27 February 2025
EMA/157144/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Deqsiga

International non-proprietary name: human normal immunoglobulin

Procedure No. EMEA/H/C/006423/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
AMS	Aseptic meningitis syndrome
ANX	Anion exchange chromatography
AR	Adverse Reaction
AUC	Area under the concentration versus time curve
B19V	Parvovirus B-19
BW	Body weight
CI	Confidence interval
Cl	Clearance
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
Cmax	Maximum concentration
Cmin	Minimum concentration
CVID	Common variable immunodeficiency
F	Bioavailability
FADS	Full analysis data set
FSDS	Full safety data set
GNDS	Guy's neurological disability scale
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IBD	international birth date
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgRT	Immunoglobulin replacement therapy
IGI, 10%/ IGIV, 10%	Immune Globulin Infusion (Human), 10% Solution (referred to Kiovig)
ITP	Idiopathic thrombocytopenic purpura
IUIS	International Union of Immunological Societies
IV	Intravenous(ly)
IVIg	human normal immunoglobulin product for intravenous administration
LPS	Lipopolysaccharide
medDRA	Medical Dictionary for Regulatory Activities
MMN	Multifocal motor neuropathy
NMT	not more than
PADS	Per-protocol analysis data set
PE	Plasma exchange
PET	Positron emission tomography
PID	Primary immunodeficiency
PK	Pharmacokinetic
PSAF	proven specific antibody failure
RSI	reference safety information
SADS	safety analysis data set
SAE	Serious adverse event
SCIg	human normal immunoglobulin product for subcutaneous administration
S/D	Solvent/detergent
SEM	Standard error of mean
SID	Secondary immunodeficiency
SOC	System order class
t1/2	Half-life
Tmax	Time to maximum concentration
TRALI	Transfusion-related acute lung injury

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Takeda Manufacturing Austria AG submitted on 8 March 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Deqsiga, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indications:

Replacement therapy in adults, and children and adolescents (0 to 18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, and children and adolescents (0 to 18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease (in conjunction with acetylsalicylic acid; see section 4.2).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

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

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).

This application is submitted as a multiple of Kiovig authorised on 19 January 2006 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 March 2021	EMA/SA/0000051712	Jens Reinhardt, Andrea Laslop

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Use of the proposed process validation and comparability approaches to demonstrate the similarity of Kiovig and TAK-880 manufacturing processes, the use of Kiovig virus clearance data to support TAK-880 virus clearance, the design of the stability study to support the qualification of the modified anion exchange chromatography step used in the manufacturing process
- Acceptability of a non-clinical package based on established Kiovig non-clinical data and further supplemented by in vitro and in vivo studies
- Use of the clinical efficacy and safety data available for Kiovig to support the marketing authorisation application (MAA).

1.6. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Eva Skovlund

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	8 March 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	14 June 2024
The CHMP Co-Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	28 June 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	18 June 2024
The PRAC agreed on the PRAC assessment overview and advice to	N/A

CHMP during the meeting on	
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	25 July 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	11 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	18 November 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	28 November 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	12 December 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	27 January 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	10 February 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Deqsiga on	27 February 2025
The CHMP adopted a report on similarity of Deqsiga with Strimvelis on	27 February 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Deqsiga is proposed to be used as replacement therapy in humoral immunodeficiency situations encountered in primary immunodeficiencies (PID) and a number of secondary immunodeficiencies (SID). It was also proposed to be used in immunomodulatory indications of primary immune thrombocytopenia (ITP), Guillain-Barré syndrome (GBS), Kawasaki's disease, multifocal motor neuropathy (MMN), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

2.1.2. Management

Many patients with primary and secondary antibody deficiencies require immunoglobulin replacement therapy – often a life-saving treatment – to protect against infections. Within this population, there is a rare subgroup of IgA-deficient patients who may not tolerate most immunoglobulin preparations (i.e., those containing higher levels of IgA) because they are IgA-sensitive.

While immunoglobulin replacement therapy is not indicated for isolated IgA deficiency, some patients have concomitant IgG (subclass) deficiency, autoimmune or inflammatory disorders requiring immunoglobulin therapy. In addition to infections, IgA-deficient patients are at increased risk for autoimmune diseases that might also require immunoglobulin treatment.

Anaphylactic reactions have been associated with IgA deficiency, although they rarely occur. Although the precise role of anti-IgA antibodies as a trigger of anaphylaxis in these patients has not been clearly established, historically there have been reports of the severity of reactions to IVIg being linked to IgA content of the product (Cunningham-Rundles et al., 1993, Hedderich et al., 1986).

It has been suggested that there may be a threshold phenomenon such that products containing less IgA are better tolerated (Rachid and Bonilla, 2012). Therefore, the IgA-sensitive patient population will better tolerate immunoglobulin products with a low IgA content. Alternatively, the SC route of administration has also been suggested (Bonilla, 2008, Quinti et al., 2008), however, human normal immunoglobulin product for subcutaneous administration (SCIg) might not be an option to all patients, as not every IgA sensitive patient may tolerate SCIg and/or wish to accept SCIg treatment e.g. due to the shorter treatment intervals often needed, which will require more frequent infusions.

To date Gammagard S/D is the IVIg with the lowest IgA content nationally approved in some EU member states (<3 µg/mL [5% solution]) thereby fulfilling that medical need for IgA-sensitive patients. Since its launch in the 1990s in the EU, Gammagard S/D has been used to treat patients in different indications who require a low IgA content.

2.2. About the product

Deqsiga (TAK-880) is a 10% human plasma derived immunoglobulin solution. Its development is based on Kiovig but differs regarding the IgA content.

Thus, TAK-880 (IVIg, 10%, Reduced IgA) is a 10% solution, with glycine as a stabiliser and a pH between 4.6 and 5.1 (selected to minimise aggregation, dimer formation and fragmentation). The 10%

solution contains less than or equal to 2 µg/mL IgA with the option to dilute to a 5% concentration and reduces the IgA concentration further to less than or equal to 1 µg/mL.

TAK-880 works by restoring abnormally low IgG levels to their normal range in the blood. At higher doses, it can help to adjust an abnormal immune system and modulate the immune response.

The applicant has applied the same indications for Deqsiga, as it is approved for Kiovig, as follows:

Replacement therapy in adults, children and adolescents (0 to 18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of < 4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, children and adolescents (0 to 18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease (in conjunction with acetylsalicylic acid; see section 4.2).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN)

The dose and dose regimen are dependent on the indication.

In comparison to Kiovig, changes are proposed in sections 4.3 and 4.4 of the SmPC of Deqsiga. As Deqsiga has a lower content in IgA, better tolerability in IgA-sensitive patients is expected, therefore only a warning regarding hypersensitivity and the IgA content of Deqsiga has been added in section 4.4.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as solution for infusion containing 100 mg/ml of human normal immunoglobulin (IV) as active substance.

Other ingredients are: glycine

The product is available in type I glass vials (50ml or 100ml) with a stopper (bromobutyl).

2.3.2. Active substance

2.3.2.1. General information

The active substance of Deqsiga (referred to as TAK-880 or IGI, 10% reduced immunoglobulin A (IgA) in the dossier and in this report) is human normal immunoglobulin solution for intravenous administration. Deqsiga and the already licensed product Kiovig are both 10% human normal immunoglobulin formulations for infusion with identical product specifications except for a reduced IgA content in Deqsiga. IgA content of Deqsiga, is ≤2 µg/ml in the final product compared to not more

than (NMT) 0.14 mg/ml in Kiovig. Notably, the IgG4 content is also lower in Deqsiga compared to Kiovig, being ≥ 0.4% and ≥ 1.7%, respectively. Deqsiga is presented as 5 g and 10 g vial only whereas Kiovig is presented as 0.5 g, 1 g, 5 g, 10 g, 20 g, 30 g.

2.3.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacturers of the active substance are Takeda Manufacturing Italia S.p.A., Rieti, Italy (from plasma pool until intermediate precipitate G) and Baxalta Belgium Manufacturing S.A., Lessines, Belgium (from precipitate G to the ultrafiltrate concentrate). Relevant GMP certificates and manufacturing authorisations are provided for the sites involved in manufacturing and testing.

The manufacturing process of IGI, 10% reduced IgA is very similar to IGI, 10% (authorised as active substance of Kiovig) except for the settings during anion exchange (ANX) chromatography. The process parameter settings during ANX chromatography were adapted to enhance IgA removal capability.

A distinct intermediate active substance stage does not occur due to the continuous manufacturing process; therefore, a fictitious active substance the "ultrafiltrate concentrate" was defined. The manufacturing process of the ultrafiltrate concentrate is divided into two process segments. In the first one, which takes place at Takeda Manufacturing Italia S.p.A., Rieti, Italy, an intermediate immunoglobulin G (IgG) fraction, referred to as "Precipitate G" is isolated from human plasma pools without additional adsorption and via a modified Cohn-Oncley cold alcohol fractionation method. In the second process segment, the "Precipitate G" is further purified continuously with solvent/detergent (S/D) treatment, cation exchange chromatography, anion exchange chromatography, nanofiltration and ultra/diafiltration against glycine buffer to the ultrafiltrate at Baxalta Belgium Manufacturing S.A., Lessines. The dedicated virus reduction steps are solvent/detergent (S/D) treatment, nanofiltration, and incubation at low pH/elevated temperature in the final formulation. Optional reprocessing is foreseen in Nanofiltration Step. In-process controls and their acceptance criteria routinely monitored during the manufacturing process are described and found acceptable.

The applicant provided a sequential procedural narrative of the manufacturing process of the active substance. No adsorption option will be used and only the manufacturing site Rieti is foreseen and was validated for the precipitate G intermediate used for the manufacturing of IGI, 10% reduced IgA.

In summary the process is sufficiently described, and the overall control strategy and the risk mitigation measures are adequate to control the process.

Control of materials

The starting material for manufacturing IGI, 10% reduced IgA is human plasma collected by plasmapheresis or obtained from whole blood donations. This is described in the Plasma Master File (certificate numbers EMEA/H/PMF/000003/04 as annually recertified), which is approved centrally. IGI, 10% reduced IgA does not contain or use any materials of animal origin in the manufacturing process. No heparin is used for manufacturing IGI, 10% reduced IgA as no adsorption steps are foreseen. The raw materials were listed with the corresponding reference to the relevant pharmacopoeia. Non-compendial raw materials including the tests and acceptance criteria were listed as well. Raw materials are accepted based upon the supplier certificate of analysis. This approach is acceptable.

Control of critical steps and intermediates

The applicant has defined as critical steps in the manufacture of IGI, 10% reduced IgA those associated with virus reduction. Details regarding the control and validation of critical steps are provided. The identified critical steps are justified.

Process validation

The applicant provided a process performance qualification (PPQ) at full scale for IGI, 10% reduced IgA. Nine process performance precipitate G lots were manufactured without adsorption of coagulation factors in Rieti. During the manufacture of all 9 precipitate G lots monitored process parameters conformed to the predefined acceptance criteria. All precipitate G intermediate characterisation results met the additional comparability evaluation acceptance criteria. Six of these investigated precipitate G lots were used to manufacture three full scale IGI 10%, reduced IgA finished product batches at the Lessines facility. Each conformance batch has been filled generating a sub-lot to support both fill sizes (50ml and 100ml). Batch sizes and parameter settings for the ANX step were challenged. During validation two batches were manufactured within the target of the optimal parameter settings for the ANX step (results of development studies for a low IgA content in the final product). One lot (with the upper batch size) was produced with borderline settings regarding the parameter of the ANX purification step. All process parameters (including CPPs) of the ultrafiltrate concentrate manufacturing process were monitored and conformed to the predefined PPQ acceptance criteria. The six conformance finished product batches met all the release specifications and predefined validation criteria.

The process validation data indicate that the upstream manufacturing process at Rieti with no adsorption consistently produces precipitate G that meets the present acceptance criteria and enriches antibodies as required. The downstream purification process from the stage of precipitate G until the concentrated ultrafiltrate was sufficiently validated. The batch analysis data and the additional characterisation on the finished product show that the finished product complies with predetermined specifications and quality characteristics. The validation revealed that the adaption of the process parameter of the ANX step led to a final product with reduced IgA values of NMT 2µg/ml but also to a reduction of the subclass IgG4.

Manufacturing process development

IGI, 10% reduced IgA is manufactured by the identical process as IGI, 10% (Kiovig) with the exception of the process parameter settings of the ANX step. Accordingly, the Manufacturing Process Development for IGI 10% (Kiovig) also applies for the IGI, 10% reduced IgA product. The critical parameters at the ANX chromatography step were identified. This was the basis for further specific development studies for the product IGI, 10% reduced IgA (NMT 2µg IgA/ mL). The settings during ANX step were investigated with DoE study and then followed by confirmation runs at laboratory scale. In summary the results of the development studies sufficiently support the set acceptance criteria for the in-process controls of the step ANX chromatography and the performance of this step to reach a content of NMT 2µg IgA/ mL at 10% protein in the IGI, 10% reduced IgA final container.

In the dossier, comparability is addressed at the level of precipitate G intermediate to be used in the manufacture of IGI 10%, reduced IgA as well as the level of finished product, and includes release testing, characterisation testing and stability testing. The different elements of the approach are divided up and use different historical comparisons. Prior to filing the MAA, the applicant received scientific advice from EMA and PEI on their comparability approach. The applicant has deviated somewhat from their presented approach (scientific advice procedure EMA/SA/0000051712) and the advice they received. Nevertheless, the discrepancies and deviations are considered minor and the presented comparability data overall is considered sufficient to support the approval of the duplicate MAA. In brief, the comparability exercise shows that in addition to lower IgA content, the differences

relative to IGI 10% finished product include lower IgG4 percentage and lower levels of impurities. The lower levels of impurities indicate an improved purity profile, and do not cause concern.

Characterisation and impurities

Three pre-clinical and three conformance lots were used in the characterisation studies for IGI 10%, reduced IgA. Full scale-Precipitate G lots supplied by Takeda Rieti were further manufactured to IGI 10%, reduced IgA product at Takeda Lessines. IgG subclass distribution, antibody spectrum, and Fc functions tests were performed. Mouse protection test and opsonisation to verify overall functional integrity of the antibody molecules were only performed with IGI 10% lots. The results demonstrate that the Fc and Fab portion are maintained intact in the purified polyclonal immunoglobulin G and the product retains the broad spectrum of antibody specificities. The subclass distribution is maintained except for the relative IgG4 percentage. The IgG4 level is at the lower end of the reported range for normal plasma in IGI 10%, reduced IgA and lower than for IGI 10%, but appears to have no effect on Fc functionality or antibody titres. The difference in relative IgG4 percentage is further justified in the clinical part of the dossier.

The potential impurities of the product IGI, 10%, reduced IgA are identified, and reference is also made to testing and measurement of impurities documented in study reports of IGI, 10%. Alcohol, octoxinol, tri-n-butyl phosphate TnBP, polysorbate 80, silicon and aluminium are defined as process related impurities. As product-related impurities prekallikrein activator activity, PL-1 amidolytic activity, anti-A / anti-B haemagglutinins, anti-D, IgA, IgM and procoagulant activities are defined. Product-related substances are albumin, fibrinogen and plasminogen. The reduced IgA conformance lots were also tested for residual levels of FXI, FXIa, TGA, prekallikrein activator and anticomplement activity. The results of the three validation batches of IGI, 10%, reduced IgA demonstrate sufficient reduction of process and product related impurities in the final product. A risk assessment on nitrosamines is provided.

2.3.2.3. Specification

A distinct intermediate active substance stage does not occur due to the continuous manufacturing process; therefore, a fictitious active substance the "ultrafiltrate concentrate" was defined. No control of this formal active substance stage is performed. All quality control tests are performed for IGI 10%, Reduced IgA final finished product.

The Ph. Eur. reference standard "Human immunoglobulin for electrophoresis BRP" or alternatively in-house reference standard qualified against primary standard is used.

2.3.2.4. Stability

Stability data from the active substance of IGI 10%, reduced IgA are not available because of the continuous manufacturing process. Stability data from the intermediates Fractions II+III and Precipitate G which can be stored are provided in Section 3.2.S.2.4 Controls of Critical Steps and Intermediates of the dossier. The data obtained for these intermediates support the intended storage period for these intermediates.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

IGI 10%, reduced IgA is a purified IgG liquid product formulated with glycine at 10% w/v protein concentration supplied in single-dose glass vials that nominally contain 5 g and 10 g protein per vial.

The finished product IGI 10%, reduced IgA is filled in Type I glass vials with nominal capacities of 50 ml (50ml x 20mm neck) and 100 ml (100ml x 32mm neck). The containers meet the requirements for Type I glass per the current European Pharmacopoeia (EP). The vials are closed with rubber stoppers (20mm and 32mm), coated with either omniflex or omniflex+ (inert, flexible fluorinated polymer) treatment. Both stoppers meet the chemical requirements of the current EP <3.2.9> „Rubber Closures for Containers for Aqueous Preparations for Parenteral Use".

