectively 18 vs 3 patients).

During the completed Phase III studies 100 PID patients were administered IgPro20 at weekly intervals for up to 41 weeks in study ZLB06\_001CR and for up to 66 weeks in study ZLB04\_009CR. In study ZLB06\_001CR, subjects were treated with mean dose of 120.1 mg/kg bw per week during the efficacy period, and in the study ZLB04\_009CR 1.8 times higher doses were administered (213.2 mg/kg bw). The total infusion rate was higher in study ZLB04\_009CR than in study ZLB06\_001CR (respectively 37.6 ml/h versus 26.3 ml/h).

Data of 4095 s.c. infusions (cumulative number) were presented.

## Adverse events

### Study ZLB06\_001CR

50 subjects (98.0%) had at least 1 AE, 31 subjects (60.8%) had at least 1 AE that was at least possibly related to study drug, and 48 subjects (94.1%) had at least 1 temporally associated AE (within 72 h).

There were 527 AEs and 1831 infusions, resulting in an AE rate per infusion of 0.288. The rate of AEs that was considered at least possibly related to study drug was 0.106, for temporally associated AEs it was 0.177 (324 events) and for both temporally associated and possibly related it was 0.090 (165 events).

The most common adverse event was "local reaction" with 110 events in 1831 infusions (0.060) experienced by 25/51 patients (49%). The term "local reaction" encompassed a large number of findings at the injection site, in all except for one patient these were also temporally associated and causally related. The majority of the local reactions (87%) were mild in intensity. Over the course of the study these reactions decreased and very few experienced any after infusion 24. Other common related adverse events in ~ 6% of the patients were headache, pruritis, fatigue and pyrexia.

**Table. Incidence of subjects with common adverse events (experienced by ≥ 4 subjects) by preferred term and rate per infusion, irrespective of causality in AT population of study ZLB06\_001CR**

Preferred term	All events		Temporally associated (72 h)	
	Number (%) of subjects (N=51)	Number (rate) of events (N=1831)	Number (%) of subjects (N=51)	Number (rate) of events (N=1831)
<b>Any preferred term</b>	<b>50 (98.0)</b>	<b>527 (0.288)</b>	<b>48 (94.1)</b>	<b>324 (0.177)</b>
Local reaction <sup>a</sup>	25 (49.0)	110 (0.060)	24 (47.1)	105 (0.057)
Bronchitis	16 (31.4)	26 (0.014)	7 (13.7)	11 (0.006)
Pyrexia	14 (27.5)	14 (0.008)	7 (13.7)	7 (0.004)
Headache	13 (25.5)	54 (0.029)	9 (17.6)	20 (0.011)
Cough	13 (25.5)	26 (0.014)	7 (13.7)	9 (0.005)
Upper respiratory tract infection	12 (23.5)	17 (0.009)	9 (17.6)	10 (0.005)
Nasopharyngitis	12 (23.5)	20 (0.011)	8 (15.7)	12 (0.007)
Diarrhoea	10 (19.6)	16 (0.009)	7 (13.7)	10 (0.005)
Sinusitis	7 (13.7)	11 (0.006)	4 (7.8)	7 (0.004)
Rash	5 (9.8)	5 (0.003)	4 (7.8)	4 (0.002)
Pruritus	4 (7.8)	14 (0.008)	4 (7.8)	13 (0.007)
Respiratory tract infection	4 (7.8)	5 (0.003)	3 (5.9)	3 (0.002)
Oropharyngeal pain	4 (7.8)	12 (0.007)	2 (3.9)	5 (0.003)
Vomiting	4 (7.8)	5 (0.003)	2 (3.9)	2 (0.001)

N = Total number of subjects or infusions in the study.

<sup>a</sup> Local reaction is not a MedDRA preferred term, it groups AEs of the preferred terms infusion related reaction, infusion site erythema, infusion site haematoma, infusion site induration, infusion site inflammation, infusion site mass, infusion site oedema, infusion site pain, infusion site pruritus, infusion site rash, infusion site reaction, infusion site swelling, injection site erythema, injection site extravasation, injection site haematoma, injection site induration, injection site inflammation, injection site nodule, injection site oedema, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, and puncture site reaction.

