

## SCIENTIFIC DISCUSSION

### 1. Introduction

Since the early 1980s, highly purified preparations of IgG for intravenous administration (IVIG) were developed by a number of manufacturers whereas the first products consisted of so-called modified products (modification of the Fc-part of the IgG to allow intravenous administration). Nowadays non-modified, so-called native IVIGs are the standard of care for the replacement therapy of patients with primary immunodeficiency and they are part of the therapy regimen of the other indications mentioned before.

Primary Immuno Deficiency (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 administration of IgG. Therapeutic options for treatment of PID are transplantation of bone marrow-derived stem cells, and recently, gene therapy.

IGIV also has been used in the treatment of secondary immunodeficiencies such as those occurring in patients with multiple myeloma and B-cell chronic lymphocytic leukemia, acquired immunodeficiency syndrome (AIDS) or in patients undergoing bone marrow transplantation.

IGIV also has been used in the treatment of ITP. Therapeutic options for the treatment of ITP mainly include intravenous immunoglobulins, oral corticosteroids, anti D-immunoglobulins and splenectomy. In addition to its use in therapy for PID and ITP. IGIV products are also effective in the management of immune mediated disorders such as Kawasaki syndrome, and Guillain Barré syndrome.

The main mechanism of action of immunoglobulin in the case of immunodeficiency is replacement of functionally deficient immunoglobulins. In the case of immune-mediated diseases like ITP, the mechanism of action is less well understood. Several mechanisms have been postulated, such as reticuloendothelial blockade, an increase in T suppressor cells or natural killer cells, and a decrease in antibody synthesis.

### About the product

KIOVIG is a plasma-derived product consisting of a highly purified preparation of human IgG. It is supplied as a ready-to-use liquid formulation with a pH of 4.6 to 5.1. 98% of the protein is gamma globulin with a normal subclass distribution. The new manufacturing process results in an intact IgG molecule with complete functional activity. The final product contains only trace amounts of IgA and IgM. Glycine is used as a stabiliser. KIOVIG is supplied in single-dose vials that nominally contain 1 g, 2.5 g, 5 g, 10 g and 20 g protein per vial.

The applicant currently has two human normal intravenous immunoglobulins (IVIG) products on the market, both in the USA and in Europe (Gammagard S/D and Endobulin S/D [EU]/Iveegam EN IVIG [US]).

The submitted Marketing Authorisation Application (MAA) concerns a so-called next generation product (KIOVIG) that is a 10% triple virally reduced immunoglobulin (TVR).

The three dedicated virus inactivation/removal steps consist of:

- solvent/detergent treatment (S/D)
- nanofiltration (35 nm)
- low pH incubation (pH of final product 4.6 to 5.1) at an elevated temperature

In addition to these dedicated steps, the cold ethanol fractionation process also contributes to the virus clearance capacity of the process.

The following indications are applied for:

#### Replacement therapy in

Primary immunodeficiency syndromes such as:

- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiency
- Severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogammaglobulinemia and recurrent infections

Children with congenital AIDS and recurrent infections

Immunomodulation - Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count. - Guillain Barré syndrome - Kawasaki disease

#### Allogeneic bone marrow transplantation

The posology is applied for as described in the core SPC for IVIG and is individualised according to the clinical condition to be treated.

## **2. Quality aspects**

### **Introduction**

#### **Drug Substance**

KIOVIG (IGIV, 10%) is manufactured from human plasma for fractionation and full details of this starting material are provided in Baxter's Plasma Master File which has been submitted to the EMEA under the certification procedure.

Due to the continuous manufacturing process of KIOVIG prior to the final formulation steps, no distinct intermediate Drug Substance stage is available. For formal reasons a fictitious Drug Substance is defined. This is the Ultrafiltrate Concentrate, a purified S/D treated and nanofiltered IgG concentrate, isolated from human plasma.

- **Manufacture**

The manufacturing process has been based on the processes used to manufacture two intravenous immunoglobulin products, Gammagard S/D and Endobulin S/D for which Baxter holds Marketing Authorisations within the EU.

The manufacturing process of the Ultrafiltrate Concentrate is divided into the production of the intermediate Precipitate G, which takes place in the three Baxter fractionation sites Los Angeles, Rieti (IT) and Vienna (AT), and into its subsequent continuous processing beyond the Ultrafiltrate Concentrate stage (the "drug substance") to the Drug Product at the Baxter facility Lessines. The production of the intermediate Precipitate G, a raw IgG fraction, starts with controlled thawing of the pooled plasma and the separation of the cryoprecipitate. Then, seven different adsorption options can be applied to the cryo-poor plasma at each of three Baxter facilities (Los Angeles, Vienna and Rieti) in order to remove coagulation factors and antithrombin. These options comprise either no adsorption or one adsorption step or diverse combinations of these adsorption steps.

Usage of such optional adsorption is an already approved practice for other immunoglobulin preparations of the applicant which have been on the market for a long time. Factors not adsorbed by practising the diverse adsorption options are eliminated from the protein solution by the downstream fractionation and purification steps afterwards as shown by the process validation.

Subsequently, modified COHN-ONCLEY cold ethanol fractionation steps yield the Precipitate G. This is shipped to Lessines (BE) where it is further purified by use of cation exchange chromatography and anion exchange chromatography.

Two (of the total of three) virus inactivation/elimination steps, a S/D treatment (using Polysorbate 80, TNBP and Octoxynol 9) and a nanofiltration, which were validated according to Guideline CPMP/BWP/268/95, are included in this downstream purification.

The manufacture of the fictitious Drug Substance is then finished by ultrafiltration and diafiltration to meet the final product release criteria of osmolality (240 - 300 mOsmol/kg), pH (4.6 - 5.1), and concentration of human IgG (9.0 - 11.0%).

### **Control of Materials**

The KIOVIG starting material human plasma, classified as source plasma or recovered plasma, originates from the USA, Germany, Austria, Czech Republic, Sweden and Switzerland. It 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). It is described in the Plasma Master File of Baxter AG, Vienna. This PMF is certified by EMEA.

The applicant's plasma safety program is based on an applicant donor acceptance program which includes routine donor screening and donation testing for the required infectious agents markers. Each single plasma unit used for the manufacture of the product is tested for ALT (SGPT), HBs-antigen, HIV-1/-2 antibody and HCV-antibody. Only plasma found non-reactive for HBs-antigen, HIV-1/-2-antibody and HCV-antibody, with SGPT (ALT)-values not exceeding twice the upper limit of normal is used in the manufacture of the product.

An inventory hold program and a *System to Trace the Path of Any Donation* are established. In addition, each plasma pool is tested for HBs-antigen, HIV-1/-2-antibody, HCV-antibody by ELISA, as well as for viral nucleic acids of HAV, HBV, HCV, HIV-1/-2 and Parvovirus B19 by HIQ-PCR. Only plasma pools non-reactive for HBs-antigen, HIV-1/-2-antibody, HCV-antibody, HAV RNA, HBV DNA, HCV RNA, HIV-1/-2 RNA, and containing not more than  $10^5$  I.U. of PVB19 DNA/ml are used for manufacture of the product.

In the manufacturing process of KIOVIG, no other material of human origin is used. Heparin of porcine origin is used in the adsorption steps of coagulations factors and antithrombin III. This substance is already approved for the manufacture of other immunoglobulins of the applicant. Control of other incoming raw materials utilising a supplier qualification program and performing adequate tests guarantees their continuous quality.

### **Control of Critical Steps and Intermediates**

Critical steps in the manufacturing process are identified. Tests and acceptance criteria are established to ensure that the process is controlled.

It is shown by stability studies that the fractionation intermediates "Fraction II+III Precipitate" and Precipitate G can be stored for 12 months at  $\leq -20^\circ\text{C}$  prior to further processing.