The quality of the container/closure system is in compliance with compendial requirements and is considered acceptable. All possible organic extractables from the stoppers have a human daily exposure below the respective tolerable daily intake. Details for the packaging components are provided. The container closure integrity has been demonstrated. In the case of IGI 10% Solution, reduced IgA, overfill only ensures that a sufficient volume of the product is provided.

Extraction studies of the process components made of polymeric materials inclusive rubber stopper were performed. The toxicological risk assessment revealed negligible risk to patient safety.

The physicochemical and biological properties of IGI 10%, reduced IgA are described sufficiently. IGI, 10% Solution and IGI 10% Solution, reduced IgA share the same formulation and therefore formulation development data from IGI, 10% (Kiovig) solution are also applicable to IGI 10%, reduced IgA. The possibility to dilute IGI, 10% (Kiovig) for use was tested and is also applicable to IGI 10% reduced IgA. Tests revealed that IGI, 10% can be diluted with 5% glucose to a 5% protein solution without impairment of physicochemical and aseptic attributes of the medicinal product.

2.3.3.2. Manufacture of the product and process controls

The manufacturer of the finished product is Baxalta Belgium Manufacturing S.A., Lessines, Belgium. The manufacturing site is appropriately authorised and GMP compliant.

The finished product manufacturing process starts with the ultrafiltrate concentrate defined as active substance and includes formulation to 10.0 ± 0.1% w/v with diafiltration buffer, sterilizing filtration, aseptic filling and low pH incubation of the filled vials. A brief description of the manufacturing process of finished product including target limits was provided.

Three consecutive PPQ batches, were processed at manufacturing scale and have been produced at Takeda Lessines facility. Each PPQ batch has been filled in both fill sizes (50mL and 100mL). The three PPQ batches which were subsequently filled into six finished product lots met all validation criteria. All process parameter and in-process controls for the steps formulation, sterile filtration, aseptic filling, and incubation were validated and conformed to the acceptance criteria. The product quality attributes of all PPQ lots met the IGI, 10% Solution, Reduced IgA release specifications. The manufacturing process has been described in sufficient detail. The critical steps in the manufacturing process have been identified and are adequate. Acceptable process validation data are presented.

2.3.3.3. Product specification

The finished product specifications contain tests for: appearance (visual inspection, Ph. Eur.), anticomplement activity (haemolytic assay Ph. Eur.), anti A and anti B hemagglutinins (hemagglutination Ph. Eur.), anti-D antibodies (hemagglutination Ph. Eur.), glycine (Fourier transformed infrared spectrophotometry), HAV Antibodies (ELISA), HBsAg antibodies (ELISA), IgA (ELISA), molecular size distribution (IgG Content) (Size Exclusion High Performance Liquid Chromatography Ph. Eur.), Octoxynol 9 (ultra performance liquid chromatography (UPLC-MS)), osmolality (Osmometry Ph. Eur.), Parvo B19 Antibodies (ELISA), pH (potentiometry Ph. Eur.), PKA (Prekallikrein Activator Activity) (USP), polysorbate 80 (Ultra Performance Liquid Chromatography (UPLC-MS)), protein identity (Immunoelectrophoresis Ph. Eur.), purity (Capillary Zone Electrophoresis), bacterial endotoxins (Limulus Amoebocyte Lysate kinetic chromogenic test EP/USP), sterility (membrane filtration Ph. Eur.), total protein (Kjeldahl Method Ph. Eur. or UV method (USP)), and tri-(n-butyl) phosphate (Ultra-Performance Liquid Chromatography (UPLC-MS)).

The specifications set for IGI 10%, reduced IgA product are the same as for IGI, 10% (Kiovig) except the IgA specification. This specification is with "not more than or equal 2 µg/mL" explicit reduced compared to the amount of IgA in IGI 10% finished product specifications (≤ 140 µg/mL). The final product meets the pharmaceutical and analytical criteria of the relevant Ph. Eur. monograph 0918 on IVIG. The specifications for some of the parameters are even tighter than those required. Therefore, the finished product specifications are acceptable. Residual process related impurities TNBP, Polysorbate 80 and Octoxynol 9 are also included. The excipient used is glycine. The range represents common standards for IGIV and is therefore acceptable.

The analytical procedures suggested for the control of the finished product are in general adequate and follow the requirements of the relevant monograph of Ph. Eur. Information concerning critical reagents, reference materials, equipment and test validity criteria used and validated were included in the test summaries. Validation reports for the individual methods were provided. The analytical procedures for appearance, pH determination and osmolality testing are pharmacopeial methods and as such, no assay validations were performed. This is acceptable.

Three production conformance batches resulting in six IGI 10%, reduced IgA finished product batches from the process validation were presented in section batch analysis and their results confirm the set specifications and demonstrate batch-to-batch consistency. All impurities investigated were consistently reduced below detection limits or below specification limits. The control of elemental impurities is satisfactory.

The reference standards for the methods used are either international or commercially sourced. No in-house standard is listed.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

2.3.3.4. Stability of the product

The presented stability program is acceptable. Selected test-parameters and acceptance criteria are suitable to demonstrate product stability of 2 years when stored at or below 25°C. The product is not to be frozen, and it is to be kept in the outer carton in order to protect from light. Chemical and physical in use stability for the diluted product (dilution with a 5% glucose solution to a final concentration of 50 mg/mL (5%) immunoglobulin) has been demonstrated for 21 days at 2°C to 8°C as well as 28°C to 30°C.

This proposed shelf life for IGI 10% reduced IgA drug product is 2 years at room temperature. This is based on the available stability data for lots filled with 50ml and 100ml manufactured at the commercial scale. The provided data for 2-year storage at 5 ± 3°C (5°C) and at 25°C ± 2°C/60 ± 5% relative humidity (RH) (25°C) support the shelf-life of 2 years. All data are within acceptance criteria and there were no significant changes / trends of the stability parameter for the IGI 10% reduced IgA finished product when stored at +5°C and at +25°C. As expected at the accelerated storage condition (40 ± 2°C/75 ± 5% RH) out of limit (OOL) results for molecular size distribution were observed already after 1 month. The results of the performed stability investigations reflect the stability recommendations as indicated in the SmPC.

2.3.3.5. Adventitious agents

TSE Safety

Deqsiga (IGIV 10%, Low IgA) is manufactured from human plasma from U.S. and EU origin; donor selection reduces the risk of inclusion of plasma from donors at risk of TSE diseases. Reference to a valid plasma master file for the manufacturer, Takeda, is given. Reduction of prion protein for the Deqsiga manufacturing process (Fractionation to Filtration and nanofiltration) has been demonstrated by representative studies from the Kiovig process, using sensitive bioassays. No materials of animal origin are used during the manufacture of Deqsiga. The cleaning buffers for equipment with product contact are shown to be able for prion inactivation.

Virus safety

Deqsiga is manufactured from human plasma from U.S. and EU origin without addition of animal-derived substances conferring to a virus risk. Reference to a valid plasma master file for the manufacturer, Takeda, is given. 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 on viral nucleic acids. Four steps (fractionation to filtration, S/D treatment, Planova filtration, and 21 days incubation at low pH, 30°C) have been studied regarding their effectiveness in inactivating/removing viruses. Validation studies were performed according to Guideline CPMP/BWP/268/95. At least double runs have been performed for relevant model viruses used in the risk assessment. For West Nile virus as specific virus, only single runs have been performed for S/D treatment and low pH at elevated temperature. This is acceptable, because these data are considered supportive. Enveloped viruses are effectively inactivated and removed by the validated steps which results in a high safety margin of the product towards enveloped viruses. An exception is for BVDV at the alcohol fractionation step where only marginal virus reduction is observed. However, all other validated steps are also efficient for this virus. Alcohol fractionation and nanofiltration are also effective for removal of non-enveloped viruses such as HAV, B19 and HEV, even though the removal of HAV and B19 by nanofiltration largely depends on the presence of binding antibodies in plasma intermediate to these viruses. To ensure that virus-antibody complexes are efficiently removed at this step, a minimum concentration of HAV and B19V antibody content is specified for the final product. Removal of HEV by the nanofiltration step may also depend on the

presence of virus-specific antibodies within the plasma pool. Safety with respect to non-enveloped viruses where no specific antibodies are present (demonstrated for EMCV and MVM) is mainly dependent on the fractionation step, supported somewhat by the nanofiltration step, possibly due to binding effects on the pre-filter (depth filter). A risk assessment was provided for HIV, HCV, HBV, HAV, B19V and HEV and safety in the final dose with respect to these viruses has been demonstrated. Appropriateness and applicability of the several virus clearance studies, done for the Kiovig process, to the Deqsiga manufacturing process have been shown.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance of IGI 10%, reduced IgA is human polyvalent polyclonal immunoglobulin G (IgG) isolated from human blood. The manufacturing process of IGI, 10% reduced IgA (Deqsiga) is very similar to the approved IGI, 10% (Kiovig) from the same applicant except the settings during ANX chromatography. Due to the continuous manufacturing process; a fictitious active substance the "ultrafiltrate concentrate" was defined. The manufacturing process of the ultrafiltrate concentrate is divided into two process segments. In the first one, an intermediate immunoglobulin G (IgG) fraction is isolated from human plasma pools. In the second process segment, the "Precipitate G" is further continuously purified. The manufacturing of active substance and finished product of IGI, 10% reduced IgA (Deqsiga) is appropriately validated and controlled. The minor clarifications with regard to manufacturing process description, control of the step ANX column, raw material, consistency of data in the impurity section and process validation were adequately addressed.

IGI 10%, reduced IgA is a purified IgG liquid product formulated with glycine at 10% w/v protein concentration supplied in single-dose glass vials that nominally contain 5 g and 10 g protein per vial. The finished product process is sufficiently described. Critical process parameters were defined and adequate in-process controls were set. The batch analysis data and the additional characterisation on the finished product show that the finished product complies with predetermined specifications and quality characteristics. The validation revealed that the adaptation of the process parameter of the ANX step led to a final product with reduced IgA values of NMT 2µg/ml but also to a reduction of the subclass IgG4. The final product meets the pharmaceutical and analytical criteria of the relevant Ph. Eur. monograph 0918 on human immunoglobulins for intravenous administration. The specifications set for IGI 10% reduced IgA product are the same as for IGI, 10% (Kiovig) except the IgA specification. This specification is with "not more than or equal 2 µg/mL" explicit reduced compared to the amount of IgA in IGI 10% finished product specifications (⩽ 140 µg/mL). Sufficient stability data guarantee acceptable quality during the claimed shelf life. Minor issues with regard to standard batch size, manufacturing description, validation data of visual inspection and description of analytical procedures were adequately addressed.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Like Kiovig, TAK-880 is a 10% human plasma derived immunoglobulin solution with glycine as a stabiliser and a pH between 4.6 and 5.1. The main difference of TAK-880 versus Kiovig (IGI, 10%) is its low IgA content (not more than 2 µg/mL IgA). In addition, the characterisation revealed an immunoglobulin gamma 4 (IgG4) content at the lower end of the reported range for normal human plasma below the historical limit of 1.6% for Kiovig. The intended indications are identical to those for Kiovig, but for a small subset of IgA-deficient patients that would require treatment with IVIg product with a low IgA content.

Therefore, non-clinical data obtained with IGI, 10% in support of the original MAA for Kiovig in 2004 are also applicable to TAK-880.

In addition to the already available non-clinical data for Kiovig, the applicant performed in vivo safety pharmacology studies in guinea pigs and in hypertensive rats to specifically assess the safety of TAK-880 in comparison to Kiovig.

Induction of the immune response to therapeutic treatment can result in hypersensitivity reactions in patients, potentially leading to serious adverse events and thereby could pose a safety risk. Therefore, this risk for TAK-880 was specifically addressed *in vitro*. The potential of TAK-880 to stimulate immune cells and induce hypersensitivity reactions in comparison to Kiovig in healthy human whole blood was assessed by inflammatory cytokine and chemokine release assay, complement activation assay, and assessment of immune cell activation by flow cytometry.

To evaluate if the lower IgG4 level has an impact on efficacy in autoimmune diseases, efficacy of TAK-880 in comparison to Kiovig was evaluated in vivo using a mouse model of immune thrombocytopenia (ITP).

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

The primary pharmacodynamics of IGI, 10% (Kiovig) were assessed in one in vitro (opsonophagocytic activity) and one in vivo study in mice (the mouse protection test). These studies demonstrated efficacy for IGI, 10% that was comparable to GAMMAGARD S/D.

Efficacy of TAK-880 in comparison to Kiovig was evaluated in vivo using an animal model of autoimmune disease, the mouse model of ITP. Comparable dose-dependent efficacy of two TAK-880 PPQ lots were observed.

2.4.2.2. Secondary pharmacodynamic studies

The pharmacodynamics of solely IV administered IGI, 10% is generally well established as clinical pharmacodynamic data on IGI, 10% are available from the long-term use.

2.4.2.3. Safety pharmacology programme

The safety of TAK-880 was specifically addressed in two GLP compliant in vivo studies investigating the anaphylactoid and hypersensitivity potential. Both in vivo models (hypotensive effect in rats and bronchospastic activity in guinea pigs) revealed no increase in anaphylactoid potential through three different lots of TAK-880.

The anaphylactoid and hypersensitivity potential was already investigated with IGI, 10% (Kiovig) and Gammagard S/D in these two in-vivo models. Kiovig was also tested in anaesthetised beagle dogs and the effects on the cardiovascular, the respiratory and the coagulation system were assessed during a 3-hour observation period. Furthermore, the thrombogenic potential of IGI, 10% (Kiovig) was tested in anaesthetised rabbits after IV injection using a semiquantitative method according to the Wessler test. The supportive data of the four different GLP-compliant safety pharmacology studies with Kiovig did not indicate significant and relevant occurrence of anaphylactic reactions, no major influences on the respiratory, or development of disseminated intravascular coagulation for the compared preparations.

2.4.2.4. Pharmacodynamic drug interactions

Not required.

2.4.3. Pharmacokinetics

The pharmacokinetics of solely IV administered IGI, 10% is well established.

One GLP-compliant pharmacokinetic study was conducted comparing one lot of Kiovig and with one lot of Gammagard S/D in rats after i.v. administration of 1000 mg/kg. There was no significant difference between the products and lots tested, in vivo recovery varied between 70 and 80 %, and the half-life between 136 and 166 hours.

No distribution, metabolism and excretion studies have been conducted with IGI, 10%, or IGI, 10% reduced IgA (TAK-880).

2.4.4. Toxicology

2.4.4.1. Single dose toxicity

Acute toxicity was investigated in mice and rats using the intravenous route for Kiovig in comparison with Gammagard S/D and formulation buffer after i.v. administration of high volumes (25-100ml/kg). The acute toxicity of intravenous Kiovig was less than that of the reference product Gammagard in mice and rats. No Observed Adverse Effect Level (NOAEL) in mice was 5,000 mg/kg for IGI, 10% but 2,500 mg/kg for GAMMAGARD S/D. An additional study in rats with doses of 2000 mg/kg and volumes of 20ml/kg gave no indications of toxicity. The NOAEL was 2,000 mg/kg for IGI, 10% but below 2,000 mg/kg for GAMMAGARD S/D in rats received a single dose of 2,000 mg/kg by the IV route.

No single-dose toxicity studies were performed with TAK-880.

2.4.4.2. Repeat dose toxicity

The high immunogenicity of repeated administered human Ig in non-human primates and other animal species omits the performance of those repeat-dose toxicity studies in animals. Repeated dose toxicity studies were not performed.

2.4.4.3. Genotoxicity

Although genotoxicity studies are not required for such products as per ICH S6 (R1), one lot of Kiovig was tested for mutagenicity in an Ames test and found to be negative.

2.4.4.4. Carcinogenicity

Carcinogenicity studies were not performed. This is in accordance with ICH Guideline S6 (R1), which states that "standard carcinogenicity bioassays are generally inappropriate for biological/biotechnology-derived pharmaceuticals."

2.4.4.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were conducted with either Kiovig or TAK-880. It is known that immunoglobulin products cross the placenta, increasingly during the third trimester. However, clinical experience with immunoglobulins suggests that no harmful effects are to be expected. In addition, no adverse effects on fertility have been described so far.

2.4.4.6. Toxicokinetic data

Not required.

2.4.4.7. Local Tolerance

Local tolerance of IGI, 10% was investigated in rabbits. Kiovig, Gammagard S/D, Gamimune N (10%) or formulation buffer were administered intra-arterially, paravenously or intravenously into the right ear, with saline administered via the left as a negative control. 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. Kiovig showed similar local tolerance to currently available products.

No specific local tolerance studies were performed with TAK-880. This is acceptable as IGI, 10% (Kiovig) and TAK880 share the same formulation.