## **Study ZLB04\_009CR**

All subjects had at least one AE that was considered at least possibly related to the study drug and occurred within 72 h of infusion. There were 1749 AEs and 2264 infusions in this study, resulting in an AE rate per infusion of 0.773. The rate of AEs that were considered at least possibly related to study drug was 0.634 (1436 events). This rate remained approx. the same for temporally associated and possibly related AEs (0.617).

The majority of AEs were infusion related local reactions namely 1313 in 2264 infusions (0.580) experienced by 49 patients (100%). If one excluded the local reactions, there were 409 AEs, resulting in an AE rate of 0.181, whereby only a fraction of these were considered related (0.043). Most of the injection site reactions (94.8%) were reported by the subjects to have been "very slight" or "slight" in intensity.

The next most common related AEs were headache seen in approx. one quarter of the patients followed by injection site bruising, vomiting, pain and fatigue in ~6% of the patients. In general the AE profile corresponds to that seen in other SCIG products.

**Table. Incidence of subjects with common adverse events (experienced by  $\geq 4$  subjects) by preferred term and rate per infusion, irrespective of causality in ITT population of study ZLB04\_009CR**

Preferred term	All events		Temporally associated (72 h)	
	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)	Number (%) of subjects (N=49)	Number (rate) of events (N=2264)
<b>Any preferred term</b>	<b>49 (100)</b>	<b>1749 (0.773)</b>	<b>49 (100)</b>	<b>1566 (0.692)</b>
Injection site reaction	49 (100)	1314 (0.580)	49 (100)	1298 (0.573)
Sinusitis	14 (28.6)	20 (0.009)	7 (14.3)	10 (0.004)
Headache	13 (26.5)	40 (0.018)	12 (24.5)	32 (0.014)
Nasopharyngitis	11 (22.4)	15 (0.007)	8 (16.3)	8 (0.004)
Cough	8 (16.3)	9 (0.004)	5 (10.2)	6 (0.003)
Diarrhoea	7 (14.3)	8 (0.004)	5 (10.2)	6 (0.003)
Bronchitis	6 (12.2)	9 (0.004)	5 (10.2)	6 (0.003)
Fatigue	6 (12.2)	6 (0.003)	4 (8.2)	4 (0.002)
Injection site bruising	5 (10.2)	19 (0.008)	5 (10.2)	18 (0.008)
Back pain	5 (10.2)	11 (0.005)	4 (8.2)	5 (0.002)
Acute sinusitis	5 (10.2)	7 (0.003)	4 (8.2)	5 (0.002)
Nausea	5 (10.2)	5 (0.002)	4 (8.2)	4 (0.002)
Abdominal pain upper	5 (10.2)	5 (0.002)	3 (6.1)	3 (0.001)
Upper respiratory tract infection	5 (10.2)	6 (0.003)	3 (6.1)	3 (0.001)
Rash	5 (10.2)	7 (0.003)	2 (4.1)	3 (0.001)
Pain in extremity	4 (8.2)	7 (0.003)	4 (8.2)	6 (0.003)
Viral infection	4 (8.2)	7 (0.003)	3 (6.1)	3 (0.001)
Migraine	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Pain	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Epistaxis	4 (8.2)	6 (0.003)	2 (4.1)	3 (0.001)
Pharyngolaryngeal pain	4 (8.2)	6 (0.003)	2 (4.1)	2 (< 0.001)
Arthralgia	4 (8.2)	5 (0.002)	2 (4.1)	3 (0.001)
Urinary tract infection	4 (8.2)	4 (0.002)	1 (2.0)	1 (< 0.001)

N = Total number of subjects in population or total number of infusions given in the study.

### Study ZLB04\_008CR

Was a single-centre, randomised, assessment-blinded, 4-way crossover, Phase I study in 28 healthy, male Caucasian subjects between 18 and 45 years of age. It investigated the local tolerability of IgPro20 (both 12 and 15 ml), IgPro16 (a 16% IgG solution) compared to 16% Vivaglobin.

The primary endpoint was local tolerability which was based on the subjects' assessment of pain by VAS scale (from 0 mm (no pain) to 100 mm (unbearable pain)) and assessment of various other symptoms (erythema, oedema/induration, local heat, and itching – from none increasing in categories until severe) by a blinded investigator for up to 72 hours after the end of infusion. The secondary endpoint of safety was assessed in terms of AEs, clinical laboratory evaluations, viral safety, electrocardiograms (ECGs), vital signs, and physical examination.