### **Process Validation and Evaluation**

To prove the consistency and comparability of the manufacturing process and the quality of the Precipitate G originating from the three fractionation sites, Precipitate G conformance lots originating from the three fractionation sites are manufactured. To prove the consistency and comparability of the manufacturing process and the quality of the Drug Product, Drug Product conformance lots manufactured utilising these different Precipitate Gs are produced, as well. For the overview and results, see below (Drug Product, section **Process Validation and Product Characterisation**).

### **Shipping Control and Monitoring**

For further processing, Precipitate G is shipped from the fractionation sites Los Angeles and Vienna to the facility Lessines. Precipitate G from the Rieti facility is either shipped directly to Lessines or through Baxter Vienna. The temperature required for shipment of Precipitate G must be  $\leq -20^\circ\text{C}$ . Temperature is monitored during shipment. The ability of the outer package and container to maintain the required temperature of  $\leq -20^\circ\text{C}$  during the shipping has been ensured. The ability of the transportation conditions to maintain the thermal stability is shown.

### **Manufacturing Process Development**

For manufacturing process development including the final step of low pH incubation, the following procedural steps were pre-defined and characterised:

- the use of optional adsorption steps to remove coagulation factors and antithrombin from the cryo-poor plasma prior to alcohol fractionation,
- the use of 8% alcohol to separate the fibrinogen enriched Fraction I to obtain the supernatant for Fraction II+III precipitation,
- the precipitation of Fractions II+III,
- the clarification of the dissolved Fractions II+III using depth filters,
- the production of an IgG enriched intermediate, Precipitate G, for downstream production,
- the cation and anion exchange chromatography as the main IgG purification steps,
- the liquid formulation of the final product at a low pH and
- the implementation of three dedicated virus reduction steps, S/D treatment, nanofiltration and low pH incubation at elevated temperature in the final container.

### **Characterisation**

Structural and functional integrity has been characterised based on the requirements of the relevant Ph Eur monograph and on the Note for guidance on clinical development of IVIG. As part of this characterisation studies, comparison of pre-clinical, clinical and conformance lots manufactured at different manufacturing sites and scales were performed.

### **Control of Drug Substance**

There is no quality testing of the Drug Substance, as no distinct intermediate Drug Substance stage can be defined. Quality control tests are performed at the Drug Product stage only.

### **Reference Materials**

Reference Standards used are described sufficiently.

### **Container Closure System**

The Container closure system is sufficiently described and qualified

- Stability

There is no storage of the Drug Substance. The Ultrafiltrate Concentrate (Step 15 of the manufacture), which corresponds to the Drug Substance, is immediately further processed and filled into final containers.

### **Drug Product**

#### **Description and Composition**

KIOVIG is an isotonic solution for infusion with approximately 100 mg of protein per ml, of which at least 98% is gammaglobulin (pH 4.6 - 5.1). It contains 0.25M Glycine as stabiliser. KIOVIG is supplied in single-dose vials that nominally contain 1 g, 2.5 g, 5 g, 10 g and 20 g protein per vial. The vials consists of neutral Type I borosilicate glass vials which meet the requirements of the Ph. Eur. These containers have filling capacities of 10 ml, 30 ml, 50 ml, 100 ml and 200 ml. The vials are closed with bromobutyl rubber stoppers, coated with either silicone or with omniflex (an inert and flexible fluorinated polymer) treatment. Both stoppers meet the chemical requirements of the current Ph. Eur.

Overfilling of each size ensures that the nominal amount of product can be drawn from the vial. Overfill does not influence the strength of KIOVIG, and is, therefore, acceptable.

The applicant wishes to license the possibility to dilute the product for use in patients who may not tolerate the high protein concentration. Therefore, tests were performed which show that KIOVIG can be diluted with 5% glucose to a 5% protein solution without impairment of its physicochemical and aseptic attributes.

- Pharmaceutical Development

Formulation experiments performed lead to a medicinal product in which quality and convenience features for clinical use were combined, and which meets the pharmaceutical and analytical criteria of the relevant Ph. Eur monograph.

- **Manufacture of the Product**

The manufacturing process of the final product KIOVIG is performed at Baxter's facility Lessines. It represents the continuation of the processing of Precipitate G. Beginning at the Ultrafiltrate Concentrate stage the manufacturing process comprises the following steps without any holding step:

- the final formulation where the protein content is adjusted to  $10.2 \pm 0.2\%$  and the pH is adjusted to 4.4 to 4.9,
- the 0.2 $\mu$ m filtration,
- the filling, the stoppering and the sealing under aseptic conditions, and, finally,
- the final Incubation at low pH and elevated temperature.

Two different batch sizes of the final product KIOVIG can be manufactured based on either 6000 or 14000 litres of human plasma. The resulting bulk solution can be divided into several sub-lots before filling into vials of different sizes.

### **Control of Critical Steps and Intermediates**

Critical steps of the manufacturing process are identified. Tests and acceptance criteria are established to ensure that the process is controlled.

### **Manufacturing Process Development (Process Validation and Product Characterisation)**

Three fractionation sites working with some differences in their manufacturing procedures (see above) are used to produce Precipitate G which is then utilised for the production of the commercial KIOVIG Drug Product in the Lessines facility. In addition, Rochester as a further fractionation site produced the Precipitate G for the production of the KIOVIG clinical lots. Therefore, comprehensive comparability and consistency studies were performed. Data comparing the manufacturing processes and quality parameters of the Precipitate G and the resulting Drug Product are presented. In total, twenty conformance lots of Precipitate G produced at commercial scale in Los Angeles, Vienna and Rieti were investigated. A bracketing approach was used narrowing all various options and variations. The chosen options were justified and are considered acceptable.

The scope of the program was primarily the investigation of the manufacturing process control parameters and of the release parameters of precipitate G (purity) as well as additional product characteristics (gammaglobulin purification, IgG purification, enrichment of bacterial and viral antibodies, reduction of IgA and fibrinogen, IgG subclass distribution). The presented data show that the manufacturing process of Precipitate G is controlled and is capable to consistently meet the pre-determined acceptance criteria of process control parameters. They show that the product complies with its predetermined specifications and that the IgG is purified in a comparable manner with comparable subclass distribution, antibody contents and reduction of impurities.

Precipitate G lots produced for conformance purposes in Los Angeles, Vienna and Rieti were processed without blending into ten final bulk lots at the Lessines facility. Investigation of the manufacturing process control parameters was performed and it was demonstrated that the found values were within the pre-determined limits.

Out of the ten final bulk lots, twenty-one Drug Product sub-lots were produced. These were investigated for pre-determined tentative product specification parameters (for final product control, these have been adapted slightly based on the validation results). Furthermore, these sub-lots were investigated for additional quality characteristics (IgG purification, spectrum and enrichment of viral/bacterial antibodies, Fc function, IgG subclass distribution, removal of impurities – product related: IgM, IgA, albumin, fibrinogen, factor XII, “amidolytic activities”, plasminogen, - process related: Heparin, Aluminium, S/D components, ethanol).

The data show that the manufacturing process results in a consistent Drug Product independently of the origin of Precipitate G. The IgG is consistently purified throughout the manufacturing process to approximately 100% of the protein. The Drug Product maintains a broad spectrum of relevant bacterial and viral antibodies. The enrichment fulfils the Ph Eur requirements. The results indicate that

all lots show a comparable intact Fc-function of the antibodies and have an IgG subclass distribution comparable with the normal range found in normal human serum. Finally, the data show acceptable removal of product-related and process-related impurities.

The downstream purification process of the intermediate Precipitate G also has the ability to eliminate still existing small negligible differences in quality of Precipitate G occasionally observed in the Precipitate G product characterisation.