2.4.4.8. Other toxicity studies

Three in vitro studies using blood samples from eight healthy donors, investigated the induction of cytokines/chemokines, the activation of immune cells, complement or basophil granulocytes. TAK-880 (low-IgA, low IgG4) was compared to 10% IVIg product Kiovig (well-established safety profile). Samples were analysed for release of cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFNγ and TNFα), chemokines (MIP-1α, MIP-1 β, IP-10 and MCP-1) and for immune cell activation (expression of CD25 and CD69). The results obtained from all eight blood donors and under both non-stimulatory and stimulatory conditions indicate that there was no difference between TAK-880 and IG 10% (Kiovig) in their ability to induce dose dependent immune cell activation or the secretion of cytokines/chemokines. In all donors, an in vitro activation of complement (C5a activation assay) compared to the negative control was observed. The increase of C5a induced by TAK-880 was comparable to the marketed Kiovig product. Also, the ability to activate basophils in a human in vitro activation assay using fresh human whole blood of TAK-880 was comparable to IGI, 10% (Kiovig).

In summary, the potential of TAK-880 to activate the complement system, basophils, immune cells or secretion of cytokines/chemokines is in a comparable range to the marketed 10% IVIg product Kiovig.

2.4.5. Ecotoxicity/environmental risk assessment

Human normal immunoglobulin is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, human normal immunoglobulin is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

TAK-880 has been developed based on human normal Immunoglobulin (IV), IGI, 10%, and will be used for the same indications as Kiovig. The main difference of TAK-880 versus Kiovig is the low IgA content (not more than 2 µg/mL IgA), similar to IgA levels in GAMMAGARD S/D. The additional characterisation revealed TAK-880 contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents but also an immunoglobulin gamma 4 (IgG4) content at the lower end of the reported range for normal human plasma and below the historical limit of 1.6% for Kiovig. Therefore, non-clinical data obtained with Kiovig are also applicable to TAK-880. The non-clinical data package is in line with what was outlined in the advices received from CHMP.

In vitro and in vivo nonclinical studies of antibody function of IG, 10% were performed in support of the original MAA for Kiovig in 2004 (spectrum of antibodies against bacteria and viruses, evaluation of opsonophagocytosis effects and the in vivo mouse protection test). The safety pharmacology of IGI, 10% (Kiovig) was assessed in four GLP-compliant nonclinical studies addressing the risk of IGI, 10% causing anaphylactoid or thrombogenic reactions in humans. These studies demonstrated efficacy and safety profiles for IGI, 10% that were comparable to two marketed IV immunoglobulin products (GAMMAGARD S/D and GAMIMUNE N, 10%) used as controls. The pharmacodynamics of solely IV administered IGI, 10% is generally well established.

Therefore, the limited programme to determine the pharmacological and toxicological characteristics of TAK-880 is acceptable to the CHMP.

An in vivo PD study was conducted to compare the effect of TAK-880 and Kiovig on platelet numbers in a mouse model of ITP. ITP is a translatable model of immune complex-mediated autoimmune disease with clear endpoint that has been routinely employed for development of immunomodulatory treatments leveraging on modulation of Fc gamma receptor and complement pathways. Prior studies have consistently demonstrated dose-dependent efficacy of immunoglobulins in the mouse model of ITP (Leontyev et al., 2012). Comparable dose-dependent efficacy of two TAK-880 PPQ lots were observed indicating that the lower IgG4 levels in TAK-880 compared to Kiovig do not influence efficacy.

The pharmacokinetics of solely IV administered IG 10% is well established. Results from one PK study were presented comparing one lot of Kiovig with one lot of Gammagard S/D in rats after i.v. administration of 1000 mg/kg. However, data derived from rodents differ significantly from human kinetics and are therefore not predictive. Human clinical studies revealed that the median half-life of the IG was ~36 days after IV administration. The CHMP agreed that no PK studies for TAK-880 are needed.

Data on the Distribution, Metabolism, Excretion, and Pharmacokinetic Drug Interactions in animals were not performed, this is in accordance with ICH Guideline S6 (R1) - Preclinical Safety Evaluation of Biotechnology – Derived Pharmaceuticals (EMA/CHMP/ICH/731268/1998). The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids.

Acute toxicity studies were performed in mice and rats using IGI, 10% (Kiovig) in comparison with GAMMAGARD S/D. The acute toxicity studies demonstrated no clinical findings or histopathological changes related to treatment with IGI, 10%. The NOAEL for mice and rats was 5,000 mg/kg and 2,000

mg/kg, respectively. No single-dose toxicity studies were performed with TAK-880. The toxicity data generated with IGI, 10% are considered also valid for TAK-880 as TAK- 880 maintains the same product characteristics as Kiovig except for IgA content and IgG4 content.

Repeated dose toxicity studies, carcinogenicity studies and reproductive and developmental toxicity studies were not performed, which is considered as acceptable due the proteinaceous nature of the test article. Repeated dosing would lead to induction of and interference by developing antibodies in animals. Although genotoxicity studies are not required, one lot of Kiovig was tested for mutagenicity in an Ames test and found to be negative.

Local tolerance of IG 10% (Kiovig) was investigated in rabbits and showed similar local tolerance to currently available products. No local tolerance studies were performed with TAK-880. This is acceptable to the CHMP as IG 10% (Kiovig) and TAK-880 share the same formulation.

Overall, the toxicity program for the development of TAK-880 is sufficient. Since TAK880 does not differ from IGI, 10% (with the exception of IgA and IgG4) the toxicity data generated with IGI, 10% are applicable for TAK-880.

To evaluate the potential for hypersensitivity reactions, 3 studies were specifically performed with TAK-880 to investigate the immune response to the product. In the three in vitro studies using blood samples from eight healthy donors, the induction of cytokines/chemokines, the activation of immune cells, complement or basophil granulocytes were measured. TAK-880 (low-IgA, low IgG4) was compared to 10% IVIg product Kiovig (well-established safety profile). There was no difference between TAK-880 and IG 10% (Kiovig) in their ability to induce dose dependent immune cell activation (expression of CD25 and CD69) or the secretion of cytokines/chemokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IFNγ and TNFα/MIP-1α, MIP-1 β, IP-10 and MCP-1). The increase of C5a induced by TAK-880 and the activation of basophils were comparable to the marketed Kiovig product. In summary, the potential of TAK-880 to activate the complement system, basophils, immune cells or secretion of cytokines/chemokines is in a comparable range to the marketed 10% IVIg product Kiovig. The differences in relative IgG4 concentrations between TAK-880 and Kiovig did not result in differences in immune system stimulation.

Studies on potential impurities were not performed as impurities are also identical to the marketed product Kiovig.

The formulation of TAK-880 (IGI 10%, reduced IgA) is identical to IGI, 10% (Kiovig). The product is formulated using the excipient glycine. The range of glycine represents common standards for IGIV and is therefore safe.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, human normal immunoglobulin is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

Deqsiga, IGI, 10% reduced immunoglobulin A (TAK-880), has been developed based on human normal Immunoglobulin (IV), IGI, 10%, and will be used for the same indications as Kiovig. Since TAK-880 does not differ from IGI, 10% (with the exception of IgA and IgG4), the non-clinical data generated with Kiovig are also applicable for TAK-880. These studies demonstrated efficacy and acceptable safety profile for IGI, 10%.

The pharmacological data package is in line with the demands of the ICH Guideline S6 R1 and considered acceptable to support the MA of TAK-880. The main difference of TAK-880 versus Kiovig is

the low IgA content (not more than 2 µg/mL IgA) and a lower immunoglobulin gamma 4 (IgG4) content. However, it is not expected that this will influence the efficacy or safety of the product.

The provided non-clinical data package is considered sufficient for the approval of Deqsiga, IGI, 10% reduced immunoglobulin A (TAK-880).

2.5. Clinical aspects

Due to the comparability of TAK-880 and Kiovig (identical source material and excipient, identical manufacturing process steps except for adjustments of a single manufacturing step; identical drug product specifications except for IgA and additional characterisation revealing IgG4 content) supported by additional in vivo nonclinical safety data, extensive biochemical characterisation and comprehensive comparability approach, the applicant considers that the clinical safety and efficacy of TAK-880 is adequately supported by the already available clinical data for Kiovig. Accordingly, no additional clinical studies were considered necessary to support the marketing authorisation application (MAA) for TAK-880.

Table 1. IgG subclass and IgA distribution in IVIg products (% and µg/mL)

	Kiovig*	**Deqsiga****	**Gammagard S/D*****
IgG1, %	51.6–67.4	57.6–64.6	≥56.9
IgG2, %	24.2–41.9	31.1–37.8	≥16.0
IgG3, %	2.2–8.3	3.5–4.2	≥3.3
IgG4, %	1.6–3.7	0.4–0.7	≥0.3
IgA, µg/mL (IVIg %)	≤ 140 (10%)	≤2 (10 %)	<3 (5%)

Abbreviation: IgG, immunoglobulin G; IVIg, intravenous immunoglobulin.
*Source of Kiovig data provided from historical reference ranges.
**Source of Deqsiga data provided from TAK-880 conformance lots.
***Gammagard data taken from the corresponding approved EU product information (approximate values).

For the related product Kiovig (IVIg 10%) clinical data from 5 studies are available: 2 studies in subjects with PID [studies 160101 - (Church et al., 2006) and Study 160001 (Björkander et al., 2006), conducted in the EU], one study in subjects with ITP [Study 160002 (Varga et al., 2006), in the EU], one study in subjects with MMN [Study 160604 (Hahn et al., 2012) in the US, Canada and EU] and one study in subjects with Alzheimer's Disease [Study 160701 in the US and Canada (Gelmont et al., 2016)].

2.5.1. Introduction

GCP aspects

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.

- **Tabular overview of clinical studies**

Study ID	Enrolment status	Design Control type	Study treatment	Study population	Gender M/F

	# Subjects by Arm Entered/ Completed				Age Range
160001	Completed 24 enrolled/ 22 treated and analysed	Open-label, uncontrolled	IVIg, 10% / GAMMAGARD S/D	subjects with primary immunodeficiency (PID) disorders	14 M /8 F 26-70 years
160002	Completed 28 enrolled/ 23 treated and analysed	Open-label, uncontrolled	IVIg, 10%	subjects with chronic idiopathic thrombocytopenic purpura (ITP)	13 M / 10 F 18-68 years (median: 49)
160101	Completed 61 enrolled and treated	Double-blind, uncontrolled	IVIg, 10%	subjects with primary immunodeficiency (PID) disorders	28 M / 33 F 6-72 years (median 34)
160604	Completed 44 in safety and ITT datasets; 37 in efficacy dataset	Double-blind, Placebo-controlled	IVIg, 10%; Placebo	subjects with multifocal motor neuropathy (MMN)	32 M / 12 F 31-72 years (median 52);
160701	Completed 702 enrolled/ 390 treated and analysed	Double-blind, Placebo-controlled	IVIg, 10% (200mg/mL or 400mg/mL); Placebo	subjects with mild to moderate Alzheimer's Disease (AD)	177 M / 213 F 50-89 years (median 71)

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Pooled analyses of results across PID studies

Pharmacokinetic parameters for total IgG were summarised over the US and European studies of IVIg 10% administered IV in subjects with PID (clinical studies 160101 and 160001). All subjects who fulfilled the criteria for inclusion in the pharmacokinetic analysis data set were included in the analyses across studies, i.e., 57 in Study 160101 and 22 in Study 160001.

To compare AUC of Studies 160101 and 160001, the intervals of the study product infusions administered prior to the pharmacokinetic infusion were adjusted to either 21 or 28 days for Study 160101. In Study 160001 the interval per protocol was 21 days. AUC was then intra/extrapolated to 21 or 28 days and standardised by dose. Also C_{max} and C_{min} were standardised by dose to be comparable between clinical studies 160101 and 160001. Steady state total IgG trough levels of the 2 PID studies were compared and summarised across studies. Steady state trough levels per subject were estimated as the geometric mean of the subject's last 2 measurements available in the study.

Trough levels were summarised by median over all infusions per subject to calculate the median and a 95% CI over the set of evaluable subjects. The number of subjects included in the analysis of trough levels was 22 in Study 160001 and 61 in Study 160101.

Pharmacokinetic data from clinical studies 160101 and 160001 are comparable with the exception of in-vivo recovery and incremental recovery which are slightly lower in Study 160001 (**Table 2**).

Table 2. Summary of pharmacokinetic parameters (FADS)

Parameter	Unit	Study	N	Median	95% CI for median
C_{max}	(mg/dL)/(mg/kg)	160001	22	4.02	3.60 to 4.57
		160101	57	4.54	4.23 to 4.85
		Pooled	79	4.47	4.08 to 4.78
C_{min}	(mg/dL)/(mg/kg)	160001	22	2.21	1.80 to 2.55
		160101	57	2.26	2.04 to 2.50
		Pooled	79	2.25	2.11 to 2.43
In-vivo recovery	%	160001	22	89	84 to 101
		160101	57	112	104 to 121
		Pooled	79	104	98 to 114
Incremental recovery	(mg/dL)/(mg/kg)	160001	22	1.85	1.71 to 2.14
		160101	57	2.32	2.17 to 2.60
		Pooled	79	2.17	2.05 to 2.36
AUC $_{0\text{-}21/28}$	(g/dL.h)/(mg/kg)	160001	22	1.42	1.20 to 1.64
		160101	57	1.77	1.59 to 1.88
		Pooled	79	1.60	1.51 to 1.77
Half-life	Days	160001	22	30.1	27.1 to 43.3
		160101	57	35.5	31.4 to 41.6
		Pooled	79	32.5	30.8 to 37.6

Median total steady state IgG trough levels after administration of IGIV, 10% were 851 mg/dL (95% CI 756 to 1006) in Study 160001 (N = 22) and 1105 mg/dL (95% CI 1021 to 1145) in Study 160101 (N = 83). The median total IgG trough level determined for the 2 studies taken together was 1021 mg/dL (95% CI 912 to 1105). Total IgG trough levels were above 6 g/L (600 mg/dL) as defined in the relevant Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg), EMA/CHMP/BPWP/94038/2007 Rev. 6. Median trough levels were slightly higher in Study 160101 which may be due to the slightly higher doses administered per infusion. The mean total weight adjusted dose per infusion was 0.41 g/kg in Study 160001 while in Study 160101 it was 0.471 g/kg.

Comparison of the pharmacokinetics between subgroups treated at intervals of 3 and 4 weeks shows higher values for C_{max}, in vivo recovery, incremental recovery, $AUC_{0\text{-}21/28}$, and $t_{1/2}$ in the subgroup with a treatment interval of 4 weeks.

MMN Study 160604

In study 160604 (N=44) in MMN patients, the median serum trough level of total IgG over all study parts in which subjects received IGI, 10%, regardless of dosing intervals and length of infusion cycles, was 16.40 g/L (95% CI 15.70; 17.10). The relationship between serum IgG concentration and efficacy was not assessed.

Absorption

See SmPC section 5.2: *Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.*

Distribution

See SmPC section 5.2: *It is distributed relatively rapidly between plasma and extravascular fluid; after approximately 3 to 5 days equilibrium is reached between the intra- and extravascular compartments.*

Elimination

See SmPC section 5.2 Pharmacokinetic properties: *IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.*

Dose proportionality and time dependencies

Not applicable.

Special populations

There are only limited data for Kiovig in paediatric patients with PID from Study 160101 (children (≤12 years; n=5) and adolescents (13 to 17 years; n=10)). IgG trough levels were well above the level of at least 600 mg/dL. Other PK parameters were similar to those in adults, with the exception of a longer median half-life (41.3 days for children, 45.1 days for adolescents, 31.6 days for adults (N = 64 (pooled study 160001 and 160101)).

Pharmacokinetic interaction studies

Not applicable.

Pharmacokinetics using human biomaterials

Not applicable.

2.5.2.2. Pharmacodynamics

Mechanism of action

TAK-880 works by restoring abnormally low IgG levels to their normal range in the blood. At higher doses, it can help to adjust an abnormal immune system and modulate the immune response.

Primary and Secondary pharmacology

Biological activity was assessed in non-clinical studies with Kiovig. Functional integrity of the antibody molecules in Kiovig was determined by Fc receptor functions tests and opsonophagocytosis assay. The neutralizing capacity of Kiovig was tested in vivo in mice challenged with Gram-negative and Gram-positive bacteria (*Streptococcus pneumoniae* and *Klebsiella pneumoniae*).

Furthermore, efficacy of TAK-880 in comparison to Kiovig was evaluated in an in vivo study using a mouse model of ITP. ITP is a translatable model of immune complex-mediated autoimmune disease with clear endpoint that has been routinely employed for development of immunomodulatory treatments leveraging on modulation of Fc gamma receptor and complement pathways. Prior studies have consistently demonstrated dose-dependent efficacy of immunoglobulins in the mouse model of ITP (Leontyev et al., 2012). The results of the ITP study demonstrated comparable efficacy of TAK-880 to Kiovig, despite lower IgG4 content in TAK-880.

2.5.2.3. Summary of the applicant justification regarding IgG4 content

The IgA content in TAK-880 is comparable to Gammagard S/D, the only marketed product with IgA content equal to or lower than 3 µg/mL. The safety and efficacy of TAK-880 are based on the evidence generated for Kiovig.