The design of the study to assess the extent of the commonly expected local reactions is acceptable. The VAS scales are a commonly used method for pain measurement and are generally considered to be sensitive and reliable.

There were no clinically relevant differences between the 4 treatments with regard to pain perception. Apart from one outlier, the reported values for mean maximum pain were fairly low (on the VAS 100 mm scale: 6.8 and 9.3 mm). For the other parameters (erythema, oedema/induration, local heat, and itching and AEs), no new tolerability or safety signals emerged – the main related AE was headache (14.3% observed in IgPro20 15 ml vs. 3.6% in Vivaglobin arm).

### **Study ZLB06\_003CR**

Study ZLB06\_003CR was a single-centre, randomised, single-blind, 2-way crossover, Phase I study in 20 healthy male volunteers (20 to 45 years of age). It primarily investigated the safety and tolerability of IV administration of IgPro20 given at the SC dose used for IgG replacement therapy (single dose of 50 mL of IgPro20 in short infusion of 45 minutes), compared to IV administration of the IVIG product Privigen at the same dose.

The design to assess the safety of inadvertent IV administration of IgPro20 during intended SC use is considered acceptable.

Fourteen subjects experienced 39 TEAES (10 experienced 17 TEAES vs 12 experienced 22 TAES, respectively in IgPro10 vs IgPro20), all of which resolved without sequelae.

The most frequent AE was chills, followed by chest discomfort, feeling cold, and headache. Most AEs were of mild intensity. The study results do not show any significant difference in the related and temporally associated AEs between IgPro 10 given intravenously and IgPro 20 given intravenously. This is reassuring to the treating physician and patient in home treatment that the nature and rate of side-effects will be similar to Privigen, if IgPro20 is inadvertently given intravenously.

## **Serious adverse event/deaths/other significant events**

### **Study ZLB06\_001CR**

No deaths occurred during the study. However, a 5 year-old patient with SAEs (pneumonia) died from respiratory failure (acute exacerbation of chronic pneumonia) 4 days after infusion 5 in the ongoing extension to this study (ZLB07\_002CR). The final study report of ZLB07\_002CR is awaited for the first quarter of 2013.

7 SAEs (0.004) occurred in 5 subjects (diarrhoea; pneumonia [2 events], pyrexia; bronchiolitis; appendicitis; and sciatica) all of which unrelated to the study drug. Three patients were under 12 years-old and one patient was 18. Three patients had previous medical history for their effects. All the patients recovered without sequelae.

### **Study ZLB04\_009CR**

There were no deaths in this study.

10 SAEs (0.004) occurring in 7 patients (gastroenteritis; small intestinal obstruction and chest pain; tooth abscess, cellulitis, and urinary tract infection; hemoglobin decreased; chest pain; musculoskeletal stiffness; and papillary thyroid cancer) were not related to the study drug. All the patients were older than 18 years-old. Five subjects have medical histories which could explain their AEs. All SAEs resolved without sequelae except 2 (papillary thyroid cancer and abdominal pain).

## **Studies ZLB04\_008CR and ZLB06\_003CR**

There were no deaths or serious adverse events during the course of these studies.

## **Laboratory findings**

### **Study ZLB06\_001CR**

Haematology, serum chemistry, and urinalysis analytes were evaluated at screening, at Weeks 1, 4, 28, and at the completion visit. In addition to numerous individual fluctuations, a total of 22 haematology values in 3 subjects were assessed as abnormal and clinically significant and mainly concerned low Hb, Hk and high WBC. Underlying conditions (anaemia, infection) could explain these values. Haemolysis did not occur. For blood chemistry in 2 patients a clinically relevant elevation was seen for LDH, which is a general indicator of tissue breakdown. As haematology and other blood chemistry values showed no clinically relevant changes, it is therefore difficult to assess the origin of these elevations.

### **Study ZLB04\_009CR**

The evaluations were performed at the same time points as in study ZLB06\_001CR and additionally due to the longer duration at week 40. Again individual fluctuations were seen in study population with very few cases reaching clinical significance. Haemolysis (defined as + DAT and a decrease in Hb > 2g/dL) did not occur. 19 abnormal values in blood chemistry were assessed as clinically significant in 4 subjects; 15 of them occurred in one subject with chronic hepatitis. Relevant increases in LDH were seen in 4 patients and non-relevant in 6 patients.