A characterization study was provided to demonstrate the structural and functional integrity of the Precipitate G and of the Drug Product using data acquired by testing of the pre-clinical, clinical and conformance lots, and to demonstrate that this integrity were not influenced by the different upstream fractionation facilities and by the different adsorption options. The preclinical lots were produced in a small scale starting from 200 l of plasma. The clinical lots and conformance lots were produced in full commercial scale (3 000 / 45 000 l plasma). Seven clinical lots are derived from Precipitate G produced in Vienna practising two of the diverse adsorption options and three clinical lots are derived from Precipitate G produced in Rochester practising no adsorption.

The IgG subclass distribution and the antibody spectrum were compared, functional properties were characterised based on a mouse protection tests, on three Fc-function assays and on Opsonophagocytosis tests. The results demonstrate that the subclass distribution is comparable to that found in the normal serum, and that a broad spectrum of clinically relevant antibody specificities is present, and that the IgG holds intact Fc and Fab segments exerting their biological functions - regardless of the manufacturing facility or option used.

#### **Development of Container Closure System and Microbiological Attributes**

The container closure system was tested according to Ph. Eur. to show its suitability for storage and shipping of the medicinal product. Its mechanical and thermal stability has been shown. Its compatibility is demonstrated, no measurable leach out is observed. It has been shown that the KIOVIG container/closure system is able to maintain the sterility of the biologic product.

#### **Control of Excipients**

No excipients of animal or human origin or no novel excipient are used in the manufacturing process of KIOVIG.

The major excipient is glycine which is formulated at a target concentration of 0.25 M to maintain the product at isotonic condition. Its specification is provided. The specification meets the requirements of Ph. Eur.

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

The reference standards for the methods used to test the Drug Product at the Baxter Lessines facility are purchased as part of a kit or as stand-alone materials, and as primary standards or as international standards such as BRP.

#### **Container Closure System**

The description of the primary packaging material is given in sufficient detail.

#### **Secondary Packaging Components**

There are no secondary packaging requirements for the KIOVIG except for the labeling of the outer packaging.

- Product Specification

The final product specifications are in compliance with the relevant Ph. Eur. monograph 0918 on IVIG. The specifications for some of the parameters are even tighter than those required. The justification of the chosen tests is provided. When alternative methods are used, they have been validated against the respective Ph.Eur. method. Thus, the Drug Product specification is acceptable.

Results of the analysis for 18 manufacturing scale lots (including sub-lots of different filling size) of the KIOVIG product finished at the Baxter Lessines facility are provided. Data for eight KIOVIG

clinical lots and for the 10 conformance lots (21 sub-lots) are provided. It is indicated, which lots derived from Precipitate G manufactured in Los Angeles, Vienna or Rieti. The analytical procedures and specifications used to test KIOVIG Drug Product are described. All commercial scale lots passed the final release specification for KIOVIG.

- **Stability of the Product**

The formulated KIOVIG bulk solution may be stored in some cases for a maximum of 11 days prior to final filling. This storage has been validated in a hold time study with KIOVIG bulk solution. In this study total protein content was determined at three levels of the containers used (top, middle and bottom) for a period of 11 days. Protein data show no significant differences and in this way, homogeneity of the solution has been demonstrated.

Regarding the final container lots, the presented stability program, taking into account material from different sites and the bracketing approach for different fill sizes, is acceptable.

Selected test-parameters and acceptance criteria are suitable to demonstrate product stability. Although only one clinical lot has been tested for 30 months and the real-time data to accept a 36 month shelf life are limited, the overall available data base is considered sufficient to support a shelf-life of 24 months (2-8°C). Based on the results of the ongoing stability study, this shelf life might be extended to the applied shelf life of 36 months.

The applicant proposes storage at 25°C for a maximum of 9 months within the first 24 months of shelf life. Data from stability studies provided support very well the storage time of 24 months and a one time period of up to 9 months at room temperature within the shelf life. This can be accepted since in the SPC the precautions of the storage are appropriate described under point 6.3 and 6.4.

## **Appendix**

### **Facilities and Equipment**

A description of all the facilities for the commercial manufacture, the product flow, material flow and personnel flow is provided. The preparation, cleaning and sterilisation of the equipments are described. The prevention of cross contamination is illustrated. Floor plans for all facilities are provided. The information is detailed.

### **Adventitious agent safety**

#### **Risk on contamination with animal TSE**

No materials of bovine or other TSE-susceptible animal species are used during production. The composition of media fills and compliance with TSE-Guideline EMEA/BWP/401/rev. 02 has been shown. The prion removal capacity of the KIOVIG production process was investigated in the study submitted to EMEA 30<sup>th</sup> September 2005 in accordance with the position statement on vCJD and plasma-derived medicinal products, EMEA/CPMP/BWP/2879/02 rev 1.

The Applicant submitted TSE-spiking results from studies on extraction of the Fr II+III precipitate to investigate the prion removal capacity.

The study was performed using an adequately down-scaled laboratory process and performance of the down scaled model was checked by biochemical analysis of product intermediates. PrP<sup>Sc</sup>-spiked runs were performed at the upper pH-limit during extraction of precipitate II+III which is assumed 'worst case limit' in respect to co-extraction of Prions with IgG.

Two different spike preparations from hamster brain were studied. Prions were detected by Western Blot. Appropriate controls for interference of test matrix with PrP<sup>Sc</sup> detection have been performed. Both spike preparations were removed down to the detection limit. Due to the limited input of solubilized PrP<sup>Sc</sup> preparation only >2.1 log removal could be demonstrated. However, ≥3.6 log removal could be demonstrated using clarified brain homogenate. Partitioning of PrP<sup>Sc</sup> to the discarded side fraction (i. e. insoluble fraction after extraction of Paste II+III) could be demonstrated.

**Tab 2. Loads of TSE agents (log) during Fractionation II+III plus subsequent extraction, fumed silica treatment and Filtration. (Study reg652e)**

<b>Agent</b>	<b>Hamster adapted Scrapie 263K</b>	
	<b>Crude hamster brain homogenate (10% w/v) suspension clarified by low speed centrifugation</b>	<b>Detergent solubilized (0.1% lysolecithin) and sonicated brain homogenate</b>
<b>Spike</b>		
<b>Detection Method</b>	<b>Western Blot</b>	
<i>Spiked Starting Material (Supernatant I)</i>	5.0	3.5
<i>After addition of EtOH</i>	4.5	3.5
<i>After 10h in EtOH</i>	4.5	3.0
<i>Supernatant after centrifugation</i>	2.5	<1.5
<i>Re-suspended Precipitate II+III</i>	4.6	3.1
<i>Combined Filtrate and Post wash Fraction</i>	<1.4	<1.4
<i>Filter cake</i>	4.2	2.2
<b>Rf<sup>a</sup></b>	≥3.6	≥2.1

<sup>a</sup>: reduction factor calculated from “Spiked Starting Material” and “Combined Filtrate and Post wash Fraction”.

In summary, a significant capacity of the KIOVIG production process to remove spiked PrP<sup>Sc</sup> has been demonstrated. The results are comparable to that described for other immunoglobulins.

It should be noted that the confidence which can be placed on a figure for the ability of a process step to remove the agent of TSE is lower than for its ability to remove model viruses for the reasons described in the CHMP Guideline on the Investigation of manufacturing processes for plasma-derived medicinal products with regard to vCJD risk (CPMP/BWP/5136/03), Section 3.6, Interpretation and limitations of data.