Regarding the potential concern about a possible impact of the lower IgG4 content on the efficacy/safety of TAK-880, key aspects of the applicant's perspectives are summarised below:

a. In healthy individuals, IgG4 is the least abundant of IgG subclasses with the widest range in concentration (0.03-5.39 g/L (French and Harrison, 1984), 0.004-2.68 g/L (Rasmussen et al., 2021), 0.05-1.54 g/L (Li et al., 2017) and 0.0-1.55 g/L (Harkness et al., 2020)). At clinical doses, TAK-880 restores total IgG levels and that of IgG4 within normal range (0.05-0.08 g/L with 0.4 g/kg dose, 0.24-0.42 g/L with 2 g/kg dose).

b. The International Union of Immunological Societies (IUIS) consensus guideline does not recommend IgG-replacement therapy in selective IgG4-deficiency provided vaccine response is normal (measured as total immunoglobulin titres in response to vaccination and not individual IgG subclass). Additionally, there is no documented evidence of increased risk of inflammation in selective IgG4-deficient individuals.

c. Under physiological conditions, the qualitative differences of IgG subclasses are defined based on their affinity and immune effector functions. In the context of an immune response to a specific antigen/allergen, IgG4 sub-class levels increase only upon long-term exposure and generate tolerance inducing conditions to a specific stimulus. In contrast, immunoglobulin products are composite of tens of thousands of individual plasma donations from healthy donors. In line, various marketed products with varying levels of IgG subclasses, including that of IgG4, have proven to be safe and efficacious.

d. The proposed mechanism of immunomodulation of Ig therapies given at supraphysiological levels is based on interaction with cognate receptors/ligands to dampen effector functions. IgG4 has the lowest affinity towards prominent immune effector receptors. Even when administered at supraphysiological concentrations, IgG4 still represents the lowest concentration relative to all other IgG subclasses in circulation and thereby its role can only be secondary. This further substantiates the observed clinical efficacy dependent on Ig dose and independent of minor analytical differences in the IgG subclass distribution in various immunoglobulin products.

e. The TAK-880-specific studies using whole blood assays demonstrated that there was no difference between TAK-880 and Kiovig in their hypersensitivity potential. These studies were performed under both resting, immune stimulatory conditions and measured for their ability to induce immune cell activation or the secretion of cytokines/chemokines. The data demonstrated that there is no increased safety risk associated with the effects of TAK-880 in circulation compared to Kiovig. Additionally, reduced levels of IgG4 did not alter various inflammatory cytokine release measured under all conditions evaluated.

f. The efficacy of TAK-880 in an autoimmune disease model of ITP is comparable to that of Kiovig.

The non-clinical efficacy/safety package is therefore considered to adequately address TAK-880 efficacy/safety in all indications requested.

2.5.3. Discussion on clinical pharmacology

Like Kiovig, its duplicate TAK-880 is a 10% solution, with glycine as a stabiliser and a pH between 4.6 and 5.1 (selected to minimise aggregation, dimer formation and fragmentation). TAK-880 has lower IgA and IgG4 contents.

The applicant has not performed PK studies with Deqsiga, but submitted PK data on Kiovig in patients with PID. The PK of Kiovig is supported by two PK studies in patients with PID (studies 160001 and 160101). Dosing and dosing intervals slightly differed between studies, however, both studies fulfilled the regulatory requirements of the relevant guideline at the time they were assessed (CPMP/BPWG/388/95 rev 1). Overall, the data are well presented and the PK results for Kiovig obtained in the PID studies are in line with those reported in the literature and in other studies with similar products. The median trough total IgG levels for the two studies combined is 1021 mg/dL (95% CI 912 to 1105), which is well above the recommended 6 g/L to protect from serious bacterial infections and as defined in the relevant guideline on core SmPC for human normal immunoglobulin for IVIg (EMA/CHMP/BPWP/94038/2007 Rev. 6).

Only limited data are available for paediatric patients with PID from Study 160101 (children (≤12 years; n=5) and adolescents (13 to 17 years; n=10)). However, no differences in PK between paediatric and adult patients are expected based on the data available and based on real-world knowledge of IVIg treatment in paediatric patients.

Serum IgG trough levels were also assessed in adult MMN patients (study 160604).

Overall, the PK profile of Kiovig is consistent with that of other marketed IVIg. The PK of Kiovig is expected to be the same for Deqsiga in the proposed indications.

Applicant justification regarding IgG4 content

A potential concern with regard to the comparability of Deqsiga and Kiovig is the IgG4 levels below the historical limit of 1.6% for Kiovig. Therefore, following the scientific advice, the applicant has provided a detailed discussion of the impact of the low IgG4 content of TAK-880 on PK, efficacy and safety. The justification includes an overview of the physiological immune functions of IgG4, physiological IgG4 levels in healthy individuals, IgG4 deficiency and IgG4 associated diseases. Furthermore, calculations have been provided on the expected IgG serum concentrations after TAK-880/Kiovig dosing.

To summarise, IgG4 can be dominant in responses to allergens, therapeutic proteins, autoantigens and parasite and often requires repeated or prolonged exposure to develop. In contrast to the other three IgG subclasses, IgG4 has only a low affinity to effector molecules such as Fc receptors and complement and has therefore only a low capacity to trigger effector mechanisms. Thus, IgG4 is often considered to be part of classical tolerance mechanisms by inducing tolerance and limiting inflammation. IgG4 levels are the least abundant IgG subclass in human plasma with the highest inter-individual variability, ranging from 0.03-5.39 g/L (French and Harrison, 1984), 0.004-2.68 g/L (Rasmussen et al., 2021), 0.05-1.54 g/L (Li et al., 2017) and 0.0-1.55 g/L (Harkness et al., 2020) in healthy individuals. No significant gender differences in IgG4 levels have been reported in the literature. Intra-individual levels are generally stable, yet children have lower IgG4 levels than adults. Isolated IgG4 deficiency is usually not clinically relevant and does not require treatment. In other cases, IgG4 deficiency occurs in combination with a deficiency of other antibody subclasses, e.g. IgG2, IgA or IgG1, which may require treatment. IgG4 levels above 1.35 g/L are currently accepted as a threshold for diagnosing IgG4-related diseases or IgG4 autoimmune diseases (IgG4-RD or IgG4-AID), however, around 5% of individuals have high levels without any clinical consequence.

As demonstrated by the applicant, the IgG4 levels are comparable between TAK-880 (0.4–0.7%, 0.05-0.08 g/L in plasma) and Gammagard S/D. The normal subclasses distribution in TAK-880 is also maintained (IgG1>IgG2>IgG3>IgG4). Despite the slightly different Ig and product compositions, all IVIg products are efficacious, as efficacy is typically dependent on the dose administered. Based on the calculations provided, doses of TAK-880 (0.05-0.08 g/L) approved for the treatment of immune deficiency syndromes and autoimmune diseases (0.4 g/kg to 2 g/kg) are expected to restore IgG4

levels to the physiological range. Furthermore, given the low affinity for immune effector receptors and the fact that TAK-880 is composed of thousands of individual plasma donations from healthy donors, making the presence of significant levels of stimulus-specific IgG4 antibodies highly improbable, lower IgG4 levels are not expected to affect efficacy in autoimmune diseases. The applicant claims that IgG4 subclass immunoglobulins are 'irrelevant' in the context of immunomodulatory effects from IVIg treatment. However, there is some, yet limited, evidence of IgG4-deficient patients with inflammation who benefitted from IVIg. Not all properties of IgG4 in IVIg are fully recognised.

Non-clinical studies with TAK-880 and Kiovig also show no differences in their hypersensitivity potential and cytokine production. In an in vivo autoimmune model of ITP, TAK-880 was comparable or even slightly more effective than Kiovig in restoring platelet counts.

Overall, the applicant's justification is endorsed by the CHMP, the lower levels of IgG4 do not impact the safety and efficacy of Deqsiga in the treatment of the proposed indications.

It is concluded that, from a clinical pharmacology perspective, there are no significant differences between Kiovig and Deqsiga.

2.5.4. Conclusions on clinical pharmacology

No PK data were collected for Deqsiga as it is a duplicate marketing authorisation. However, available PK data for the related IVIg product Kiovig in PID patients were provided.

The applicant has provided sufficient justification that the low level of IgG4 in Deqsiga is unlikely to have a significant impact on the safety and efficacy of the product in the intended indications.

Overall, the clinical pharmacology data are considered acceptable to support the marketing authorisation of Deqsiga.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

Not applicable.

2.5.5.2. Main studies

PID Study 160001

Table 3. Summary of efficacy for trial 160001

Title: Prospective Open-Label Study of Pharmacokinetics, Efficacy and Safety of Immune Globulin Intravenous (Human), 10% TVR Solution in Patients with Hypo- or Agammaglobulinemia	
Study identifier	Protocol number: 160001 EudraCT number: not applicable
Design	Phase II, prospective, open label, uncontrolled, multi-centre study of pharmacokinetics, efficacy, and safety of IGIV, 10% TVR in up to 22 subjects with hypo- or agammaglobulinemia. Subjects were treated every 21 days, initially with GAMMAGARD S/D (first 3 infusions), administered to standardise the IgG replacement therapy of all subjects to the same i.v. product and to acquire data

Table 3. Summary of efficacy for trial 160001

	with a licensed product. This was followed by Kiovig (IGIV, 10% TVR Solution) for the remaining 9 infusions. Study was open label, no randomisation. Efficacy was determined by the rate of infections, which was calculated as the number of infections per subject per month. Efficacy was also determined by the frequency of antibiotic use, which was calculated by the number of courses of antibiotics (oral/i.v.).		
	Pharmacokinetic parameters for the primary endpoint included in vivo recovery, half-life, and trough levels of total immunoglobulin G (IgG) after treatment with Kiovig (IGIV, 10% TVR Solution). The other pharmacokinetic parameters included area under the curve (AUC), maximum concentration (Cmax), and time to maximum concentration (Tmax).		
	Duration of main phase: approximately 27 weeks Duration of run-in phase: approximately 9 weeks Duration of extension phase: not applicable		
Hypothesis	No formal hypothesis testing was applied. Study was designed to investigate pharmacokinetics, efficacy and safety of Immune Globulin intravenous (human) 10% TVR solution		
Treatment phase	Kiovig (IGIV, 10% TVR Solution)	Treatment with Kiovig (IGIV, 10% TVR Solution) was preceded by 3 infusions of licensed product Gammagard S/D (reconstituted to a 10% solution). 22 subjects were enrolled (no randomisation) and treated.	
	Gammagard S/D	Twenty-two subjects received 3 infusions each with Gammagard S/D and 21 subjects received 9 infusions each with IGIV, 10% TVR Solution.	
Endpoints and definitions	Efficacy endpoint	Infections	The infection rate per subject was determined as the number of infections that occurred during the time on prophylaxis with Kiovig (IGIV, 10% TVR Solution) divided by the time on prophylaxis with IGIV, 10% TVR Solution.
		Antibiotic Use	The frequency of use of antibiotics while on prophylaxis with Kiovig (IGIV, 10% TVR Solution).
	Primary pharmacokinetic endpoint	PK	The primary pharmacokinetic endpoints were the in vivo recovery, half-life, and trough levels of total IgG during infusions of Kiovig (IGIV, 10% TVR Solution).
	Relevant secondary endpoint	PK	Pharmacokinetic parameters: area under the curve (AUC), maximum concentration (Cmax), time to maximum concentration (Tmax).
Database lock	09-Dec-2003		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	All subjects who received IGIV, 10% TVR Solution were included in all analyses (N=22). Full analysis set, PK analysis set and Safety analysis set were identical and included all N=22 subjects who received Gammagard S/D and Kiovig (IGIV, 10% TVR Solution). One subject was withdrawn due to developing diffuse large B-cell lymphoma during the Kiovig treatment phase. Analyses are based on the Kiovig (IGIV, 10% TVR Solution) treatment phase (9 infusions), descriptive statistical measures were calculated and presented, no hypotheses have been tested. The primary efficacy outcome was the rate of infection and frequency of antibiotic use.		

Table 3. Summary of efficacy for trial 160001

	The median and a non-parametric 95% confidence interval for the median were calculated for these rates.	
Descriptive statistics and estimated variability	Treatment phase	Kiovig (IGIV, 10% TVR Solution)
	Number of subjects	22
	Infections (Median of rate per month)	0.48
	95% confidence interval of median	0.34; 0.69
	Intravenous antibiotics (median rate of treatment courses per month)	0
	95% confidence interval of median	0; 0
	Oral antibiotics (median rate of treatment course per month) 95% confidence interval of median	0.18 0.16; 0.56
Notes	Twenty-four subjects were screened. Twenty-two subjects were included for treatment in the study. One Subject had PID as well as thrombocytopenia and was withdrawn because of medical reasons. One Subject did not have PID. Twenty-one Subjects completed the study. One subject was withdrawn due to diffuse large B-cell lymphoma in April, 2003. The primary pharmacokinetic endpoints in this clinical study of Kiovig (IGIV, 10% TVR Solution) were in vivo recovery, half-life and trough levels of total IgG after treatment with Kiovig (IGIV, 10% TVR Solution). For the determination of in vivo recovery and half-life, testing for total serum IgG was performed on serum samples collected • directly before • 15 minutes (± 5 minutes) after completion of infusion • on Days 1, 3, 7, 14 (±2 days) and 21 (±2 days, i.e., directly before the next infusion) after the sixth, seventh or eighth infusion (i.e. the third, fourth or fifth infusion of Kiovig (IGIV, 10% TVR Solution). Trough levels for IgG subclasses (i.e. IgG1, IgG2, IgG3 and IgG4) and total IgG were determined in serum collected 21 days after each infusion (i.e., before the next infusion) of IGIV, 10% TVR Solution. For total IgG, the median in vivo recovery rate was 89% (95% CI: 84%; 101%) and the median incremental recovery was 1.85 (mg/dL)/(mg/kg). The median AUC after administration of a mean dose of 0.41 g/kg was 545 g·h/dL. The median terminal half-life was 30.1 days (95% CI: 27.1 days; 43.3 days). Median terminal half-lives for IgG subclasses were 28.3, 31.3, 20.9 and 24.2 days for subclasses IgG1, IgG2, IgG3 and IgG4, respectively. The median steady state trough level of total IgG after the treatment phase (after the second and third infusion of Gammagard S/D and after the eighth and ninth infusion with Kiovig (IGIV, 10% TVR Solution, respectively) was 817 mg/dL (95% CI: 756; 905) with Gammagard S/D and 851 mg/dL (95% CI: 756; 1006) with Kiovig (IGIV, 10% TVR Solution). The median percentage of total IgG trough levels of Kiovig (IGIV, 10% TVR Solution) relative to Gammagard S/D was 105% (IQR: 100% to 109%) and 105% (IQR: 100% to 108%) for the Rochester and Vienna manufacturing facilities, respectively. Among 22 subjects, the median rate of infections classed as being mild or moderate per month of Kiovig (IGIV, 10% TVR Solution) treatment was 0.48 (95% CI: 0.34; 0.69). Two subjects received 1 course each of intravenous antibiotics.	

Table 3. Summary of efficacy for trial 160001

	The median rate of treatment courses with oral antibiotics per month of prophylaxis with Kiovig (IGIV, 10% TVR Solution) was 0.18 (95% CI: 0.16; 0.56). Conclusion: These results demonstrate that the introduction of two further virus inactivation/reduction steps (nanofiltration and low pH treatment at elevated temperature) in the manufacture of Kiovig (IGIV, 10% TVR Solution) did not alter the pharmacokinetic properties of the immunoglobulin. The median total serum IgG steady state trough levels of Kiovig (IGIV, 10% TVR Solution) and the licensed product Gammagard S/D were similar. The median terminal half-life was 30.1 days and the median steady state trough level of total IgG after the treatment phase with IGIV, 10% TVR Solution was 851 mg/dL. The rate of infections per month of IGIV, 10% TVR Solution treatment was 0.48.

PID Study 160101

Table 4. Summary of efficacy for trial 160101

Title: A Clinical Investigation to Assess the Safety and Efficacy of Immune Globulin Intravenous (Human), 10% in Subjects with Primary Immunodeficiency Disorders	
Study identifier	**160101**
Design	This was a Phase 3, uncontrolled, randomised, double-blind, multi-centre study which evaluated the safety and efficacy of Kiovig (IGIV, 10% TVR) in subjects with PID. Subjects were treated every 21 to 28 days for a minimum of 12 months. Kiovig (IGIV, 10% TVR) used in this study was manufactured using 3 different adsorption pathway options to ensure consistency among the pathway options. All subjects received 4 consecutive infusions of study product manufactured by each pathway for a minimum of 12 infusions. The order of administration for each of the preparations was determined by randomisation. Both investigator and subject were blinded with respect to the sequence of administration of study product. For subjects who continued treatment beyond 12 months, additional infusions of Kiovig (IGIV, 10% TVR) were to follow the same randomised sequence as those for Months 1 to 12. Efficacy of Kiovig (IGIV, 10% TVR) was determined by the mean number of acute serious bacterial infections per subject per year.
	Pharmacokinetic parameters for IGIV, 10% TVR was determined from total IgG levels at Infusion 4 to ensure an adequate wash-out period. Pharmacokinetic parameters included the area under the curve from pre-infusion to 21 days post-infusion ($AUC_{0\text{-}21d}$), maximum concentration (C_{max}), minimum concentration (C_{min}), elimination half-life, incremental recovery (K), and in-vivo recovery (IVR). All pharmacokinetic parameters were examined according to adsorption pathway to investigate consistency among the pathway options. In addition, median serum levels were reported for total IgG and IgG subclasses, and IgG trough levels were measured prior to each infusion throughout the 12-month efficacy period.
	Duration of main phase: Minimum of 12 months Duration of Run-in phase: not applicable Duration of Extension phase: not applicable
Hypothesis	The mean number of acute serious bacterial infections (ASBIs) was tested per the null hypothesis (H_0) of $\geqslant$ 1 acute serious bacterial infection per subject per year; The rate of other bacterial infections commonly occurring in PID subjects (summarised by the mean number of these infections per subject per year) and the corresponding exact 95% confidence interval (CI) for this rate was estimated using Poisson distribution.