### **Study ZLB04\_008CR**

There were 5 subjects with increased bilirubin, 6 had increased creatine phosphokinase (CPK) and 2 subjects had lipase and amylase increases, 5 subjects had low lymphocyte counts of 20% (normal range 25 - 45%), but only as single outlier values. The increases in bilirubin are of note in otherwise healthy males. As a possible explanation the company proposes "Occasionally and intermittently elevated total bilirubin concentrations are found in the Caucasian population known as the Morbus Meulengracht, a hereditary benign metabolic disorder of the liver". CK increases may be explained by physical activity in this healthy population. Intermittent lipase and amylase increases are seen in the general population. However, the 3 to nearly 4 fold increases of lipase and amylase seen here are rather high and are also seen in another subject from trial ZLB06\_003CR.

### **Study ZLB06\_003CR**

Two subjects experienced moderate to severe neutropenia. There were no signs of hemolysis. One patient had increased lipase.

## **Physical examination and vital signs**

Although there were numerous individual fluctuations in vital signs, no clear trends or patterns emerge from the data. No relevant findings or new signals arise from the changes in physical examination or vital signs.

## Safety in special populations

### Study ZLB06\_001CR

#### *Age*

The incidence of children and adolescents with related and temporally associated adverse events was lower (~39%) compared to adults (71%), as were the rates of AEs per infusion (~0.22 vs. 0.36).

#### *Underlying disorder*

Although the incidence of subjects with at least possibly related AEs was higher in subjects with CVID compared to subjects with XLA (76.7% vs. 40.0%), no distinct differences were seen between the 2 categories with regard to rates of events per infusion. Thus, no clear conclusion can be drawn with regard to the relationship of the underlying disorder and resulting AEs.

#### *Previous replacement therapy*

No relevant differences with regard to AEs could be discerned for patients previously receiving IVIG (n= 31) or a different SCIG (n=20) replacement therapy.

#### *Starting infusion rate*

No relevant differences with regard to AEs could be discerned for the different starting infusion rates (< 15 mL/h; 15 to 25 mL/h and >25 mL/h)

### Study ZLB04\_009CR

#### *Gender*

There were 22 males and 27 females in the study. The overall AE rate per infusion was similar in males and females (0.746 vs. 0.794), as was the rate of causally related AEs (0.601 vs. 0.660). Local reactions apart, females had a higher proportion of related AEs in the other AE categories (8 males [36.4%] vs. 17 females [63.0%]) this was predominantly due to headache being increased in women (m:f 18%: 29%), but also due to how the causality was rated e.g. upper abdominal pain and back pain were classified more frequently as "related" in females compared to males. Thus, no clear conclusions can be drawn from the data regarding possible differences in AEs between the sexes.

#### *Age*

The small number in the age groups 2-<12y (n=3), 12 -16 (n= 7) and > 65 (n= 6) do not allow for firm conclusions. Although related AE rates seem higher in the 12-16 year-olds, seen in conjunction with the paediatric data from study ZLB06\_001CR, where children (n= 18) and a small number of adolescents (5) had a lower incidence of related and temporally associated AEs compared to the adult population a change in the wording of the SPC for adolescents does currently not seem warranted.

#### *Dose*

There were 2 patients in the < 100 mg/kg group, 10 patients in the 100 – 150 mg/kg group and 37 patients in the >150 mg/kg group. For 20 infusions the dose was not known. The overall AE rates per infusion was between 0.669 in the < 100 mg/kg group and 0.806 in the 100-150 mg/kg group and 0.765 in the highest dosing group.

No clear pattern emerged between the groups with regard to the nature and rate of the AEs.

#### *Infusion rate*



No distinct differences in AE rate per infusion (0.887 vs. 0.686) arose from the 2 categories of infusions rates (15-25 ml/h (n= 21) and >25 ml/h (n= 28)).

## **Safety related to drug-drug interactions and other interactions**

No formal interaction studies were performed.

## **Discontinuation due to adverse events**

### **Study ZLB06\_001CR**

Six subjects (11.8%) discontinued from the study due to 14 AEs, 7/14 AEs were considered at least possibly related (r) to study drug. (0.008): myalgia, pyrexia, nausea, chest pain, and C-reactive protein increased; injection site pain (r) and injection site pruritus (r); pulmonary tuberculosis; injection site reaction (r), fatigue (r), and feeling cold (r); injection site reaction (r) and hypersensitivity (r); and anaemia.