#### **Adventitious viruses**

The potential contamination of plasma pools with HIV, HBV, HCV, HAV, and B19V is limited by testing of individual donors according to the requirements, by testing of mini pools and plasma pools for fractionation for viral nucleic acids. Three steps (SD-Treatment, Planova 35N Filtration, and 21 days incubation at low pH, 30°C) have been implemented in order to inactivate/remove viruses. Validation studies were performed according to Guideline CPMP/BWP/268/95.

Enveloped viruses are effectively inactivated and removed by these steps which results in a high safety margin of the product towards enveloped viruses. The safety with regard to the non-enveloped viruses HAV and B19V, mainly depends on the presence of antibodies. Virus-antibody complexes are efficiently removed by nanofiltration and neutralisation of HAV and B19V further contributes to HAV and B19V safety. Therefore, the following specifications for the antibody content against HAV and B19V in the final product (≥ 3.5 IU/ml anti-HAV and ≥ 35 IU/ml anti-B19V antibodies) have been set in order to ensure additional factors contributing to safety against HAV and B19V. Safety with respect to non-enveloped viruses for which no specific antibodies are present is more difficult to assess. Large non-enveloped viruses or pH labile viruses are effectively removed/inactivated while the reduction capacity with regard to small, pH stable model viruses such as MMV is limited. However, such viruses (and hypothetical TSE agents) are normally removed to a significant extent by the ethanol-fractionation steps (i.e. mainly the separation of fraction III from fraction II). These studies have been provided and a significant removing capacity of this step for small non-enveloped viruses, where no specific neutralizing antibodies are present in the product intermediate (e.g. MMV, EMCV), has been demonstrated. Nevertheless, according to filter clogging occurring at the post wash during depth filtration, reduction factors achieved with HAV and EMCV at high pH limit have to be interpreted with caution. Therefore, to complete robustness data it is suggested to repeat this step with HAV and EMCV at high pH limit in an on-going procedure (follow-up measure).

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

The issues primarily identified, which were related to

- the lack of detailed comparative description of the manufacturing processes,
- the need to clarify the comparative testing strategy of products originating from the different fractionation sites,
- the process strategy and batch definition,
- the reprocessing and further processing of batches failing critical manufacturing steps,



- the description of the strategy to control the process,
- the validation of the fractionation process with regard to the removal of non-enveloped viruses, had been largely resolved by the applicant – except for some remaining minor points listed in the section 2.7 to be addressed as follow-up measures.

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

The term “triple inactivated IVIG” used by the applicant with reference to the three virus inactivation/removal steps of the manufacturing procedure should not be used because it is misleading for all viruses since these steps are primarily applied to the inactivation/removal of enveloped viruses. Inactivation/removal of non-enveloped viruses is restricted to large and pH-sensitive non-enveloped viruses while small or pH stable non-enveloped viruses are expected to be removed during the Cohn-fractionation as known for other approved IVIG products. In summary, a high safety margin has been demonstrated for HIV, HBV, HCV, HAV, and B19V. The proposed wording in SPC section 4.4 is accepted:

*“KIOVIG is made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.*

*The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.*

*There is reassuring clinical experience regarding the lack of hepatitis A or Parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.*

*It is strongly recommended that every time that KIOVIG is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.”*

### **3. Non-clinical aspects**

#### **Introduction**

The active ingredient of KIOVIG (IGIV, 10% TVR) is human polyvalent immunoglobulin G (IgG). The structural and functional integrity of the IgG molecules are maintained during the manufacturing process. The subclass distribution and broad spectrum of antibody specificities present in human plasma are retained and the product exerts all the critical biological activities of polyvalent antibody molecules. The exact mechanism of action other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

The non-clinical studies have addressed the efficacy (*in vitro* and *in vivo*), safety pharmacology, acute toxicity and local tolerance of the three lots of KIOVIG in comparison with that of a authorised immunoglobulin. The range of studies is appropriate for this product.

Three lots were used in the non-clinical studies. One lot was manufactured from cryo-poor plasma that was subjected to no adsorption (Option 1), one lot from cryo-poor plasma subjected to the FEIBA and Antithrombin-III adsorption steps (Option 3), and one lot from cryo-poor plasma subjected to Factor IX, Factor VII and Antithrombin adsorption steps (Option 6). These three options bracket the seven possible options that can be used to manufacture the product. This is a common approach for blood products and thus acceptable.

Safety pharmacology and toxicological studies were conducted in accordance with GLP and in accordance with the relevant guidelines.

## Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

Two *in vitro* studies (antibody spectrum and evaluation of opsonic activity) and one *in vivo* study (protection of mice against infection) are presented.

The antibody spectrum for three lots of IGIV, 10 % TVR (01C21AN11, 01C21AN21, and 01D05AN11) were compared. These were obtained from three preclinical using adsorption options 1, 3 and 6, respectively.

Antibodies against cytomegalovirus, *Haemophilus influenzae* Type B, Hepatitis A virus, Hepatitis B virus, Measles virus, Parvovirus B19, Poliomyelitis virus type I, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and Varicella-zoster virus were measured. Comparable values were seen in each of the three lots.

The opsonic activity of the same three lots was evaluated in an opsonophagocytosis assay in human neutrophils (polymorphonuclear leukocytes, PMNs), in comparison to an IGIV reference product, (Study 13437). The test system included PMNs prepared from fresh heparinised human blood, gram negative (*Escherichia coli* O55:K59) and gram-positive (*Streptococcus agalactiae*, Group B) bacteria and a complement source (normal human serum adsorbed against the appropriate bacteria, NHS-Abs). The assay assesses the function of the entire IgG molecule by binding the Fab portion of the antibody to a bacterial organism, leaving the Fc portion available to bind with a PMN. The opsonic activity of the three lots of KIOVIG was similar to that of the reference product against both the gram negative and gram-positive bacteria.

In an *in vivo* study, the same three lots of IGIV, 10 % TVR were evaluated for activity against virulent, mouse-lethal, human pathogens, in comparison with two lots of the reference product and with human albumin. The test article was administered IV to female mice about 18 to 20 hours before IP challenge with one of five 10-fold dilutions of *Streptococcus pneumoniae* ( $9.7 \times 10^1 - 9.7 \times 10^5$  cfu/ml) or *Klebsiella pneumoniae* ( $1.17 \times 10^1 - 1.17 \times 10^5$  cfu/ml). The immunoglobulin dose was about 500mg/kg (0.3 ml of a 3.3 % solution to mice of approximately 20g).

For each test article, the estimated median lethal dose (LD<sub>50</sub>) of each challenge organism and the log<sub>10</sub> dilution inverse that yields 50 % survival (log<sub>10</sub>LD<sub>50</sub>) is tabulated below.

	S. pneumoniae			K. pneumoniae		
	LD <sub>50</sub> (cfu/mouse)	log <sub>10</sub> LD <sub>50</sub>	standard error	LD <sub>50</sub> (cfu/mouse)	log <sub>10</sub> LD <sub>50</sub>	standard error
KIOVIG	1.1 x 10 <sup>4</sup>	4.04	0.170	3.9 x 10 <sup>4</sup>	4.60	0.163
Gammagard S/D	1.25 x 10 <sup>4</sup>	4.10	0.155	2.7 x 10 <sup>4</sup>	4.44	0.172
Human albumin	7.74 x 10 <sup>0</sup>	-	1.463	5.55 x 10 <sup>0</sup>	-	0.927

No statistical comparison performed against albumin control as most mice are not expected to survive in the albumin control group

The results suggest that KIOVIG was as effective as or better than the reference product at protecting against *S. pneumoniae* or *K. pneumoniae*-induced infection.

- Safety pharmacology

Three lots of KIOVIG and 2 lots of the authorised immunoglobulin were compared. The positive control was one lot of an immunoglobulin preparation for i.m. administration with the exception of study 3, where an activated FVIII was used: Throughout the experiment the blood pressure lowering activity after intra-arterial injection (as a result of an anaphylactoid reaction) was compared in anesthetized spontaneously **hypertensive rats**, bronchospastic activity after intra-arterial injection in anesthetized **guinea pigs**, thrombogenicity in anesthetized **rabbits** after i.v. injection.