Table 4. Summary of efficacy for trial 160101

Treatment groups	IGIV, 10% Triple Virally Reduced (TVR) Pathway 1		Intravenous immunoglobulin 300 to 600 mg/kg body weight every 21 to 28 days, minimum of 12 months, 18 subjects
	IGIV, 10% Triple Virally Reduced (TVR) Pathway 3		Intravenous immunoglobulin 300 to 600 mg/kg body weight every 21 to 28 days, minimum of 12 months, 19 subjects
	IGIV, 10% Triple Virally Reduced (TVR) Pathway 6		Intravenous immunoglobulin 300 to 600 mg/kg body weight every 21 to 28 days, minimum of 12 months, 20 subjects
Endpoints and definitions	Primary efficacy endpoint	ASBI	The primary efficacy endpoint was defined as the acute serious bacterial infection rate i.e., the mean number of acute serious bacterial infections per subject per year.
	Relevant secondary efficacy endpoint	Other bacterial infections commonly occurring in PID patients. The number of hospitalisations secondary to infectious complications.	Secondary efficacy endpoints were the mean rate of other bacterial infections commonly occurring in PID subjects and the number of hospitalisations secondary to infectious complications. Other bacterial infections commonly occurring in subjects with PID also met specific diagnostic requirements (i.e. validated) defined by the FDA.
	Relevant secondary endpoint	PK	Pharmacokinetic parameters for IGIV, 10% TVR included area under the curve from pre-infusion to 21 days post-infusion ($AUC_{0\text{-}21d}$), maximum concentration (C_{max}), minimum concentration (C_{min}), elimination half-life, incremental recovery (K), and in-vivo recovery (IVR). All pharmacokinetic parameters were examined according to adsorption pathway to investigate consistency among the pathway options. In addition, median serum levels were reported for total IgG and IgG subclasses, and IgG trough levels were measured prior to each infusion throughout the 12-month efficacy period.
Database lock	06 May 2004		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The comparison of the mean number of acute serious bacterial infections per subject per year to the fixed threshold $\geqslant$ 1 acute serious bacterial infections per subject per year (in accordance with FDA recommendations) was done in 3 ways: 1. using the observed rate for the intent-to-treat population (intent-to-treat analysis) 2. using the observed rate for the per protocol population (per-protocol analysis), and 3. using a 'worst-case' estimate of the true rate in the intent-to-treat population (sensitivity conservative analysis). The estimated "worst-case" rate for the intent-to-treat population used the observed number of infections plus an adjustment based on the highest rate observed for subjects who did not complete the full 12 months of treatment. In addition, ninety-five percent confidence intervals (95% CIs) for these rates were calculated.		

Table 4. Summary of efficacy for trial 160101

	The intent-to-treat population included all subjects who received any amount of study product, whether or not they completed all 12 months of study product infusions (N=61). The per-protocol analysis included subjects who a) met all inclusion/exclusion criteria or were approved by the sponsor; b) completed the full 12-months course of treatment and all infusions; and c) did not have IgG trough level less than 450 mg/dL in 3 consecutive infusions (N=58).			
Descriptive statistics and estimate variability		*Intent-to-treat population*	*per protocol population*	*"worst-case" estimate in intent-to-treat population*
	Number of subjects	61	58	61
	ASBI (mean rate per subject per year)	0	0	0
	95% confidence interval of mean rate	(0.000; 0.060)	(0.000; 0.064)	(0.000; 0.060)
	Other Bacterial Infections (mean rate per subject per year)	0.07	-	-
	95% confidence interval of mean rate	(0.018; 0.168)	-	-
Effect estimate per comparison	Primary endpoint	<u>Analysis Population</u>		<u>Intent-to-treat</u>
		One-sided hypothesis test utilizing a large sample normal approximation of the exact Poisson probability distribution, test of null hypothesis (H0) of ASBI rate $\geqslant$ 1 per subject per year at the 1% significance level		-
		95% confidence interval of mean rate		(0.000; 0.060)
		P-value (see description of test above)		<0.0001
		<u>Analysis Population</u>		<u>Per protocol</u>
		One-sided hypothesis test utilizing a large sample normal approximation of the exact Poisson probability distribution, test of null hypothesis (H0) of ASBI rate $\geqslant$ 1 per subject per year at the 1% significance level		-
		95% confidence interval od mean rate		(0.000; 0.064)
		P-value (see description of test above)		<0.0001
		<u>Analysis Population</u>		<u>Intent-to-treat, "Worst-case" estimate</u>
		One-sided hypothesis test utilizing a large sample normal approximation of the exact Poisson probability distribution, test of null hypothesis (H0) of ASBI rate $\geqslant$ 1 per subject per year at the 1% significance level		-
		95% confidence interval od mean rate		(0.000; 0.060)
		P-value (see description of test above)		<0.0001

Table 4. Summary of efficacy for trial 160101

	Of the 61 treated subjects, 3 discontinued before completing the efficacy period. Of these 3 subjects, 2 withdrew consent and 1 subject was withdrawn by the investigator for non-study product-related reasons. Of the 58 subjects who completed the efficacy period, 50 chose to continue treatment and 8 subjects discontinued in the optional post-efficacy period. 6 of these subjects withdrew consent, 1 withdrew due to an AE and 1 discontinued because the investigator withdrew from the study. **Efficacy Results:** There were no validated acute serious bacterial infections in any of the 61 treated subjects. The annualised rates of acute serious bacterial infections for all analysis populations (intent-to-treat, per-protocol, and sensitivity conservative) were significantly less ($p << 0.0001$) than the acceptable rate of 1 infection per year. Thus, this study met the primary efficacy objective. Additionally, only 4 validated other bacterial infections commonly occurring in subjects with PID were reported. None were serious or severe, and none resulted in hospitalisation. (Infections that did not fulfil the specific diagnostic criteria for validated infections were reported as AEs and are described in the "Safety Results".) **PK Results:** A total of 57 treated subjects were included in the pharmacokinetic assessment of IGIV, 10% TVR at Infusion 4. The median value for $AUC_{0\text{-}21d}$ was 29,139 mg·days/dL (95% CI: 27,494 to 30,490) overall (i.e. IGIV, 10% TVR made from all 3 adsorption pathway options combined). The overall median value for elimination half-life was 35 days (95% CI: 31 to 42). Median total IgG decreased from 2040 mg/dL at 30 minutes after the infusion to 1040 mg/dL 21 to 28 days after the infusion. Median total IgG trough levels varied from 960 to 1120 mg/dL prior to each infusion during the efficacy period. Median values for each pharmacokinetic parameter ($AUC_{0\text{-}21d}$, C_{max}, C_{min}, elimination half-life, K, and IVR) were similar and the 95% CIs showed no differences among the IGIV, 10% TVR produced from pathway options 1, 3, and 6. Median total IgG trough values also appeared similar for IGIV, 10% TVR produced from each of the 3 pathway options. These pharmacokinetic data indicate that IGIV, 10% TVR produced from the 3 different pathway options are consistent. Conclusion: Kiovig (IGIV, 10% TVR) was efficacious as an IgG replacement therapy for the prevention of infections in subjects > 24 months of age with PID.
Analysis description	To assess the primary endpoint for efficacy, the null hypothesis (H0) of acute serious bacterial infection rate $\geqslant 1$ per subject per year versus an alternative hypothesis (Ha) of acute serious bacterial infection rate <1 per subject per year was to be tested at the 1% significance level, in accordance with FDA recommendations. This one-sided hypothesis test utilised a large sample normal approximation of the exact Poisson probability distribution. In addition, ninety-five percent confidence intervals (95% CIs) were calculated for the acute serious bacterial infection rate, as well as for the other bacterial infection rate.

ITP Study 160002

Table 5. Summary of efficacy for trial 160002

Title: Prospective Open-Label Study of the Efficacy and Safety of Immune Globulin Intravenous (Human), 10% TVR Solution in Adult Subjects with Chronic Idiopathic Thrombocytopenic Purpura			
Study identifier	Protocol number: 160002 EudraCT: Not applicable		
Design	The study was a prospective, open-label, un-controlled, international, multi-centre trial. After screening, subjects eligible for treatment received a total dose of 2 g of IGIV, 10% TVR Solution per kg body weight equally divided over 2 to 5 days. A maximum of 2 booster doses each ranging from 400 mg to 1,000 mg per kg body weight were permitted if the platelet count dropped to ≤20 x 10^9/L. Subjects who achieved a platelet increase to ≥50 x 10^9/L at least once prior to Day 15 after initiation of treatment and did not require a booster dose before Day 15 after onset of the treatment course were considered treatment responders and were followed until Day 29. Non-responders terminated the study on Day 15. 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. Twenty-eight subjects were enrolled, 23 were treated and analysed.		
	Duration of main phase: up to 29 days Duration of Run-in phase: not applicable Duration of Extension phase: not applicable		
Hypothesis	No hypotheses were tested. Descriptive analyses were performed.		
Treatments group	Kiovig (IGIV, 10% TVR Solution)		Single arm uncontrolled non-randomised study 28 subjects were enrolled and 23 were treated and analysed. A screening period of up to 2 weeks preceded treatment. Subjects received a total dose of 2 g of IGIV, 10% TVR per kg body weight equally divided over 2 to 5 days. A maximum of 2 booster doses were permitted. Treatment responders and were followed until Day 29. Non-responders terminated the study on Day 15.
Endpoints and definitions	Primary endpoint	Number of treatment responders	The primary endpoint of the study was the number of treatment responders, a responder being defined as a subject who i) had a platelet increase to ≥50 x 10^9/L at least once prior to Day 15 *and* ii) did not require a booster dose prior to Day 15, where Day 15 referred to the fifteenth day from initiation of treatment (Day 1). Otherwise, the subject was considered a non-responder.
	Relevant secondary endpoint	Time taken to achieve a platelet count of >50 x 10^9/L	The median and 95% confidence interval for the time to platelet response were estimated from the beginning of the first infusion until the first measurement of a platelet count of ≥ 50 x 10^9/L by the Kaplan-Meier technique. To account for different lengths of the observation periods among subjects, data was considered censored after the last available platelet count for each subject. Missing platelet counts before the subject's first count of 50 x 10^9/L or more were considered <50

Table 5. Summary of efficacy for trial 160002

			x 10^9/L. Missing platelet counts after that time point did not affect the Kaplan-Meier estimate.
	Relevant secondary endpoint	Duration of platelet response	Duration of platelet response was defined as the duration in days from the day the platelet count reached or exceeded 50 x 10^9/L to either the first day the platelet count fell to <20 x 10^9/L or the last day with available platelet count data, whichever occurred first. Median and a two-sided 95% non-parametric confidence interval for duration of platelet response were given (by SAS procedure UNIVARIATE options CIPCTLDF, TYPE=ASYMMETRIC).
	Relevant secondary endpoint	Maximum platelet count	Medians, quartiles and their non-parametric two-sided 95% confidence intervals (by SAS procedure UNIVARIATE options CIPCTLDF, TYPE = ASYMMETRIC) were used to describe the maximum platelet count, which was defined as the highest platelet count achieved on or after Day 5. The main focus was on the analysis of maximum platelet level excluding platelet counts after booster doses, if any were given. The same analysis was also performed for maximum platelet levels including platelet counts after booster doses, if any. In addition, maximum platelet count following booster doses was analysed as described above categorised by time point of administration (before Day 15/on or after Day 15).
	Relevant secondary endpoint	Regression of haemorrhages	The median time to complete cessation of any haemorrhages was estimated by the Kaplan-Meier method (and included the two-sided 90% confidence interval for the median). This analysis was performed for the subset of subjects who reported with haemorrhages at Day 1. The data for this analysis was obtained from the initial and interval medical history (MH2, IMH) and adverse experience (AE, SAE) case report forms. The number of subjects (percentages) with haemorrhage(s) at Day 1 was also provided. Time to regression of haemorrhages was expressed in integer days. The day when regression of haemorrhages occurred was defined as the first day when the subject's bleeding related adverse experiences had all stopped and no new bleeding was reported to have started on that day. This variable was only defined for subjects who experienced some bleeding related AE on Day 1, all others were considered "not at risk"; the minimum time to regression of haemorrhages is therefore 1 day (all haemorrhages stopped on Day 2). Data was censored at the day of study termination, if applicable.
Database lock	08 Mar 2004		
Results and Analysis			
Analysis description	**Primary Analysis**		

Table 5. Summary of efficacy for trial 160002

Analysis population and time point description	The Full Analysis Data Set (FADS) comprised all subjects who received IGIV, 10% TVR Solution and who were monitored for platelet count for any period of time (N = 23). The Per-Protocol Analysis Data Set (PADS) comprised all subjects who fulfilled all selection criteria, received IGIV, 10% TVR Solution, and who were monitored for platelet count for any period of time (N = 21)		
Descriptive statistics and estimate variability	Analysis Data Set	FADS	PADS
	Number of subjects	23	21
	Primary endpoint, treatment response (number/proportion of responders)	17 (73.9%)	15 (71.4%)
	95% CI of proportion	53.5; 87.5%	50.0; 86.2%
	Time (days) to Platelet Response (median)	4	4
	95% CI of median	4; 4	4; 4
	Duration (days) of platelet response (median) 95% CI of median	25 22; 28	25 21; 28
	Maximum platelet count [10^9/L] (median (1^{st}- 3^{rd} quartile) 95% CI of respective quartile (Results are the same considering the maximum platelet count prior to and inclusive the booster dose)	122 (59-268) 64 to 236 (17 to 97 - 126 to 405)	122 (59-268) 64 to 294 (17 to 97 - 126 to 405)
	Time (days) to regression of haemorrhages (with haemorrhages at day 1) (median) 95% of median	2 0; 4	4 0; 4
Notes	Twenty-eight subjects were enrolled into the study. Of these, 5 discontinued the study prior to treatment with the study drug. One subject withdrew consent immediately, therefore no data were collected from that subject. A second subject withdrew consent prior to initiation of treatment. Results of blood tests performed at screening showed that a further subject had ALT and AST levels surpassing the values permitted by the eligibility criteria. Two other subjects did not qualify for treatment because the platelet counts prior to infusion were too high. **Efficacy Results:** A total of 23 subjects received the study drug. However, two of these did not meet all selection criteria. Therefore, efficacy results were calculated separately for the subjects who received IGIV, 10% TVR Solution and were monitored for platelet count for any period of time (Full Analysis Data Set –FADS, N=23) and for the subjects who met all selection criteria, received IGIV, 10% TVR Solution and were monitored for platelet count for any period of time (Per-Protocol Analysis Data Set - PADS, N=21). Fifteen subjects in the PADS and 17 in the FADS were treatment responders (71.4% in the PADS and 73.9% in the FADS). Eleven subjects in the PADS presented with an increase to >100 x 10^9/L and 8 also reached >200 x 10^9/L during the course of the study. In the FADS, 12 subjects achieved a platelet count of >100 x 10^9/L and 9 reached >200 x 10^9/L. Among the treatment responders, 7 subjects in the PADS and 9 in the FADS had a platelet count of >20 x 10^9/L at the end of the study without receiving a booster. In		

Table 5. Summary of efficacy for trial 160002

	7 of the treatment responders (FADS = PADS) a platelet count of >50 x 10^9/L was observed at the end of the study without a booster dose. While a median platelet count of >50 x 10^9/L was observed on Day 29 in the two analysis sets, the median value had fallen to <50 x 10^9/L on Day 22. Three subjects (FADS = PADS) had received booster doses between Day 22 and Day 29. These 3 subjects had platelet counts <50 x 10^9/L on Day 22 while platelet counts increased to >50 x 10^9/L on Day 29. Eight of the subjects (FADS = PADS) who were receiving systemic corticosteroids already at study entry also received doses equivalent to 20 mg or less of prednisone per day during the treatment and follow-up period. With one exception (a subject who was a non-responder to treatment) doses remained stable or were tapered during the study. Among these 8 subjects, 7 (87.5%) were treatment responders according to the study protocol. Among the 13 (PADS) and 15 (FADS) subjects who did not receive systemic corticosteroids, 8 (61.5%; PADS) and 10 (66.7%; FADS) responded to study drug treatment. Secondary endpoints were the time taken to achieve a platelet count of >50 x 10^9/L, duration of platelet response, maximum platelet count, and regression of haemorrhages. Within 4 days from the beginning of the first infusion platelet response (⩾50 x 10^9/L) was achieved in at least 50% of the subjects in both the PADS and the FADS. All of the treatment responders in the PADS and the FADS achieved a platelet count of ≥50 x 10^9/L by Day 8 (within 7 days from initiation of treatment). Fourteen treatment responders in the PADS (93.3%) and 15 in the FADS (88.2%) achieved this platelet count by Day 5 (i.e. within 4 days of initiation of treatment). 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 first platelet count of ≥50 x 10^9/L was observed to either the first day of observation of a decrease to <20 x 10^9/L or the last day with available platelet count data. The median of the maximum platelet counts achieved on or after Day 5 prior to administration of a booster dose of study drug was 122 x 10^9/L (1st quartile 59 x 10^9/L, 3rd quartile 268 x 10^9/L) in both the PADS and the FADS. Results remained the same when maximum platelet counts after booster doses were included in this analysis. The highest median platelet count in treatment responders in the PADS and the FADS was 182 x 10^9/L (range 17 to 435 x 10^9/L) observed on Day 8. The median platelet count in treatment responders in either analysis data set was 163 x 10^9/L (range 42 to 271) on Day 5. Five subjects in the PADS and 6 in the FADS 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) in the PADS and 2 days (90% CI 0 to 4 days) in the FADS. Conclusion: The results obtained in this study demonstrate that IGIV, 10% TVR Solution is effective in the treatment of adult subjects with chronic ITP.
Analysis description	The statistical analysis methods are described above along with the definition of the primary and secondary efficacy endpoints. The analysis was pre-specified.