Except for the AEs of pulmonary tuberculosis and anaemia that were ongoing at final assessment, all of the AEs resolved without sequelae. The case of pulmonary tuberculosis is not viewed by the CHMP as related to the study; from the narrative provided it may be an exacerbation of a pre-existing infection – however, this is merely speculative.

### **Study ZLB04\_009CR**

A total of 3 AEs in 3 patients were classified as leading to discontinuation from the study (< 0.001), 2 of which were considered at least possibly related to study drug: dermal hypersensitivity reaction associated with the infusions, myositis, chronic hepatitis (this condition existed long before the study and the reason for discontinuation was violation of an exclusion criterion). The company has adequately discussed the development of myositis in one patient. There does not seem to be any clear causal relationship with IgPro20. Some symptoms seem to have been pre-existing prior to study entry; liver values and CK were increased at screening. No reports of myositis developing from IVIG or SCIG were found in the literature.

### **Studies ZLB04\_008CR and ZLB06\_003CR**

No discontinuations.

## **Post marketing experience**

The product was not licensed at the time of submission of the Marketing Authorisation Application.

### **2.6.1. Discussion on clinical safety**

Both Phase III studies encompassed 100 PID patients (adults and children) who received IgPro20 during a period of 28 -54 weeks, thereby meeting the requirements of SCIG Guideline CPMP/BPWG/283/00, which requests data from at least 30 patients, including children, followed for 12 – 24 weeks.

There was a noticeable difference in the rate of AEs per infusion between study ZLB06\_001CR and study ZLB04\_009CR: 0.288 vs 0.773, this difference was also reflected in the related AEs (0.106 vs. 0.634) and temporally associated AEs (0.177 vs. 0.692). In both studies the main adverse event was a local injections site reaction, as would be expected from an SCIG. The discrepancy in AE rates was

mainly due to the higher rate of local reactions in study ZLB04\_009CR (0.06 vs 0.592). It is difficult to assess how much of this was due to the different doses applied (approx. twice higher doses were administered in the study ZLB04\_009CR) and how much due to the different assessment of local tolerability (only patient's perception 24 hours to 72 hours after the administration for study ZLB06\_001CR and for study ZLB04\_009CR in addition to patient's perception the investigator assessed local tolerability within 15 to 45 minutes after the end of the infusion).

However, almost all AEs (99%) in both studies were mild or moderate in intensity. Local reactions were also mostly mild in intensity and diminish in frequency over time. The tolerability of IgPro20 was rated as good to very good by most patients.

While infections were also reported as AEs, they were expected due to the underlying disease of PID and the extensive history of chronic infections in most subjects; patients in study ZLB06\_001CR suffered more from cough, bronchitis and URTI, more patients in study ZLB04\_009CR had sinusitis and acute sinusitis. The rate of nasopharyngitis was similar in both studies.

Other common AEs were headache, diarrhoea, rash, fatigue that occurred at a similar rate in both studies. Other pain syndromes (headache as a related AE, back pain, abdominal pain, migraine, arthralgia) occurred more frequently in study ZLB04\_009CR. Pyrexia was more frequent in study ZLB06\_001CR than in study ZLB04\_009CR. (17.6% vs.4.1%).

No clear conclusion can be drawn with regard to the relationship of AEs and the underlying disorder, infusion rate and gender.

Comparing SCIG and IVIG administration is fraught with difficulty, as the nature and frequency of side-effects differ. The rates for systemic AEs (e.g. headache, nausea + vomiting, pyrexia, pain) with IVIGs are in general higher than those seen in the submitted SCIG studies. However, the rates in the literature can vary considerably for IVIGs as has been shown in an article by R. Pierce and N. Jain (Transfusion Medicine Reviews, Vol. 17, Issue 4, October 2003, Pages 241-251 Risks associated with the use of intravenous immunoglobulin) "*Depending on the particular disease/ patient population studied, the AE incidence reported on a per-infusion basis appears to vary markedly (ranging from 2%-25%). This is the case even while comparing trials of the same manufacturer's IGIV product*". Judging by the submitted data, it can be concluded that treatment with IgPro20 shows good tolerability and very low related adverse event rates.