In a safety pharmacological study in anesthetized **beagle dogs** three lots of KIOVIG and one lot of the comparator were tested. The effects on the cardiovascular, the respiratory and the coagulation system were assessed during a 3-hour observation period.

The results of the studies did not indicate significant and relevant occurrence of anaphylactoid reactions, no major influences on the respiratory, or development of disseminated intravascular coagulation for the compared preparations.

### **Pharmacokinetics**

A comparison of the pharmacokinetics of KIOVIG and a reference product in rats shows their elimination half-lives is similar. In vivo recovery varied between 70 and 80 %, and the half-life between 136 and 166 hours. However, this is not predictive for the values in man, where the half-life of a human protein will be longer. In patients with hypo- or agammaglobulinaemia, the median terminal half-life of IgG was 30.1 days.

### **Toxicology**

- Single dose toxicity

Two studies are provided. One acute toxicity study was done in mice with three lots of KIOVIG in comparison with 2 lots of the comparator product, and formulation buffer after i.v administration of high volumes (25-100ml/kg). After the fast administration of the high volumes of the test substances a animals in both groups died showing symptoms of volume overload

An additional study in rats with doses of 2000 mg/kg and volumes of 20ml/kg gave no indications of toxicity.

The NOAEL was 2000 mg/kg for KIOVIG and < 2000 mg/kg for the reference product

- Repeat dose toxicity (with toxicokinetics)

Repeated-dose toxicity studies were not conducted, given the potential for antigenicity following administration of a human protein to an animal species. This is acceptable for intravenous immunoglobulins.

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

Although not needed for plasma-derived products as immunoglobulins, an *in vitro* mutagenicity test is presented to cover possible effects of the residual solvent/detergent reagents. A classical Ames test using *Salmonella* strains with and without metabolic activation was performed. There was no statistically significant increase of the mutation frequency up to a concentration of 100 µl of KIOVIG per plate.

- Carcinogenicity (with toxicokinetics) / Reproductive and developmental studies

Carcinogenicity studies and reproductive and developmental toxicity studies were not performed, which is considered as acceptable due the proteinous nature of the test article; this is in accordance with the Note for Guidance on Preclinical Safety Evaluation of Biotechnology – Derived Pharmaceuticals (CPMP/ICH/302/95).

- Local tolerance

One study was performed to evaluate the local tolerance of KIOVIG in comparison with two reference products. The study was performed in rabbits with intra arterial, i.v. and paravenous injection and an observation period of 72h. Slight irritations were observed in the intra-arterial and paravenous route, but not after the i.v. administration, which is the route of administration in humans.

- Other toxicity studies

Literature on the solvents/detergents used in the manufacture of KIOVIG has been presented reviewed by the applicant. Tri-n-butyl phosphate, Triton X-100 and polysorbate 80 were discussed. Based on the maximum doses for KIOVIG of 2000mg/kg (single dose in Kawasaki disease) or up to 800mg/kg every 2 to 4 weeks (for replacement therapy in primary immunodeficiency) and the measured levels of the detergents in the lots (<0.2ppm for TNBP and Triton X-100 and <20ppm for polysorbate 80), the amount of TNBP and Triton-X administered would be 0.4µg/kg as a single dose or 0.16µg/kg every 2 to 4 weeks, and of polysorbate 80 would be 40µg/kg (single dose) or 16µg/kg every 2 to 4 weeks. These levels are far below those that have shown toxic effects in animals (and in humans) and are considered to have negligible impact on the safety of the product.

#### **Ecotoxicity/environmental risk assessment**

KIOVIG is manufactured from pooled human plasma, which is screened for markers of virus contamination. The manufacturing process includes three dedicated virus reduction steps (solvent detergent treatment, nanofiltration and incubation at low pH in the final container), which have been shown to provide a high margin of safety against enveloped as well as non-enveloped viruses. As naturally occurring proteins, the immunoglobulins in KIOVIG are metabolised and degraded in the human body by the same pathways as endogenous antibodies. The only excipient (glycine) is a naturally occurring amino acid in humans and the environment. The product is not considered to be a risk to the environment.

## **4. Clinical aspects**

### **Introduction**

The studies performed to support the requested indications:

- Replacement therapy in

Primary Immunodeficiency Syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogammaglobulinemia and recurrent infections.

Children with congenital AIDS and recurrent infections.

- Immunomodulation
- Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease

#### Allogeneic Bone Marrow Transplantation

are in line with the requirements laid down in the note for guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (CPMP/BPWG/388/95 rev. 1) and encompass the following trials:

- PK, efficacy and safety **study 160001**; prospective, open-label, uncontrolled, multi-centre in 22 primary immunodeficient (PID) patients
- PK, efficacy and safety **Study 160101**; randomised, open-label, multi-centre in 61 PID patients
- Efficacy and safety **study 160002**; prospective, open-label, uncontrolled, multi-centre; in 23 ITP patients

The indications follow the wording of the so-called “established” indications listed in the core SPC for normal immunoglobulin (IVIg) for intravenous administration (CPMP/BPWG/859/95 rev. 1).

The European Clinical Studies 16001 (PID) and 160002 (ITP) were both conducted in according note for guidance on good clinical practice (CHMP/ICH/135/95) and the ethical principles conveyed by the “Declaration of Helsinki”. The US Clinical Study 160101 was conducted per the principles set forth in the United States (US) Food and Drug Administration (FDA) Code of Federal Regulations (21 CR, parts 50, 54, 56, 312 and 314), ICH Guidelines for GCP and the Declaration of Helsinki. Hence, the EU as well as US clinical studies were performed in accordance with GCP principles and ethical requirements equivalent to the provisions of Directive 2001/20/EC as stated by the applicant.

#### **Pharmacokinetics**

The company performed three open-label studies, 2 in PID (PID 1600001 EU, PID 160101 US) and 1 in ITP patients, (ITP 1600002 EU) to evaluate pharmacokinetics (PK), efficacy and safety. In each study the correct patient population was included, CPMP/BPWG/388/95 rev. 1) and the US study complied with the FDA requirements and the posology as recommended by the core SPC (CPMP/BPWG/859/95 rev 1) was adhered to.

In **study 160001** performed in 22 PID patients, the primary pharmacokinetic endpoints were the trough levels, half-life, of total IgG and in vivo recovery.

The median steady state trough level of total IgG achieved after the administration of KIOVIG and a authorised IVIg are similar (817 mg/dL and 851 mg/dL, respectively) and clinically adequate. These levels are above those required in the SPC CPMP/BPWG/859/95 rev.2 of 4-6 g/L and fulfil the current clinical requirements. The median trough levels observed with different lots of KIOVIG manufactured at different sites (Rochester and Vienna) were comparable.

The median terminal half-life of KIOVIG for total IgG was 30.1 days (95% CI: 27.1; 43.3 days). The median terminal half-lives for IgG subclasses was 28.3, 31.3, 20.9 and 24.2 days for subclasses IgG1, IgG2, IgG3 and IgG4, respectively.

The median in vivo recovery rate of total IgG was 89% (95% CI: 84%; 101%) with a median incremental recovery of 1.85 (mg/dL)/(mg/kg).

The median AUC, Cmax and Cmin levels for the total IgG, after administration of a median dose of 0.41 g/kg were 545 g.h/dL, 1630 mg/dl and 848 mg/dl respectively. These values also correspond to those of other IVIG products and literature data.