MMN Study 160604

Table 6. Summary of efficacy for trial 160604

<table>
<tr><td colspan="2"><u>Title:</u> A Randomized, Double-Blind, Placebo Controlled, Cross-over Study of the Effectiveness of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) for the Treatment of Multifocal Motor Neuropathy</td></tr>
<tr><td>Study identifier</td><td>Protocol number: 160604
EudraCT Number: 2009-013841-27.</td></tr>
<tr><td>Design</td><td>This was a randomised withdrawal, double-blind, placebo-controlled, cross-over study of the efficacy, safety and tolerability of IGIV, 10% in adult patients with MMN. The study consisted of 5 parts lasting 12 weeks each: 3 stabilisation phases of open-label treatment with IGIV, 10%, and 2 double-blinded cross-over periods in which subjects received IGIV, 10% and placebo according to a randomised sequence. All subjects were to begin the study with Stabilisation Phase 1. Subsequently, subjects were randomised to 1 of 2 treatment sequences as shown below. Each treatment sequence comprised 2 double-blinded cross-over periods intercalated by Stabilisation Phase 2. Following the randomised sequence, all subjects were to proceed to Stabilisation Phase 3.
<table>
<tr><td></td><td>Cross-over Period 1
(double-blind)</td><td>Cross-over Period 2
(double-blind)</td></tr>
<tr><td>Sequence 1</td><td>IGIV, 10%</td><td>Placebo</td></tr>
<tr><td>Sequence 2</td><td>Placebo</td><td>IGIV, 10%</td></tr>
</table>
The last study part for all subjects was the open-label Stabilisation Phase 3 (for recovery), on IGIV, 10%.

If, during the randomised, double-blinded treatment period, the subject and the investigator agreed that the subject’s function had deteriorated to the point that the subject had unacceptable difficulty carrying out daily life activities involving the affected muscles, or the subject experienced a decline in grip strength of 50% or more in the more affected hand, then the subject was to be switched directly to the next stabilisation phase of open-label IGIV, 10% (“accelerated switch”), without breaking the blind. If subjects did not return to their overall baseline level of function according to the investigator’s evaluation after at least 1 dose of IGIV, 10% during either Stabilisation Phase 2 or 3 following an accelerated switch, the dose and/or treatment interval was permitted to be changed by the investigator after discussion with the sponsor. These subjects were to remain on open-label IGIV, 10% for the remaining duration of the study.

The analysis of the primary and co-primary efficacy endpoints was performed by 2 separate tests of the null hypothesis of no treatment effect against the one-sided alternative hypothesis of superiority of IGIV, 10% at the 2.5% level of statistical significance.

For grip strength in the more affected hand, the relative change from the Cross-over Periods’ baseline to the value at the Last Cycle Assessment at the end of the blinded Cross-over Period (1 or 2) was analysed using a fixed effects ANOVA model with factors for sequence (sequence 1 or 2), subject nested within sequence, period (Cross-over Period 1 or 2), and treatment (IGIV, 10% or placebo). The Cross-over Periods’ baseline (baseline 1 or 2) was the value of the assessment at the infusion cycle preceding the first blinded infusion of study product for the Cross-over Period (i.e. 1 week before for subjects on two-week infusion intervals and 2 weeks before otherwise). The contrast tested was the treatment effect of IGIV, 10% vs. placebo.

Guy’s Neurological Disability Score for the upper limbs was analysed as a binary variable indicating whether the score of a subject deteriorated from the Cross-over Periods’ baseline
(1 or 2) to the value at the Last Cycle Assessment at the end of the blinded Cross-over Period (1 or 2, respectively). The Cross-over Periods’ baseline (1 or 2) was the value of the assessment at the infusion cycle preceding the first blinded infusion of study product for the Cross-over Period (i.e. 1 week before for subjects on two-</td></tr>
</table>

Table 6. Summary of efficacy for trial 160604

	week infusion intervals and 2 weeks before otherwise). Deterioration was defined as a higher Guy's Neurological Disability Score for upper limbs at the end of the Cross-over Period than at the baseline of the Cross-over Period. The cross-over design was analysed by McNemar's test on the discordant pairs, i.e. those subjects who deteriorated in one, but not in the other Cross-over Period. The main analysis used all randomised subjects and depended on randomisation, not the type of study product received (intent-to-treat dataset). For all other efficacy endpoints, descriptive statistics (median, quartiles, range) were provided. In addition, box plots were used to display efficacy endpoint data over time for the 2 sequences separately in the Stabilisation Phases 1, 2, and 3 as well as in the Cross-over Periods 1 and 2. The following hypothesis tests were performed for the secondary efficacy endpoints with ANOVA/McNemar's test for continuous/binary variables as described for the primary endpoints analyses: 1. The proportion of subjects experiencing a decline of at least 30% in grip strength in the more affected hand (McNemar's test), 2. The proportion of subjects being accelerated forward into the next stabilisation phase (McNemar's test), 3. Grip strength of the less affected hand (ANOVA) 4. The overall disability sum score (ANOVA), 5. The time on peg board test (ANOVA), 6. The patient assessment on visual analogue scale (VAS) (ANOVA). In Stabilisation Phase 1, the study was single-armed. For Cross-over Period 1, Stabilisation Phase 2, Cross-over Period 2, and Stabilisation Phase 3, subjects were tabulated by sequence. Adverse events were attributed to the infusion (and hence study product) that started latest, but before or at the time of onset of the AE. In addition, the primary and secondary safety endpoints were tabulated by treatment and Cross-over-Period. Medians and their non-parametric 95% CIs were used to summarise IgG trough levels.	
	Duration of main phase: 3 study parts of 12 weeks (36 weeks total) Duration of Run-in phase: 12 week stabilisation phase Duration of Extension phase: 12 weeks stabilisation	
Hypothesis	The analysis of the primary and co-primary efficacy endpoints (grip strength in more affected hand and GNDS as binary endpoint, respectively) was performed by 2 separate hypothesis tests of the null hypothesis of no treatment effect against the one-sided alternative hypothesis of superiority of IGIV, 10% at the 2.5% level of statistical significance. Both hypothesis tests needed to reach significance at the 2.5% level for the primary efficacy analysis to be successful.	
Treatments groups	IGIV 10% versus placebo in a double-blind cross-over design Placebo: 0.25% human albumin	All subjects were to receive IGIV, 10% during the 3 open-label stabilisation phases and one double-blinded cross-over period. In the remaining cross-over period, placebo (0.25% human albumin) was to be administered. Dose range: The permitted dose of IGIV 10% dose ranged from 0.4 to 2.0 g per kg BW per infusion cycle, divided over 1 to 5 consecutive days. The dose of the blinded product (0.25% human albumin or IGIV, 10%) was to be comparable on a

Table 6. Summary of efficacy for trial 160604

		volume basis to the dose of IGIV, 10% that the subject received before being randomised.	
Endpoints and definitions	Primary Efficacy Endpoint:	Grip strength in the more affected hand assessed by dynamometer.[1]	
	Co-Primary Efficacy Endpoint:	Upper limb (Part 6) subsection of the Guys' Neurological Disability Scale (GNDS).[2]	
	Relevant Secondary Efficacy Endpoints:	Percentage of subjects with at least a 30% decline in grip strength in the more affected hand as assessed by dynamometer.	
		Number and percentage of subjects with a decline in grip strength in the less affected hand as assessed by dynamometer.	
		Number of subjects with accelerated switch (from the placebo vs. the IGIV, 10% blinded treatment) to the next stabilisation phase during the Cross-over Periods 1 and 2.	
		Patient assessment of disability (Patient Global Impression of Change Scale).	
		Overall Disability sum score.[3]	
		Timed Peg Board Test (9-HPT).[4]	
		Patient assessment on visual analogue scale (VAS): endpoints of the 10 cm scale: No symptoms – disabled, unable to use affected limbs.	
Database lock	01-Sep-2011		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat data set (N=44): All subjects who were randomised to 1 of the 2 blinded treatment sequences. Efficacy data set (N=37): All subjects who completed both blinded cross-over periods (regularly or accelerated) and for whom baseline assessments for both cross-over periods were available. The main analysis was based on the intent-to-treat dataset. In addition, an analysis based on the efficacy dataset was performed. Time point description: relative changes of the endpoints were considered from the cross-over period baseline to the value at the last cycle assessment at the end of the blinded Crossover Period (1 or 2).		
Descriptive statistics and estimate variability	*Efficacy results were reported for the treatment sequences separately*	*Sequence 1: IGIV, 10% => Placebo (Intent-to-treat data set)*	*Sequence 2: Placebo => IGIV, 10% (Intent-to-treat data set)*
	Number of subjects	22	21
	Grip strength in the more affected hand (relative	Period 1: -16.36	Period 1: -30.11

[1] Shechtman O, Gestewitz L, Kimble C. Reliability and validity of the DynEx dynamometer. J. Hand Ther. 2005;18:339-347.J.Neurol.Neurosurg.Psychiatr. 2002;72:596-601.
[2] Sharrack B, Hughes RA. The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. Mult.Scler. 1999; 5:223-233.
[3] Merkies IS, Schmitz PI, van der Meche FG, Samijn JP, van Doorn PA. Clinimetric evaluation of a new overall disability scale in immune mediated polyneuropathies.
[4] Merkies IS, Schmitz PI, van der Meche FG, Samijn JP, van Doorn PA. Connecting impairment, disability, and handicap in immune mediated polyneuropathies. J.Neurol.Neurosurg.Psychiatr. 2003;74:99-104.

Table 6. Summary of efficacy for trial 160604

	change) (mean)	Period 2: -30.52	Period 2: 23.86
	Standard deviation	Period 1: 32.84 Period 2: 29.68	Period 1: 39.10 Period 2: 103.19
	Grip strength in less affected hand (relative change) Mean (standard deviation)	Period 1: -2.52 (12.12) Period 2: -17.96 (26.74)	Period 1: -29.22 (24.34) Period 2: 19.67 (67.01)
	Overall Disability Sum Score (Relative Change) Mean (standard deviation)	Period 1: -3.14 (7.69) Period 2: -5.77 (10.29)	Period 1: -8.46 (9.29) Period 2: 0.92 (8.36)
	Timed Board Test (relative change) mean (standard deviation)	Period 1: -2.57 (16.75) Period 2: 3.90 (19.15)	Period 1: 29.89 (37.23) Period 2: 4.89 (31.51)
	Visual Analog Scale for Patient Assessment (relative change) Mean (standard deviation)	Period 1: 140.92 (320.88) Period 2: 321.75 (891.34)	Period 1: 258.09 (766.90) Period 2: 5.75 (37.98)
	Treatment Group (Results are summarised for IGIV, 10% and placebo period separately	*IGIV, 10%*	*Placebo*
	Number of subjects	42	42
	Upper Limb Section of Guy's Neurological Disability Scale (as binary variable indicating deterioration or absence of deterioration) Number (%) of subjects who deteriorated after one treatment, but not the other	5 (11.9%) deteriorated after IGIV, 10%, but not after placebo	15 (35.7%) deteriorated after placebo, but not after IGIV, 10%
	Decline of ⩾30% in Grip Strength in the More Affected Hand Number (%) of subjects	2 (4.8%)	18 (42.9%)
	Accelerated Switch from Cross-Over to Open-Label IGIV, 10% Number (%) of subjects who required a switch to open-label IGIV under one treatment, but not the other	1 (2.4%) switched to open-label treatment during blinded IGIV, 10% but did not switch during placebo administration	29 (69.0% required a switch from placebo to open-label treatment with IGIV, 10%, but not when receiving blinded treatment with IGIV, 10%

Table 6. Summary of efficacy for trial 160604

Effect estimate per comparison	Primary endpoint (Intent-to-treat analysis set)	Comparison groups	IGIV, 10% - Placebo
		Difference in LS-means	35.13
		95% CI	8.81; 61.46
		P-value	0.005
	Co-Primary endpoint (Intent-to-treat analysis set)	Comparison groups	IGIV, 10% - Placebo
		Discordant pairs	11.9% deteriorated after IGIV, 10%, but not after placebo, in contrast, 35.7% deteriorated after placebo, but not after IGIV, 10%
		P-value (Mc Nemar's test)	0.021
Notes	All 44 eligible subjects received treatment and were randomised, and thus were included in the safety and intent-to-treat datasets. Among the 44 subjects treated, 41 subjects completed the study. Two subjects discontinued due to an AE that was considered to be related to IGIV, 10%. One of them was discontinued during Stabilisation Phase 1 due to moderate muscular weakness and the other during Cross-over Period 2 due to a moderate decrease in joint range of motion. One subject withdrew from the study during Stabilisation Phase 3 due to moving out of state. **Efficacy Results:** Efficacy was assessed by comparing the relative changes that occurred during the double-blinded cross-over periods of treatment with IGIV, 10% and placebo. A "relative change" is the difference between values measured at baseline to the end of a given cross-over period, expressed as a percentage of the baseline value for that period. Baseline for a given cross-over period was defined as the last cycle-assessment at the end of the previous stabilisation phase. Results are presented separately for each Treatment Sequence (i.e. IGIV, 10% then placebo, or placebo then IGIV, 10%). **Primary and Co-Primary Efficacy Endpoints:** Maximal grip strength in the more affected hand and GNDS scores for the upper limbs showed a significant difference in efficacy between IGIV, 10% and placebo at the 2.5% level in favour of IGIV, 10%, thus, the primary and co-primary efficacy endpoints were met. As these separate tests, performed sequentially, rejected the null hypothesis of no treatment effect against the one sided alternative hypothesis of superiority of IGIV, 10%, the study demonstrates the superiority of IGIV, 10% over placebo. The mean difference in grip strength in the more affected hand, the primary endpoint, was 34.13 % (95% CI: 7.35; 60.91) across both treatment sequences, indicating a substantially greater decline in grip strength during placebo administration than during treatment with IGIV, 10%. The difference in the least squared means of relative change for IGIV, 10% and placebo of 35.13% (95% CI: 8.81; 61.46) was statistically significant (p=0.005). A significant difference was also demonstrated in a sensitivity analysis using the multiple imputation technique, confirming the robustness of the analysis.		