No deaths occurred on either studies and the SAEs were not considered to be related. One subject who had previously been treated in study ZLB06\_001CR died from respiratory failure during the ongoing extension study ZLB07\_002CR. This subject had an SAE of pneumonia that was considered by the investigator to be unrelated to the study drug. In general the 30 year survival rate in CVID is ~ 80%. As there are 2 peaks of onset, one from 1-5 years of age and the other from 16-20 years of age, some severely affected patients will die in childhood despite multiple treatment modalities. The most common cause of death is respiratory failure. The CHMP concurs with the evaluation of the company that this subject does seem to represent one of those cases with severe recurrent infections that can not be controlled despite treatment.

With regard to the laboratory findings individual fluctuations which were seen in the Phase III study population with very few cases reaching clinical significance could often be attributed to underlying causes. Some intermittent changes from baseline will also be random and may appear in the population at large (e.g. LDH, bilirubin, CK, lipase etc.) and thus also in healthy male volunteers. It is therefore impossible to conclude that any signal would emerge from these studies. The company performed a detailed repeated analysis of the elevated liver function tests (LFT), LDH and lipase and provided convincing data that in those cases where consistent (not clinically relevant) elevations were seen, the screening or/and pre- first infusion values were also increased. Currently available data on

IgPro20 does not qualify elevation of LFTs as a safety signal that would require further specific activities other than routine pharmacovigilance.

Physical examination and vital sign changes did not give rise to any new concerns.

Age did not seem to play a role with regard to any safety signals; in the study ZLB06\_001CR less children and adolescents had AEs than adults. A specific wording for children in the SPC is therefore not warranted.

### 2.6.2. Conclusions on the clinical safety

The safety data is comprehensive. The safety profile of IgPro20 is similar to marketed SCIGs. The main adverse events are local injection site reactions of mild intensity.

## 2.7. Pharmacovigilance

### Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### Risk Management Plan

The MAA submitted a risk management plan.

**Table. Summary of the risk management plan**

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
<b>Important identified risks</b> <ul style="list-style-type: none"> <li>▪ Local Reactions (very common)</li> <li>▪ Headache (common).</li> </ul>	<b>Routine pharmacovigilance</b>	Listed in EU-SPC, section 4.8 Undesirable effects
<b>Important potential risks</b> Pruritus, Fatigue, Pain, and Vomiting (all uncommon) <hr style="border-top: 1px dashed black;"/> <ul style="list-style-type: none"> <li>▪ Potential for transmission of infectious agents</li> </ul>	<b>Routine pharmacovigilance</b>	Listed in EU-SPC, section 4.8 Undesirable effects <hr style="border-top: 1px dashed black;"/> Information included in EU-SPC, section 4.4 Special warnings and precautions for use, recommending the name and batch number of the product to be recorded.

<b>Safety concern</b>	<b>Proposed pharmacovigilance activities</b> <b>(routine and additional)</b>	<b>Proposed risk minimisation activities</b> <b>(routine and additional)</b>
<ul style="list-style-type: none"> <li>▪ Potential for allergy-like (hypersensitivity) and anaphylactic reactions</li> </ul>		Information provided in EU-SPC, sections <ul style="list-style-type: none"> <li>▪ 4.3 Contraindications: Hypersensitivity to any of the components;</li> <li>▪ 4.4 Special warnings and precautions for use: Recommendation for careful monitoring of patients during and after administration;</li> </ul> and <ul style="list-style-type: none"> <li>▪ 4.8 Undesirable effects</li> </ul>
<ul style="list-style-type: none"> <li>▪ Potential for increased or unknown risks in the home-based SC (self-) administration</li> </ul>		Information in EU-SPC, section 4.2, subsection ' <i>method of administration</i> ': Home treatment should be initiated by a physician experienced in the guidance of patients for home treatment. The patient will be instructed in the measures to be taken in case of severe adverse reactions.
<ul style="list-style-type: none"> <li>▪ Potential for exacerbation of existing hyperprolinaemia</li> </ul>		Contraindication in EU-SPC, section 4.3: "Patients with hyperprolinaemia".
<ul style="list-style-type: none"> <li>▪ Potential for haemolysis (theoretical consideration)</li> </ul>		None
<ul style="list-style-type: none"> <li>▪ Potential for aseptic meningitis (theoretical consideration)</li> </ul>		None
<ul style="list-style-type: none"> <li>▪ Potential for thrombo-embolic events (theoretical consideration)</li> </ul>		None
<b>Important missing information</b> <ul style="list-style-type: none"> <li>▪ Potential off-label use in therapeutic areas which have become medical practice for IVIg products;</li> <li>▪ Safety-profile of IgPro20 in the paediatric population;</li> <li>▪ Safety-profile of IgPro20 in the geriatric population.</li> </ul>	<b>Routine pharmacovigilance</b>	None

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## User consultation

The submitted bridging study report on results of the user consultation with target patient groups regarding the package leaflet is not sufficient to show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal

products for human use. The Applicant is requested to perform full user consultation with patient target groups.