The US study 160101 interim report showed similar PK results to the EU study, however for each of the PK parameters examined the values were consistently higher. This was explained by higher dosing regimens used in the US study (455 mg/kg vs. 410 mg/kg in EU Study). Median values for AUC0-21d, Cmax, Cmin, elimination half-life, K, and IVR and median values for total IgG trough levels indicated no significant differences for KIOVIG produced from pathway options 1, 3, and 6 at Rochester and Vienna.

- Special populations

**Study 160001** was performed in 22 patients. No subgroup analysis was planned for race or age group (Caucasian (100%) adults (100% above 21 years)). As with other similar studies of IVIG in PID populations, impaired renal function and impaired liver function were not specifically examined.

**Study 160101** also included children (n= 7) and adolescents (n=10). The number of patients in each group is too small to draw any precise conclusions; therefore comparison to adult PK data is only of limited value.

For children, adolescents and adults the trough levels and other PK parameters are consistent with those described in the literature. The median total IgG levels are reliably above the level recommended in the core SPC for CPMP/BPWG/859/95 rev.1 of at least 6 g/L.

- Pharmacokinetic interaction studies

A study to evaluate the interaction of IVIGs with other drugs is not requested by the Guideline (CPMP/BPWG/388/95 rev. 1). Given the underlying nature of PID a variety of other drugs are necessary (e.g. antibiotics, analgesics) and were administered as judged necessary. No products that compromise the effects of the study product were used during the course of the study. For use of antibiotics see “efficacy”

## Pharmacodynamics

- Mechanism of action

The mode of action of human normal immunoglobulin in primary and secondary immunodeficiency is as replacement of deficient immunoglobulins. In immune regulatory disorders, several mechanisms are postulated, including reticuloendothelial cell blockade, an increase in t-suppressor cells or natural killer cells, and a decrease in antibody synthesis. The latter may be through anti-idiotypic antibodies in the IVIG preparations. This mechanism might operate in diseases such as ITP. It is also considered possible that infused antibodies block recognition of infected cells by cytotoxic T lymphocytes, preventing immune mediated damage. No study has been carried out to elucidate the mechanism of action.

Functional integrity of the antibody molecules was determined by Fc receptor functions tests and opsonophagocytosis assay. Neutralising capacity was tested in mouse protection assays with three lots.

The above is reflected under section 5.1 Pharmacodynamic properties of the SPC.

- Primary pharmacology

The dosing regimen proposed is in accordance with CHMP requirements. No dose finding studies were undertaken.

- Pharmacodynamic interactions

Pharmacodynamic interaction is described with concomitant administration of live attenuated virus vaccines. Concomitant administration of live attenuated virus vaccines is not advised. This is covered in Section 4.5 Interactions, of the SPC.

### **Clinical efficacy**

- Dose response study(ies)

No dose-response study conducted. Only clinical confirmatory studies in target indications were carried out. The dose and dosage regimen varies with different indications. The standard recommendation is to obtain trough levels of 4-6 gm/l (400-600 mg/dl). The CHMP core SPC includes recommendation on starting dose and frequency of injection to maintain this level.

- Main studies

#### **Study 160001**

Study **160001** (European PID study), a prospective open-label study to compare pharmacokinetics, efficacy and safety of KIOVIG and an immune globulin intravenous (human), in patients with hypo- or agammaglobulinemia

#### METHODS

##### *Study Participants*

Twenty-two patients between 26 and 70 years of age meeting the inclusion criteria were included in the study.

##### Inclusion criteria

- Primary Immunodeficiency Disease requiring immunoglobulin replacement therapy
- Has had regular treatment with immunoglobulin (IV or SC)
- Serum IgG level of  $\geq 5$  g/L

##### *Treatments*

Lead-in phase: Three intravenous infusions of the reference product 300-450 mg/kg b.w. every 3 weeks. This was to standardise IgG replacement therapy with an authorised licensed IVIg.

Active phase: Nine intravenous infusions of KIOVIG, 300-450 mg/kg b.w. every 3 weeks.

Infusion rate: Initial rate of 0.5 ml/kg/hour gradually increased, if no adverse event is observed, half-hourly up to a maximum rate of 8 ml/kg/hour.

##### *Objectives*

To investigate the pharmacokinetics, efficacy and safety of KIOVIG, after standardisation with an authorised product.

##### *Outcomes/endpoints*

Primary efficacy endpoints were:

- Rate of infections (number of infections per subject per month) and

- Frequency of antibiotic use (number of courses of antibiotics, oral/i.v.).

In addition, data on days off work/school was collected.

To assess efficacy (and safety), blood samples were obtained prior to each of the 3 infusions of reference product and each of the 9 infusions of KIOVIG, i.e. before all 12 infusions. Patients were to return to the clinic for an End-of-Study Visit 21 days after the 12<sup>th</sup> infusion.

#### *Sample size*

Twenty-two patients enrolled to obtain a minimum of 15 evaluable patients. This was to fulfil CHMP requirements of 15 patients with immunodeficiency of which at least 10 should have primary immunodeficiency.

#### *Statistical methods*

Median and non-parametric 95% confidence interval was calculated to summarise efficacy end-points.

### RESULTS

#### *Participant flow*

All except one patient completed the study.

#### *Outcomes and estimation*

Infection rate was a secondary efficacy endpoint. Infection rate and frequency of antibiotic use were calculated and data on days off work/school were collected. Infections were not categorized into validated and other infections

#### **Infection rate**

There were 29 non-serious infections and 1 serious infection during treatment with the reference product and 59 non-serious infections with KIOVIG. No serious infections were reported for subjects during treatment with KIOVIG.

#### **Antibiotic use:**

A total of 36 courses of oral antibiotics were administered to 17 patients while on KIOVIG and 21 courses while on the reference product. Two patients in KIOVIG group received 1 course each of intravenous antibiotics.

#### **Days off work/school:**

Among the 22 patients treated with KIOVIG, 13 missed between 0.5 and 10 days of work/school due to infection. The rate of days off work/school per month ranged from 0 to 1.58 in the observational period (approx. 6.3 months). The median monthly frequency of days off work/school was 0.40 with a 95% CI from 0.00 to 0.83.

#### **Study 160002**

Study **160002** (European ITP study) was a prospective open-label non-controlled study to evaluate the efficacy and safety of Immune Globulin Intravenous (Human), 10% TVR solution in adult Subjects with chronic idiopathic thrombocytopenic purpura (ITP).

### METHODS

#### *Study Participants*

Twenty-three patients meeting the inclusion criteria were included in the study.



### Inclusion criteria

- $\geq 18$  and  $\leq 65$  years of age
- ITP was diagnosed at least 6 months prior to study entry by history, physical exam, blood count and blood smear
- Platelet counts  $\leq 20 \times 10^9/L$
- Excluded if unresponsive to the last IVIg treatment course prior to study entry

### *Treatments*

After screening, subjects eligible for treatment were to receive a total dose of 2 g of KIOVIG per kg body weight equally divided over 2 to 5 days. If platelet counts fell to  $< 20 \times 10^9/L$ , a booster dose of up to 1 gm/kg was allowed.

### *Objectives*

The objectives of the study were to determine the efficacy and safety of KIOVIG in adult subjects with chronic idiopathic thrombocytopenic purpura (ITP).

### *Outcomes/endpoints*

Primary efficacy endpoints were determination of the number of subjects who were treatment responders, response being defined as achievement of a platelet increase to  $\geq 50 \times 10^9/L$  at least once prior to Day 15 after initiation of treatment without receiving a booster dose during that period.