Table 6. Summary of efficacy for trial 160604

Notes	As determined by GNDS scores for the upper limbs, 35.7% of subjects deteriorated while receiving the placebo, but not during treatment with IGIV, 10%, whereas 11.9% of subjects deteriorated during IGIV, 10% but not over the placebo period. This difference was significant (p=0.021); therefore the co-primary endpoint was met. An additional sensitivity analysis using a worst imputation technique did not reach statistical significance at the 2.5% level (one-sided p=0.039). **Secondary Efficacy Endpoint(s):** Results of the secondary endpoints clearly confirmed those of the primary and co-primary endpoints with the exception of analysis of VAS scores, which provided supportive evidence but did not reach significance. The remaining secondary efficacy endpoints demonstrated significantly greater efficacy of treatment with IGIV, 10% compared to placebo. Where sensitivity analyses were performed, the results consistently confirmed those of the original analyses. Six secondary efficacy endpoints were analysed using a fixed sequence in the order presented; the remaining two endpoints (Patient Global Impression of Change and ≥30% relative decline in strength of the less affected hand) were analysed separately. A relative decline of ≥30% in grip strength in the more affected hand occurred during the placebo period but not during IGIV, 10% in 42.9% of subjects, compared to 4.8% of subjects who experienced a ≥30% decline during IGIV, 10% only (p<0.001). The majority of subjects analysed (69.0%) switched to open-label treatment with IGIV, 10% during the placebo period due to functional deterioration, but did not switch when receiving IGIV, 10%. Only one subject (2.4%) switched to open-label treatment during blinded IGIV, 10% but did not switch during placebo administration (p<0.001). Deterioration of grip strength in the less affected hand was significantly greater during placebo than double-blinded IGIV, 10% treatment; the difference in least squared means of relative change was 32.54% (p<0.001). Standardised overall disability sum scores decreased to a greater extent after placebo relative to baseline for that period than for IGIV, 10%, demonstrating deterioration was more severe during the placebo treatment. The least squared mean of relative changes was 6.03% (95% CI: 2.14; 9.92) higher for IGIV, 10% than for placebo (p=0.002). The time that subjects required to complete the 9-hole peg board test with the dominant hand increased to a greater extent compared to baseline for the respective cross-over period during administration of placebo than for IGIV, 10%. The difference in least squared means was -15.57 % (95% CI: -24.37; -6.77) (p<0.001), showing a greater deterioration in peg board test times after placebo than after IGIV, 10%. Similarly, for the non-dominant hand, the least squared mean of relative changes was 26.11% less (95% CI: 38.96; -13.26) for IGIV, 10% than for placebo (p<0.001). Patients' assessments as determined by VAS showed a greater numerical degree of deterioration during the placebo period than for IGIV, 10%, with a difference in least squared means of relative change of -216.60% (95% CI: -490.41 ; 57.22). However, this result was not statistically significant (p=0.059). As defined prospectively in the Statistical Analysis Plan, low p-values were considered supportive where significance at the 2.5% was not met, thus, the results of the VAS analysis provide further evidence supporting the beneficial effect of IGIV, 10 %. Assessment of Patient Global Impression of Change indicated greater perceived deterioration relative to baseline after placebo than after IGIV, 10%, and the median score of 4.0 indicated no patient-assessed change in disability during IGIV, 10% treatment.

Table 6. Summary of efficacy for trial 160604

	A ≥30% relative decline in strength of the less affected hand was reported for placebo but not IGIV, 10% in 31.0% of subjects, but no subjects reported a relative decline ≥30% for IGIV, 10% only (p<0.001). Conclusion: In conclusion, this clinical study demonstrates that IGIV, 10% was efficacious in adults with MMN.
Analysis description	Primary and Co-primary endpoints were analysed as follows: <u>Grip Strength in the More Affected Hand</u> The result of grip strength was to be read from the digital display of the instrument and recorded to a resolution of 0.1 kg. For statistical analysis, the mean of (usually three) trials for sessions 1 and 2 was computed and the mean of the sessions was used in the statistical analysis as the result of the grip strength measurement. Only if no grip strength testing could be performed the results were considered as missing. The relative change from the cross-over period baseline to the value at the Last Cycle Assessment at the end of the blinded Crossover Period (1 or 2) was analysed using a fixed effects ANOVA model with factors for sequence (sequence 1 or 2), subject nested within sequence, period (Cross-over Period 1 or 2), and treatment (IGIV, 10% or placebo). The Cross-over Period baseline (baseline 1 or 2) was the value of the assessment at the infusion cycle preceding the first blinded infusion of study product for the cross-over period (i.e. 1 week before for subjects on two week infusion intervals and 2 weeks before otherwise). The contrast tested was, of course, the treatment effect of IGIV, 10% vs. placebo. <u>Guy's Neurological Disability Score (GNDS) for the upper limbs</u> Guy's Neurological Disability Score (GNDS) for the upper limbs were integers 0 to 5 with 0 indicating no impairment. An increase of more than 1 would have been a considerable deterioration that would not be expected to occur within three months while on immunoglobulin treatment and would have been rare even during placebo administration, because the subject would have realised deterioration early and would have requested acceleration into the next stabilisation phase in order to curb further deterioration. For this reason, GNDS for the upper limbs were analysed as a binary variable (coding deterioration as 1 and absence of deterioration as 0) indicating whether the score of a subject deteriorated from the Cross-over Period baseline (1 or 2) to the value at the Last Cycle Assessment at the end of the blinded Cross-over Period (1 or 2, respectively). The Cross-over Period baseline (1 or 2) was the value of the assessment at the infusion cycle preceding the first blinded infusion of study product for the Cross-over Period (i.e. 1 week before for subjects on two-week infusion intervals and 2 weeks before otherwise). Deterioration was to be defined as a higher Guy's Neurological Disability Score for upper limbs at the end of the cross-over period than at the baseline of the cross-over period. The cross-over design was analysed by McNemar's test on the discordant pairs, i.e. those subjects who deteriorated in one, but not in the other cross-over period.` Secondary Endpoints` The following hypothesis tests were performed for the secondary efficacy endpoints with ANOVA/McNemar's test for continuous/binary variables as described for the primary endpoints analysis: 1. The proportion of subjects experiencing a decline of at least 30% in grip strength in the more affected hand (binary variable, McNemar's test)`` 2. <u>The proportion of subjects being accelerated forward into the next stabilisation</u>

Table 6. Summary of efficacy for trial 160604

	phase (binary variable, McNemar's test) 3. Grip strength of the less affected hand (ANOVA) 4. The overall disability sum score (continuous variable, ANOVA): total score ranging from 0 ("no signs of disability") to 12 ("most sever disability") 5. The time on peg board test (continuous variable, ANOVA): the mean of the two trials for the a. dominant hand b. non-dominant hand 6. The patient assessment on VAS (continuous variable, ANOVA) The null hypotheses of no treatment effect was to be tested against the one-sided alternative hypotheses of superiority of IGIV, 10% at the 2.5% level of statistical significance in the a priori order given above. The fixed testing sequence procedure was to continue as long as the null hypotheses could be rejected. All these hypotheses could be rejected simultaneously with a familywise type I error of 2.5% one-sided. For other hypotheses, i.e. those after the first null hypothesis could not be rejected, a low p-value would provide supportive, but not confirmatory evidence of a treatment effect.

2.5.5.3. Clinical studies in special populations

Not applicable.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

In the post-hoc analysis of studies 160001 and 160101, the infection rate was summarised over the set of subjects by median and 95% CI for the median. Intervals when subjects received intravenous/oral antibiotics were not excluded from the time on IVIg prophylaxis (which was the case in the analysis of Study 160001).

In study 160001, efficacy in terms of infections was an endpoint and therefore data on infections as reported in CSR 160001 were used for this additional post-hoc analysis if start and stop dates were available for these infections. In study 160101 efficacy endpoints included serious bacterial infections and other validated bacterial infections commonly occurring in PID patients. These infections were included in the combined analysis together with all other infections that could unequivocally be identified as such from among the reported AEs by the Medical Director and for which start and stop dates were available. A total of 26 infections in the 2 studies could not be included in the analysis because no start/stop dates were recorded. Occasional variances in the results between the cross-analysis and the CSRs for clinical studies 160001 and 160101 are due to these slight differences in the definitions that were required to apply consistent data handling rules for both studies.

No serious infections occurred in clinical studies 160001 and 160101 during prophylaxis with IVIg, 10%. All non-serious infections were of mild or moderate severity. While in Study 160001 the median infection rate per month for mild infections was 0.30 (95% CI 0.16 to 0.47), no mild infections were reported in Study 160101. The median infection rate per month for moderate infections was 0.16

(95% CI 0.00 to 0.16) and 0.08 (95% CI 0.00 to 0.08) for study 160001 and study 160101, respectively. The total median infection rates per month in clinical studies 160001 and 160101 were 0.47 and 0.16, respectively. Median rates for both mild and moderate infections were lower in study 160101 compared to study 160001. No severe infections occurred in the 2 studies.

Efficacy parameters other than infection rate per month were not evaluated in the combined analysis of clinical studies 160001 and 160101 as no other comparable efficacy parameters were calculated in the 2 studies.

2.5.5.6. Supportive study

Not applicable.

2.5.6. Discussion on clinical efficacy

In the MAA for Kiovig, clinical data from two studies in PID patients (study 160001 and 160101) and one study in ITP patients (study 160002) were evaluated for efficacy. No new clinical data on efficacy and safety have been provided. The results obtained from all three studies are in line with those reported in the literature and in other studies with other IVIg products. The studies were designed according to the recommendations of the relevant guidelines of the FDA and the EMA at the time they were carried out.

In the PID patients, the total median non-serious infection rates per month over all subjects were of 0.48 (95% CI 0.32 to 0.63) in study 160001, and 0.16 (95% CI 0.08 to 0.23) in study 160101. As no acute serious bacterial infections occurred during the studies (rate: 0.00), the number of serious bacterial infections per patient per year was less than 1.0 per person per year as recommended in relevant guidelines.

Efficacy was also demonstrated in adult ITP patients. 71.4% of ITP patients in the ITT population responded to treatment with Kiovig, as evidenced by the restoration of platelet counts to levels above 50 x 10^9/L at least once prior to Day 15 from onset of the treatment course and who did not require a booster dose prior to Day 15.

Furthermore, Kiovig was shown to improve muscle strength in the upper limbs (grip strength) and reduce the patient-based assessments of disability in patients with MMN. The mean difference in grip strength in the more affected hand was 34.13% (95% CI: 7.35, 60.91) for both treatment sequences. As determined by GNDS scores for the upper limb, 35.7% of subjects worsened during placebo treatment but 10% did not during IVIg treatment, while the opposite was true for 11.9% of subjects (p=0.021). The importance of efficacy was further underlined by the need to switch to open-label Kiovig due to unacceptable deterioration during double-blind placebo infusions in 69% of patients.

Therefore, it was concluded that Kiovig is effective for the treatment of PID and ITP and thus extrapolation to other established indications of the core SmPC (SID, CIDP, GBS and Kawasaki Disease) was granted in line with the relevant EMA guidance (EMA/CHMP/BPWP/94033/2007).

Only limited efficacy data for paediatric PID patients are available, as only study 160101 included paediatric patients. This is in contrast to the current IVIg guideline (EMA/CHMP/BPWP/344788/2020 rev 4) that recommends the inclusion of at least 20 children and adolescents with an age distribution representative of this patient population. However, no differences in efficacy between paediatric and adult patients are expected based on the data available and based on real-world knowledge of IVIg treatment in paediatric patients. Overall, extrapolation to the paediatric population is justified and the paediatric indication is adequately reflected in the SmPC.

The PID and ITP studies did not evaluate long-term efficacy, and the IgG levels required to achieve and maintain response are currently unknown. Nevertheless, given that IVIg treatment is an established treatment for patients with primary immunodeficiency and ITP and that Kiovig has been available for several years, there is no reason to question the efficacy of the treatment in this context.

Overall, Kiovig provides comparable efficacy to IVIg products in the treatment of immunodeficiency syndromes and immunomodulatory indications, despite differences in manufacturing, excipients and IgG subclass composition. As discussed in the clinical pharmacology section, the lower IgG4 content of TAK-880 compared to Kiovig will not have a clinically relevant effect on efficacy in the intended indications. This is supported by in vivo data in a model of ITP showing comparable efficacy of Kiovig and Deqsiga. Therefore, it is considered that Deqsiga is likely to have comparable efficacy to Kiovig.

Upon CHMP request, the MAH has updated the indication to remove the cross-reference to section 4.4, in line with the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg).

2.5.7. Conclusions on the clinical efficacy

The efficacy of Kiovig in the proposed indications is in line with those reported in the literature and in other studies with other IVIg products. The demonstrated efficacy of Kiovig is expected to be the same for Deqsiga in the proposed indications, the reduced IgA and IgG4 content is not expected to have a clinically relevant effect on the efficacy of the product.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Table 7. Patient exposure

Trial ID	# Subjects by Arm; Entered/ Completed	Duration	Total number of Infusions with Kiovig	Frequency of Dosing
PID 160001	24 enrolled / 22 exposed	Approx. 9 months	194	Q3W mean dose per infusion 0.41 g/kg
ITP 160002	28 enrolled / 23 exposed	Approx. 4-6 weeks	81 (9 booster)	2 g/kg BW (on 2 to 5 days) Mean booster dose 0.85g/kg
PID 160101	61 enrolled and exposed	Minimum 12 months	826	300 – 600 mg/kg BW Q3W or Q4W Mean dose per infusion 0.471 g/kg
MMN 160604	44 exposed	Approx. 15 months per subject		0.4 to 2.0 g/kg BW Q2W/Q3W/Q4W median monthly dose 1.2 g/kg BW
AD 160701	702 enrolled / 390 treated and analysed (383 in the safety dataset)	70 weeks (36 infusions)	7837	200 or 400 mg/kg BW Q2W

2.5.8.2. Adverse events

PID and ITP studies 160101, 160001 and 160002

A total of 1011 AEs were reported in Studies 160101, 160001 and 160002, 313 (31%) of which were judged to be related to the study product.

In Study 160001, 14/106 non-serious AEs in 7 (N=22) subjects were judged to be possibly or probably related to study drug. Of the 803 non-serious AEs reported in Study 160101, 258 in 40 (N=61) subjects were judged to be possibly or probably related to administration of Kiovig. In Study 160002, 40/83 non-serious AEs in 13 (N=23) subjects were judged to be possibly or probably related to study drug. Of all unrelated AEs reported, 680 were non-serious and 18 were serious.

Headache was one of the most frequently reported drug-related AEs. The other related AEs that were reported in Studies 160001, 160101 and 160002 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, diarrhoea, and cough occurred in a few cases in that study.

MMN study 160604

In MMN Study 160604, 100/317 (31.5%) non-serious AEs were considered to be related to the study product. The majority of related non-serious AEs (69/100) were mild, 20 were moderate and 11 were severe.

Over the entire study, headache and muscular weakness were the only AEs considered to be related to a study product that were reported in ≥5% of subjects. Headache considered to be related to the study product occurred in 25.0% (11/44) of subjects at a rate of 2.1% of infusions with IGIV, 10% and in 4.7% (2/43) of subjects at a rate of 2.3 % of infusions with placebo. Muscular weakness considered to be related to a study product occurred in 6.8% (3/44) of subjects in 0.4 % of infusions with IGIV, 10% and in 2.3% (1/43) of subjects in 0.8% of infusions with placebo.

Alzheimer's disease study 160701

There were 876 product-related non-serious AEs in 217/383 (56.7%) subjects and 16 product-related SAEs in 13/383 (3.4%) subjects. A greater percentage of subjects treated with Kiovig experienced non-serious product related AEs compared to placebo: 307 non-serious AEs in 81/127 (63.8%) subjects in the 400 mg/kg treatment group, 372 non-serious AEs in 82/135 (60.7%) subjects in the 200 mg/kg treatment group, and 197 non-serious AEs in 54/121 (44.6%) subjects in the combined placebo group.

The highest percentage of subjects experienced a product-related non-serious AE of the SOC category "Nervous System Disorders". Within this category, the most common preferred term is "headache", with 18/127 (14.2%) subjects in the 400 mg/dose group, 25/135 (18.5%) subjects in the 200 mg/kg dose group, and 13/121 (10.7%) subjects in the combined placebo group experiencing a product-related AE of headache.

Integrated summary of ADRs

Frequency of adverse reactions from 11 clinical studies with IGI, 10% administered IV (including studies in which IGI, 10% was administered as a comparator) is summarised in **Table 8**. These comprise 6 PIDD trials (Studies 160101 – Church et al., 2005, 160001 – Björkander et al., 2006, 160601 Epoch 1 – Wasserman et al., 2011, 160602 – Misbah et al., 2009, 160603 Epoch 1 – Wasserman et al., 2012 and 160902 – Wasserman et al., 2016), 1 ITP trial (Study 160002 – Varga et al., 2006), 1 MMN trial (Study 160604 – Hahn et al., 2012) and 3 AD trials (Studies 160701 – Gelmont et al., 2016, 161003 and 161202).