## **2.8. Benefit-Risk Balance**

### **Benefits**

- Beneficial effects

In 1952 Bruton identified the first case of X-linked agammaglobulinemia in an 8-year old boy and subsequently IgG was introduced as replacement therapy for primary immunodeficiencies. The trials that followed were uncontrolled but so convincing as to render placebo-controlled trials unethical. Initially IgG therapy was given as subcutaneous injections, which were later replaced by intramuscular injections (IMIG). In the 1970's IMIGs were modified to be rendered virtually free of aggregates; other changes were made leading to the production of intravenous immunoglobulins. In the last 12-15 years the use of SCIG has become more widespread for home treatment of PID patients due to the greater convenience this route offers. Additionally, no venous access is required making SCIG a more acceptable route for children or patients with poor veins. The rate of side-effects is in general lower than with IVIG, especially with regard to systemic adverse events. Efficacy in terms of infection rate, days off school or work, use of antibiotics or in terms of the surrogate marker IgG trough levels can be maintained at the same level as with IVIGs.

Prevention of infection is the primary benefit that is expected from immunoglobulin replacement therapy. An accepted surrogate for this benefit is the trough concentration, alternatively AUC, of immunoglobulin. Prevention of serious bacterial infection was the primary endpoint in study ZLB04\_009CR and a secondary endpoint in study ZLB06\_001CR. In both studies the endpoint was clearly met. Infections, especially serious bacterial infections, could be contained to a minimum (0-1 serious bacterial infections SBI/patient/year), considering that in the historical setting patients suffered from > 4 SBI per year. Attaining sufficient trough levels/comparable AUC as a surrogate for efficacy was the primary endpoint in study ZLB06\_001CR and a secondary endpoint in study ZLB04\_009CR; this endpoint was also met. IgG trough levels with the subcutaneous route were sufficiently similar to those seen under the previous IVIG treatment (7-14 g/L) and are thus in line with levels seen in healthy subjects.

Additional beneficial effects resulting from the reduction of infections (especially SBIs) are a decrease in days off school or work and in use of antibiotics.

Furthermore, as indicated by the 39 out of 43 patients who received IgPro20 at home until Week 40, the compliance to the home-treatment with IgPro20 accounts for a relevant criterion of success.

- Uncertainty in the knowledge about the beneficial effects.

The major uncertainty with regard to the beneficial effects is the question of dosing and related outcome. In general, in the replacement therapy setting cumulative monthly doses of SCIG (given weekly) and IVIG (given once monthly) are similar. The main criterion for dosing is the clinical outcome.

The approach taken in the 2 submitted Phase III studies (Europe and USA) of switching a patient from IVIG to SCIG and calculating the necessary SCIG dose was slightly different.

However, there are many caveats with the comparison of the two studies: a) both are separate studies and not designed as a comparative study, b) regional differences in prescribing practices (e.g. antibiotics) and "accepted" length of hospital duration will differ and are therefore difficult to assess

and c) one patient in study ZLB06\_001CR with the SBI (chronic pneumonia) influenced some endpoints due to prolonged antibiotic treatment and hospitalisation, days off kindergarten etc.

The dosing and thus trough levels in study ZLB04\_009CR were approx. double that of levels observed in study ZLB06\_001CR. The secondary endpoints (other infections, days off school, use of antibiotics) were more favourable in study ZLB04\_009CR. Prima vista, it appears that the higher IgPro20 doses/higher trough levels in study ZLB04\_009CR led to lower annual rate of infections when compared to study ZLB06\_001CR. However, it is uncertain whether the discrepancy in "other infections" between the 2 studies was a direct consequence of the different dosing schemes or was it impacted by the different national standards of medical practice in capturing "other infections". Furthermore, a clear linear dose-trough level-response correlation did not result from a subgroup analysis in study ZLB06\_001CR of previous treatments when compared to the current treatment.