Secondary endpoints were

- Time to platelet response
- Duration of response
- Maximum platelet level
- Regression of Haemorrhage

Platelet counts were determined at screening and on Days 1 (initiation of treatment course), 2, 5, 8, 11, 15, 22, and 29. Blood samples for platelet determination taken on treatment days were drawn prior to study drug administration

A Full Analysis Data Set (FADS) and a Per Protocol Analysis Data Set (PADS) were to be analysed. There was no plan to have an independent efficacy assessment

### *Sample size*

Enrolment of up to 20 subjects was planned to obtain a minimum of 15 evaluable subjects was planned. Twenty-eight subjects were enrolled, 23 were treated and analysed as FADS. Of these 2 were ineligible for inclusion. 21 fulfilled PADS

### *Statistical methods*

The proportion of treatment responders as defined (see outcome/endpoints) above and a 95% confidence interval for the proportion was given using the Wilson score method without continuity correction. For descriptive purposes, separate responder rates were calculated for subjects who did and who did not receive systemic corticosteroids at the time of study drug treatment.

Calculation of the secondary endpoints included: Determination of the median and 95% confidence interval for time to platelet response by the Kaplan-Meier technique; determination (in treatment responders) of the median and 95% non-parametric confidence interval for the duration of platelet response in days from the day the platelet count reached or exceeded  $50 \times 10^9/L$  to either the first day the platelet count fell to  $20 \times 10^9/L$  or less, or the last day with available platelet count data;

description of the maximum platelet count by medians, quartiles and their non-parametric 95% confidence intervals; estimation of the median and 90% confidence interval for time to cessation of any haemorrhage by the Kaplan-Meier method.

### *Outcomes and estimation*

#### *Primary endpoint*

The number of treatment responders was 17 of 23 patients (73.9%; 95% CI for proportion 53.5 to 87.5) in the ITT population, for the per protocol population 15 of the 21 PP patients (71.4%; 95% CI for proportion 50.0 to 86.2) were treatment responders.

The median platelet count for the ITT and PP population (including treatment responders and non-responders) was  $>50 \times 10^9/L$  by study Day 5 (median:  $85 \times 10^9/L$ , range 4 to 271, mean  $117 \times 10^9/L$ ). The median and mean platelet count was highest on Day 8, ( $99 \times 10^9/L$ , range 4 to 435, and  $151 \times 10^9/L$  respectively).

In the ITT population 52% (123/23) presented with a platelet increase to  $>100 \times 10^9/L$ , and 43% (10/23) with an increase above  $150 \times 10^9/L$ . Thirty-nine percent (9/23) reached a platelet count  $>200 \times 10^9/L$ .

Eight patients received systemic corticosteroids ( $<20\text{mg/d}$ , allowed per protocol) during the treatment and follow-up period. Among these, 7 (87.5%) were treatment responders according to the study protocol. Thirteen patients (PP) and 15 patients (ITT) did not receive systemic corticosteroids. One patient (300001) started with 500 mg of methylprednisolone during the study after a non-response.

#### *Secondary endpoints:*

##### **Time to response:**

After the first infusion, platelet response ( $>50 \times 10^9/L$ ) was achieved by Day 5 in  $>50\%$  of the patients, irrespective of the administration of booster doses. The proportion of platelet responders by Day 5 was 71.4% (95% CI 52.1 to 90.8) in the PP and 69.6% (95% CI 50.8 to 88.4) in the ITT population. By Day 15 85.7% (95% CI 70.7 to 100) and 87.0% (95% CI 73.2 to 100) in both analysis sets had achieved a platelet response.

##### **Duration of platelet response:**

The median duration of platelet response was 25 days for the treatment responders in both the PADS and the FADS (95% CI 21 to 28 and 22 to 28, respectively). It was defined as the duration from the day the platelet count reached or exceeded  $50 \times 10^9/L$  to either the first day when the platelet count fell to  $<20 \times 10^9/L$  or the last day with available platelet count data.).

##### **Maximum platelet count**

The highest median platelet count in treatment responders was  $182 \times 10^9/L$  (range 17 to  $435 \times 10^9/L$ ) in the PADS and the FADS. It was observed on Day 8. The median maximum platelet count on or after Day 5 prior to administration of a booster dose of study drug was  $122 \times 10^9/L$  (1<sup>st</sup> quartile  $59 \times 10^9/L$ , 3<sup>rd</sup> quartile  $268 \times 10^9/L$ ) in both the Per-Protocol and the Full Analysis Data Sets.

The median of the maximum platelet counts achieved after a booster given before Day 15 from onset of the initial study drug treatment course was  $30 \times 10^9/L$ . The median maximum platelet counts achieved after a booster given on or after Day 15 from onset of the initial study drug treatment course was  $81 \times 10^9/L$ .

##### **Regression of haemorrhage**

In the PADS, 5 subjects presented with a haemorrhage on Day 1, i.e. the day of onset of the initial study drug treatment course. The median time to regression of haemorrhage was 4 days (90% CI 0 to 4 days).

- Supportive study(ies)

### **Study 160101**

Study **160101** (US PID study), double-blind (patient and investigator were blinded to the sequence of administration for KIOVIG preparations produced by 3 different pathways), a multi-centre, uncontrolled study to evaluate efficacy and safety. This ongoing study is being conducted to fulfil the requirements of US FDA IND (Investigational New Drug). The minimum treatment period of 12 months has been completed.

All subjects were to receive 4 consecutive infusions of study product manufactured by each of the three pathways (1,3 and 6) for a minimum of 12 infusions.

Of the 61 subjects with PID enrolled and treated, none reported an acute serious bacterial infection. This was significantly less than the hypothesized rate of 1 infection per subject per year, in accordance with FDA blood product advisory committee recommendations. The 95% CIs for these mean rates were provided. The observed rate of acute serious bacterial infections was significantly less ( $p \ll 0.0001$ ) than the hypothesized rate (i.e. 1 per year) for both the intent-to-treat and per-protocol analysis populations.

A rate of zero (0) hospitalizations secondary to infectious complications was reported.

### **Clinical safety**

- Patient exposure

A total of 106 patients were exposed to the product, varying from a single administration to multiple courses over 12 months. The exposure is sufficient to make a proper safety evaluation of the product. As the studies were open and uncontrolled it is not possible to completely eliminate bias of investigator, in particular, and also the sponsor and the patient from influencing interpretation of the results and analysis. No independent (blinded) safety or data monitoring was carried out as part of the clinical trials. As mentioned above 3 studies were performed for the evaluation of clinical safety (PID 1600001 EU, PID 160101 US, ITP 1600002 EU).

- Adverse events

Headache was one of the most frequently reported drug-related AEs in all three studies. The other related AEs that were reported in all three studies were pyrexia, urticaria, and infusion site pain. Related AEs reported in two of the three studies were rash, pruritus, pain in extremity, back pain, flushing and nausea. Fatigue, migraine, and rigors occurred relatively frequently in study **160101**, and vomiting, dizziness, flu-like illness, diarrhea, and cough occurred in a few cases in that study.

In the PID Study 160101 the majority of all AEs were mild or moderate non-serious events. Sixty-one patients were treated with KIOVIG from 7 lots (3 lots pathway 1 and 2 lots each from pathways 3 and 6) and received a total of 826 infusions. The 3 pathway options revealed no significant differences in temporally and/or causally associated AEs.

In the ITP Study 160002 a total of 84 AEs were reported in 18 subjects (78.3%). Headache was the most frequent related AE (11 cases in 8 patients, 34.8% of patients), followed by pyrexia (7 cases in 7 subjects, 30.4%) and increase in body temperature (2 cases in 2 subjects, 8.7%). Hemorrhages starting after the first infusion occurred in 6/23 patients (26.1%).

- Serious adverse event/deaths/other significant events

In PID Study 160001 no product-related SAEs and deaths were reported.

In the PID Study 160101, sixteen SAEs in 8 subjects were reported. Two episodes of aseptic meningitis in one patient were judged to be possibly related to KIOVIG; aseptic meningitis was known to be present in this patient's community and is also known to occur infrequently in association with IGIV treatment. No deaths occurred during the study period. One subject withdrew due to an AE (pruritic papular rash).

In ITP Study 160002 one SAE was reported (a prolongation of hospitalization due to the observation of a haematoma in the right thigh).

- Laboratory findings

Plasma samples from the two studies conducted in Europe (study 160001 and 160002) were stored centrally for central testing for viral genome by PCR, should any concerns regarding viral safety arise.

In study 160101, viral safety was assessed by serological screening serologically for HBsAg and antibodies to HCV and HIV-1 and HIV-2 at baseline and prior to each infusion (including end-of-efficacy), and by PCR tests for HBV, HCV, and HIV-1 genomic sequences at baseline and end-of-efficacy.

None of the 61 enrolled subjects were positive at screening and none converted from negative to positive during the first 12 months of the study.

In six patients liver enzymes (AST, ALT and AP) increase was reported. One patient had a history of intermittent elevated liver enzymes. The other cases of liver enzyme evaluation could be attribute to concomitant disease or concomitant medications. The elevation of liver enzymes is a frequent observation in clinical studies with IVIG treatment, mainly due to the reasons outlined above. This finding is reflected in the SPC.

Intermittent occurrence of decreased lymphocyte count was observed in the some patients. Low lymphocyte counts are frequently described phenomena in patients with CVID and XLA.

- Safety in special populations

The exposure has predominantly been in Caucasians with equal representation of genders in the combined results. The safety evaluation would be applicable directly to adult Caucasians of both genders with PID and/or ITP, but indirectly to all patients with other applicable immune-deficiency diseases such as chronic lymphocytic leukaemia or immune-mediated diseases such as Guillain-Barre syndrome and Kawasaki disease, including children, as separate evaluation in these sub-groups is not currently required according to CHMP guidance notes.

Only 7 children under 12 were studied, making it difficult to evaluate the safety in the paediatric age group on the basis of evidence. However the experience gained IVIG treatment during several decades did not reveal any safety signal in this population.

- Safety related to drug-drug interactions and other interactions

#### Coombs' Test

In study 160001, a Coombs' test was performed at the baseline visit, before the first infusion of IVIG, 10% TVR Solution and at the last visit. Six results for direct Coombs' tests were positive in four subjects. In study 160002, a Coombs' test was performed prior to initiation of the treatment course (day 1) and on day 8. Three of 23 subjects were positive in the direct Coombs' test after initiation of the treatment course with the study drug. None of the patients in either study presented with signs of haemolysis.

- Discontinuation due to adverse events

One patient in the US study developed a pruritic papular rash on his neck, which did not resolve even with prophylactic use of hydroxyzine. This AE was considered possibly related. The patient completed 12 months of treatment but elected to withdraw from the optional post-efficacy period.

## **Pharmacovigilance**

### **Description of the Pharmacovigilance system**

The applicant provided a description of the pharmacovigilance system. The information provided did not address all points required in ICH guideline E2E (i.e. a detailed description of the information flow, including feed back, as well as detailed description of actions, is required).

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures>

### **Risk Management Plan**

As requested by Directive 2001/83/EC as amended and the above indicated draft 'Guideline on Risk Management Systems for Medicinal Products for Human Use', the respective risk assessments/evaluations for the potential of KIOVIG to transmit viruses or TSE agents was evaluated. The risk evaluations demonstrate that Baxter's plasma control measures and the KIOVIG manufacturing process provide for a very high margin of safety with respect to the transmission of infectious agents. The risk evaluation with regard to TSE agents has recently been revised to include the results of the TSE safety study provided in the response to Quality Question 4 above ('Prion Clearance during the Fractionation II + III part of the Manufacturing process of Immune Globulin Intravenous (Human) [IGIV], 10% Triple Virally Reduced (TVR) Solution (Reg652e)'), and is also provided below.

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.

## **5. Overall conclusions, benefit/risk assessment and recommendation**

### **Quality**

The quality of KIOVIG is considered satisfactory on the basis of the submitted data and the agreed follow-up measures.

### **Non-clinical pharmacology and toxicology**

A standard package of pharmacokinetic studies is inappropriate for this product (*Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals*, CPMP/ICH/302/95).

Data on the distribution, metabolism, excretion, and pharmacokinetic drug interactions in animals were not performed, which is acceptable for proteinous products like human immunoglobulins.

A comparison of the pharmacokinetics of KIOVIG and the comparator product in rats shows their elimination half-lives are similar.

The toxicological studies gave no indications for other negative effects as expected for the administration of foreign proteins to animals in high volumes. The questions of residual solvents resulting from the introduction of the virus inactivation step were sufficiently addressed and gave no reasons for concern from the preclinical experience. Due to the vast experience with immunoglobulin products, the proteinous nature of the product and the results of the submitted data, the limited programme to characterise KIOVIG is considered as acceptable.

### *Comparability exercise*

Three lots were used in the non-clinical studies. One lot was manufactured from cryo-poor plasma that was subjected to no adsorption (Option 1), one lot from cryo-poor plasma subjected to the FEIBA and Antithrombin-III adsorption steps (Option 3), and one lot from cryo-poor plasma subjected to Factor IX, Factor VII and Antithrombin adsorption steps (Option 6). These three options bracket the seven possible options that can be used to manufacture the product.

KIOVIG manufactured from cryo-poor plasma subjected to the three different options (1, 3 and 6) demonstrated comparable safety profiles with the reference product.

## **Efficacy**

Median values pharmacokinetic parameter (AUC<sub>0-21d</sub>, C<sub>max</sub>, C<sub>min</sub>, elimination half-life, incremental recovery (K), and In-vivo recovery (IVR)) were similar and the 95% CIs showed no larger deviations among the KIOVIG produced from pathway options 1, 3, and 6. Thus KIOVIG manufactured from cryo-poor plasma subjected to the three different options (1, 3 and 6) demonstrated comparable pharmacokinetic profiles with the reference product.

The correct patient population (primary immunodeficiency syndromes (PID), and patients with idiopathic thrombocytopenic purpura (ITP),) was included in the studies; the doses administered to the PID and ITP patients were adequate to maintain protective IgG trough levels and platelet counts respectively.

The results and analysis of the studies demonstrate that KIOVIG achieves the required minimum trough levels and pharmacokinetics parameters in PID patients. The clinical end-points of incidence of infections, antibiotic use and days off school/work are comparable to approved IVIg. The US study provides supportive evidence of efficacy as shown by the absence of serious bacterial infections.

The primary endpoint of the pivotal study for ITP defined as the number of treatment responders, (a platelet increase to  $\geq 50 \times 10^9/L$  before Day 15 and not requiring a booster dose prior to Day 15) was 74% in the ITT population and thus corresponds to relevant clinical treatment recommendations, where a response can be expected in ~75% of patients.

These results are comparable to that reported in literature and consistent with acceptable efficacy of the product in this indication.

Demonstration of efficacy in these two indications investigated in the clinical efficacy trials supports the claim for the other requested indications. This approach is in accordance with note for guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (CHMP CPMP/BPWG/388/95 rev. 1).

## **Safety**

No safety signals other than expected for intravenous immunoglobulins could be discerned from the submitted data; the adverse reactions to intravenous immunoglobulins are well known and have been described in the SPC.

## **Benefit/risk assessment**

### **Recommendation**

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

#### Replacement Therapy in

Primary Immunodeficiency Syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency

- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogammaglobulinemia and recurrent infections.

Children with congenital AIDS and recurrent infections.

#### Immunomodulation

- Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease

#### Allogeneic Bone Marrow Transplantation

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