In view of the high incidence of local reactions in study ZLB04\_009CR (in 100% of subjects), increasing the dose may impact on the patients' comfort and compliance as evidenced by the higher number of withdrawals of consent in study ZLB04\_009CR. Taken together, the balance of the most effective dose and tolerability has to be individually tailored.

An effect on quality of life may be expected with the use of this 20% IGSC formulation, which reduces the infusion volume and duration of infusion compared to 10% and 16% IGSC preparations currently used in Europe and elsewhere in the world for replacement therapy. Nevertheless, this improvement was not evidenced through the analysis of HRQL instruments, neither when patients switched from IgIV to SCIG nor when they switched from "less concentrated" SCIG to IgPro20.

## Risks

For over 12 years SCIGs have been successfully applied in PID patients with very good safety records.

- Unfavourable effects

The main unfavourable effect was "local injection site reactions" as would be expected for the SCIG route of administration and was thus in line with other marketed SCIG products.

The difference in the rate of AEs per infusion between study ZLB06\_001CR and study ZLB04\_009CR: (0.288 vs 0.773), was mainly due to the higher rate of local reactions in study ZLB04\_009CR (0.06 vs 0.592). These reactions seem more frequent when higher dose (> 150 mg/kg) and higher infusion rate (>25 m l/h) are used (see study ZLB04\_009CR). Almost all AEs (99%) in both studies were mild or moderate in intensity. Local reactions were also mostly mild in intensity and diminished in frequency over time. The tolerability of IgPro20 was rated as good to very good by most patients.

While infections were also reported as AEs, they were expected due to the underlying disease of PID and the extensive history of chronic infections in most subjects.

Other common AEs were headache, diarrhoea, rash, fatigue that occurred at a similar rate in both studies.

- Uncertainty in the knowledge about the unfavourable effects

It is difficult to assess how many of the local reactions were due to the different doses applied (approx. twice higher dose was administered in the study conducted in the USA) and how much due to the different assessment procedures of local tolerability.

## Benefit-risk balance

- Importance of favourable and unfavourable effects

Favourable effects of IgPro20, as shown in clinical studies fulfil the requirements of respective guidelines (CPMP/BPWG/283/00). There are no major unfavourable effects identified for IgPro20 as compared to other human normal immunoglobulin products.

- Benefit-risk balance

The benefit-risk balance is positive considering that through weekly subcutaneous injections of IgPro20 (in a home setting) serious bacterial infections can be kept at bay in the majority of the PID patients ( $\leq 1$  SBI/patient/year) and the side-effects caused are very low in rate, mild in severity and mainly localised reactions in nature.

The overall benefit/risk balance of IgPro20 is positive.

### **2.8.1. Discussion on the benefit-risk balance**

The main benefit that is expected from immunoglobulin replacement therapy is prevention of infection. A surrogate measure of trough IgG concentrations is widely recognised in this kind of therapy. Beneficial and sufficient effect of IgPro20 on these outcomes is clearly demonstrated in line with guideline requirements.

Different dosing strategies exist in immunoglobulin replacement therapy. Results of studies performed with IgPro20 suggest that higher doses might provide lower infection rate, but also might be related to higher incidence of local reactions and decreased patients' comfort and compliance. Therefore, the balance of the most effective dose and tolerability has to be individually tailored.

Analysis of HRQL instruments in currently available studies has failed to show a positive IgPro20's impact on the quality of life, but such effect might be expected from the demonstrated relatively good compliance with home treatment.

Safety information on IgPro20 is obtained from a population size that exceeds the minimum requirements set by guidelines, show results that are consistent with results from other SCIGs and do not raise any additional concerns.

### **Risk management plan**

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that: routine pharmacovigilance was adequate to monitor the safety of the product and no additional risk minimisation activities were required beyond those included in the product information.

#### **2.8.2. Similarity with authorised orphan medicinal products**

Not applicable

#### **2.8.3. Market exclusivity**

Not applicable

#### **2.8.4. Significance of paediatric studies**

Not applicable

#### **2.8.5. Conformity with agreed Paediatric Investigation Plan**

Not applicable

## **2.9. Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Hizentra in the treatment of

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 lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

was favourable and therefore recommended the granting of the marketing authorisation.