Table 8. ADRs in clinical trials across all indications [N=687] (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202)

System Organ Class	Preferred MedDRA Term (Version 17.0)	Rate[a] per 100 Infusions (N=12,530)	Frequency Category	By Subject % (N=687)	Frequency Category
INFECTIONS AND INFESTATIONS	**Aseptic meningitis**	0.02	Rare	0.1	Uncommon
BLOOD AND LYMPHATIC DISORDERS	**Anaemia**	0.14	Uncommon	2.3	Common
	Lymphadenopathy	0.08	Rare	1.3	Common
IMMUNE SYSTEM DISORDERS	**Hypersensitivity**	0.03	Rare	0.6	Uncommon
	Anaphylactic reaction	0.02	Rare	0.3	Uncommon
METABOLISM AND NUTRITION DISORDERS	**Decreased appetite**	0.15	Uncommon	1.7	Common
PSYCHIATRIC DISORDERS	**Anxiety**	0..31	Uncommon	4.8	Common
	Insomnia	0.18	Uncommon	2.9	Common
NERVOUS SYSTEM DISORDER	**Headache**	4.21	Common	28.8	Very Common
	Dizziness	0.51	Uncommon	7.6	Common
	Migraine	0.25	Uncommon	1.7	Common
	Paraesthesia	0.07	Rare	1.2	Common
	Dysgeusia	0.04	Rare	0.4	Uncommon
	Balance disorder	0.03	Rare	0.4	Uncommon
	Dysarthria	0.01	Very Rare	0.1	Uncommon
	Amnesia	0.01	Very Rare	0.1	Uncommon
EYE DISORDERS	**Conjunctivitis**	0.07	Rare	1.3	Common
	Eye swelling	0.02	Rare	0.3	Uncommon
	Eye pain	0.02	Rare	0.1	Uncommon
EAR AND LABYRINTH DISORDERS	**Vertigo**	0.05	Rare	0.7	Uncommon
CARDIAC DISORDERS	**Tachycardia (including sinus tachycardia)**	0.10	Uncommon	1.7	Common
VASCULAR DISORDERS	**Hypertension (including blood pressure increased)**	1.85	Common	12.5	Very Common
	Flushing (including Hot Flush)	0.23	Uncommon	2.5	Common
	Phlebitis	0.03	Rare	0.6	Uncommon
	Peripheral coldness	0.02	Rare	0.4	Uncommon
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**Cough**	0.49	Uncommon	7.0	Common
	Nasal congestion	0.20	Uncommon	2.9	Common
	Rhinorrhoea	0.17	Uncommon	2.5	Common
	Oropharyngeal pain	0.15	Uncommon	2.3	Common
	Dyspnoea	0.08	Rare	1.5	Common
	Pulmonary embolism	0.02	Rare	0.4	Uncommon

Table 8. ADRs in clinical trials across all indications [N=687] (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202)

System Organ Class	Preferred MedDRA Term (Version 17.0)	Rate[a] per 100 Infusions (N=12,530)	Frequency Category	By Subject % (N=687)	Frequency Category
	Oropharyngeal swelling	0.15	Very rare	0.1	Uncommon
GASTROINTESTINAL DISORDERS	**Nausea**	1.13	Common	10.2	Very Common
	Diarrhoea	0.69	Uncommon	9.5	Common
	Vomiting	0.61	Uncommon	7.7	Common
GASTROINTESTINAL DISORDERS	**Abdominal pain (including abdominal pain upper, lower and tenderness)**	0.26	Uncommon	4.1	Common
	Dyspepsia	0.10	Rare	1.3	Common
	Abdominal distension	0.05	Rare	0.9	Uncommon
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**Rash (including erythematous, pruritic, maculo-papular, papular)**	0.92	Uncommon	11.8	Very Common
	Contusion	0.35	Uncommon	5.2	Common
	Urticaria	0.21	Uncommon	2.5	Common
	Pruritus	0.22	Uncommon	2.5	Common
	Dermatitis	0.07	Rare	1.2	Common
	Erythema	0.06	Rare	1.0	Common
	Night sweats	0.03	Rare	0.6	Uncommon
	Photosensitivity reaction	0.02	Rare	0.1	Uncommon
	Cold sweat	0.02	Rare	0.3	Uncommon
	Angioedema	0.01	Very Rare	0.1	Uncommon
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**Back pain**	0.54	Uncommon	7.7	Common
	Arthralgia	0.43	Uncommon	5.5	Common
	Pain in extremity	0.44	Uncommon	6.1	Common
	Muscle spasms	0.28	Uncommon	3.6	Common
	Myalgia	0.24	Uncommon	3.1	Common
	Muscular weakness	0.13	Uncommon	1.7	Common
	Muscle twitching	0.01	Very Rare	0.1	Uncommon
RENAL AND URINARY DISORDERS	**Proteinuria**	0.02	Rare	0.3	Uncommon
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		0.97	Uncommon	13.1	Very Common
		0.57	Uncommon	7.9	Common
		0.13	Uncommon	1.9	Common
		0.06	Rare	1.0	Common

Table 8. ADRs in clinical trials across all indications [N=687] (Studies 160001, 160002, 160101, 160601 Epoch 1, 160602, 160603 Epoch 1, 160604, 160902, 160701, 161003, 161202)

System Organ Class	Preferred MedDRA Term (Version 17.0)	Rate[a] per 100 Infusions (N=12,530)	Frequency Category	By Subject % (N=687)	Frequency Category
	Local reactions • Infusion site extravasation • Infusion site pain (including discomfort) • Infusion site swelling (including local swelling, local oedema) • Infusion site pruritus	0.01	Very Rare	0.1	Uncommon
	Fatigue (including Lethargy)	1.14	Common	11.1	Very Common
	Pyrexia (including Body temperature increased)	0.77	Uncommon	10.0	Very Common
	Chills	0.71	Uncommon	7.4	Common
	Oedema (including peripheral, Swelling)	0.26	Uncommon	4.1	Common
	Influenza like illness	0.16	Uncommon	1.9	Common
	Malaise	0.14	Uncommon	1.5	Common
	Chest discomfort	0.07	Rare	1.3	Common
	Chest tightness	0.04	Rare	0.3	Uncommon
	Feeling hot	0.02	Rare	0.3	Uncommon
	Burning sensation	0.01	Rare	0.1	Uncommon
INVESTIGATIONS	**Blood urea increased**	0.03	Rare	0.6	Uncommon
	White blood cell count decreased	0.03	Rare	0.6	Uncommon
	Alanine aminotransferase increased	0.02	Rare	0.4	Uncommon
	Haematocrit decreased	0.02	Rare	0.4	Uncommon
	Red blood cell count decreased	0.02	Rare	0.4	Uncommon
	Blood creatinine increased	0.02	Rare	0.3	Uncommon
	Respiratory rate increased	0.01	Very Rare	0.1	Uncommon

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

[a] Number of AEs divided by the total number of infusions multiplied by 100.
Source: PBRER for Human Normal Immunoglobulin (Human Normal Immunoglobulin, reporting period 01 Jun 2021 to 31 May 2022, Table 1

2.5.8.3. Serious adverse event/deaths/other significant events

Other Serious Adverse Events

Study 160001: 3 SAEs unrelated to Kiovig (autoimmune hepatitis, diffuse large B-cell lymphoma, febrile respiratory tract infection)

Study 160101: 15 SAEs in 8 subjects were reported, of which only 1 SAE possibly related (aseptic meningitis)

Study 160002: 1 SAE unrelated to Kiovig (hematoma in the right thigh and petechiae)

Study 160604: 2 SAEs of which 1 SAE related to Kiovig (pulmonary embolism)

Study 160701: 21, 32 and 26 subjects with SAEs in the 400 mg/kg arm, 200 mg/kg arm, and combined placebo arm, respectively; of which 2 and 7 SAEs related to Kiovig in the 400 mg/kg arm and 200 mg/kg arm (myocardial infarction, vasogenic cerebral oedema, anaphylactic reaction, blood pressure increased, haemoglobin decreased, cerebral haemorrhage, partial seizures, mental status changes, pulmonary embolism)

Deaths

No deaths occurred in studies 160001, 160101, 160002 and 160604.

In study 160701, there were 6 deaths in subjects receiving study product (4 of whom received Kiovig) and 1 death that occurred during the screening period prior to study product administration. In the 400 mg/kg IGIV, 10% arm, one subject died of *cardiac failure congestive* possibly related to Kiovig administration. In the 200 mg/kg IGIV, 10% arm, one subject developed a possibly related *cerebral haemorrhage* and two subjects died of *multi-organ failure* (one considered unrelated, the other unlikely related).

Other Significant Adverse Events

Study 160001

No other significant AEs occurred in the course of study 160001.

Study 160101

A total of 31 of the non-serious AEs deemed related to study product were considered not expected, based on previous experience with IGIV products. These 31 events included 12 infections or infestations, 6 respiratory disorders, 6 investigations (i.e., out-of-range laboratory values), and 7 other types of events (lymphadenopathy, conjunctivitis, and fluid in the middle ear, 2 episodes of muscle spasms, dysarthria, and amnesia). In virtually every case, these non-serious AEs that were deemed related and unexpected were either consistent with the subject's specific type of immunodeficiency or with the subject's medical history prior to entering the study.

Study 160002

Two non-serious AEs (2 instances of insomnia, mild and moderate, recovered) in one subject possibly related to the study product that were unexpected.

Study 160604

No other significant adverse events were reported in Study 160604.

Study 160701

One event of vasogenic cerebral oedema (IGIV 400 mg/kg, possibly related, resolved, discontinued study infusions)

One event of anaphylaxis (IGIV 200 mg/kg, serious and possibly associated, recovered but discontinued from the study)

2.5.8.4. Laboratory findings

Coombs test

No Coombs' test was performed during studies 160101, 160604 and 160701.

In study 160001, six results for direct Coombs' tests were positive in four subjects.

In study 160002, three of 23 subjects were positive in the direct Coombs' test after initiation of the treatment course with the study drug.

Blood Count and Serum Chemistry

A number of clinically significant laboratory parameters were reported in studies 160001, 160101 and 160002. The results were usually explained by the investigators as a consequence of ongoing infections or other observed or underlying clinical conditions. Therefore, the review of haematology and clinical chemistry parameters in studies 160001, 160101 and 160002 did not reveal any safety concerns. The results of the clinical laboratory assessments and physical findings in study 160604 also did not raise any safety concerns.

Study 160701: The number of subjects experiencing a notable decrease in haemoglobin (>1.5 g/dL) between 2 consecutive visits was greater in the Kiovig treatment groups: there were 31 (24.4%), 24 (17.8%), and 16 (13.2%) subjects with a >1.5 g/dL decrease in haemoglobin in the 400 mg/kg arm, 200 mg/kg arm, and combined placebo arm, respectively. The mechanism for decrease in haemoglobin in the Kiovig treatment groups could not be identified.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

It is well documented that specific side effects, such as thrombotic events, are more prevalent in elderly patients. These are addressed in the SmPC under 4.8.

Only limited safety data are available from the paediatric population.

2.5.8.7. Immunological events

Not applicable.

2.5.8.8. Safety related to drug-drug interactions and other interactions

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella (Peter, 1994, Siber et al., 1993). After administration of the study product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs' test), reticulocyte count and haptoglobin.

Infusions of immunoglobulin products may lead to false positive readings in assays that depend on detection of ß-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

2.5.8.9. Discontinuation due to adverse events

Study 160001: No discontinuations due to drug-related AEs.

Study 160101: One subject withdrew from the study during the optional post-efficacy period due to an AE (pruritic papular rash) which was considered possibly related to the use of the study product. This subject was treated for 9 months with study product prior to experiencing a pruritic papular rash which remained unchanged for 3 subsequent infusions.

Study 160002: No discontinuations due to drug-related AEs.

Study 160604: Two subjects discontinued due to an AE that was considered to be related to IGIV, 10%: One subject was discontinued during Stabilisation Phase 1 due to moderate muscular weakness and the other subject during Cross-over Period 2 due to a moderate decrease in joint range of motion.

Study 160701: There were 81 subjects who discontinued the study early, with 26 subjects discontinuing as the result of an AE.

2.5.8.10. Post marketing experience

The estimated number of patients exposed to IGIV, 10% during the most recent safety reporting period, i.e., from 2022 June 1 through 2023 May 31, was approximately 87,887 patient years and a total of 42,185,703 g were sold during this period. In addition, as of 2023 May 31, a cumulative total of at least 1,164 unique subjects have been administered IGIV, 10% in MAH sponsored interventional studies. No new safety signal was identified with regard to IGIV, 10% during this reporting period.

Since the international birth date (IBD) of IGIV, 10% (27 April 2025), a total of 7,355 AR reports from post-marketing sources have been received relating to Kiovig/GAMMAGARD LIQUID. In the most recent reporting period (2022 June 1 – 2023 May 31), a total of 469 AR reports from post-marketing sources were received for Kiovig/GAMMAGARD LIQUID.

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These adverse reactions are listed by System Order Class (SOC), then by Preferred MedDRA (Version 17.0) term in order of severity and included in section 4.8 of the SmPC under the frequency not known.

Intravenous administration:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Haemolysis

IMMUNE SYSTEM DISORDERS: Anaphylactic shock

NERVOUS SYSTEM DISORDERS: Cerebral vascular accident, Transient ischemic attack, Tremor

CARDIAC DISORDERS: Myocardial infarction

VASCULAR DISORDERS: Deep vein thrombosis, Hypotension

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Pulmonary oedema.

INVESTIGATIONS: Coombs direct test positive, oxygen saturation decreased

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: Transfusion-related acute lung injury

2.5.9. Discussion on clinical safety

The safety profile of Kiovig is consistent with the known safety profile of a typical IVIg. No new safety issues arise from these data. Adverse events are mostly mild to moderate in severity, transient, non-serious and non-severe. The most common related adverse events are in keeping with other IVIg (headache, pyrexia, fatigue, nausea, hypertension, local reactions).

Reported product-related serious adverse events are known adverse reactions of IVIg. Warnings on hypersensitivity, thromboembolic events, acute kidney disease and aseptic meningitis are adequately implemented in section 4.4 of the SmPC.

During the procedure, the applicant was requested to update section 4.8 to follow the guideline on core SmPC for human normal immunoglobulin for IVIg (EMA/CHMP/BPWP/94038/2007 Rev. 6). Sufficient justification has been provided for the removal or inclusion of ADRs in the SmPC.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

In addition, as Deqsiga contains lower levels of IgA, a better tolerability in IgA-sensitive patients may be expected, therefore a warning regarding hypersensitivity and the level of IgA has been included in section 4.4 of the SmPC of Deqsiga as follows: *Deqsiga has a very low IgA content (not more than 2 micrograms/mL). Preparations depleted of IgA were shown to be better tolerated by some patients who reacted to IVIg preparations with higher IgA concentrations. However, the threshold IgA concentration to which the patients would be sensitive, is not clear.*

Assessment of paediatric data on clinical safety

The paediatric safety profile comprised of 75 paediatric patients (n=39 children aged 0 – 12 years; n=36 adolescents 12 – 18 years) enrolled in 4 clinical studies. Paediatric patients demonstrated higher rates of infusion-related AEs compared to adults, which was attributed by the applicant to the consequence of higher sensitivity of children to needle insertion and pain, and conservative reporting of AEs in this population. No issues arise from these data.

Overall, it is concluded that the safety profile in paediatric patients is comparable to that in adult patients. Based on the similarity of Kiovig and Deqsiga, extrapolation to the paediatric population can be granted.

Based on non-clinical data, Deqsiga was comparable to Kiovig with regard to anaphylactoid potential in animals and hypersensitivity in human blood *in vitro*. No further conclusion on the safety of Deqsiga

can be drawn at this stage due to the lack of clinical data with Deqsiga. However, the reduced IgA and IgG4 content is not expected to have a clinically relevant effect on the safety of the product, as discussed above.

2.5.10. Conclusions on the clinical safety

The safety profile of Kiovig is similar to other IVIg products. The lower IgG4 and IgA content of Deqsiga compared to Kiovig is not expected to have a clinically relevant effect on safety. Therefore, it is concluded that the safety profile of Deqsiga is comparable to Kiovig.

2.6. Risk Management Plan

2.6.1. Safety concerns

Table 9. Summary of safety concerns

Important Identified Risks	Hypersensitivity
	Haemolysis
	Thromboembolic events (TEEs)
Important Potential Risks	Transmittable infectious agents
Missing Information	Lack of information in pregnant and lactating women

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 10. Risk minimisation measures

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Hypersensitivity	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity (Allergy) questionnaire **Additional pharmacovigilance activities:** None
Haemolysis	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation activities	Pharmacovigilance activities
	None	None
TEEs	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TEE questionnaire **Additional pharmacovigilance activities:** None
Transmittable infectious agents	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Lack of information in pregnant and lactating women	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Deqsiga (Human normal immunoglobulin) is included in the additional monitoring list as it is a biological medicinal product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Deqsiga is intended for:

Replacement therapy in adults, and children and adolescents (0 to 18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, and children and adolescents (0 to 18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease (in conjunction with acetylsalicylic acid; see section 4.2).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

3.1.2. Available therapies and unmet medical need

There is a subset of immunoglobulin-treated patients who may react to immunoglobulins containing higher levels of immunoglobulin A (IgA). All IVIg preparations carry the risk of inducing an anaphylactic reaction in IgA-sensitive patients. It has been suggested that there may be a threshold phenomenon leading to products containing less IgA being better tolerated. This threshold phenomenon is, however, not well documented.

Patients with IgA deficiency who are hypersensitive to IVIG products have been treated with IVIg preparations containing very low IgA levels; this is the only treatment option for many of these patients.

To provide a treatment option for this small subset of patients, the applicant has developed TAK-880 based on a variant of Kiovig manufacturing process. Due to modifications in the manufacturing process, TAK-880 contains low levels of IgA, similar to IgA levels in GAMMAGARD S/D.

3.1.3. Main clinical studies

Due to the comparability of TAK-880 and Kiovig supported by additional in vivo nonclinical safety data, extensive biochemical characterisation and comprehensive comparability approach, the applicant considered that the clinical safety and efficacy of TAK-880 was adequately supported by the already

available clinical data for Kiovig. Accordingly, no additional clinical studies were conducted to support the MAA for TAK-880.

Clinical data from 5 studies with Kiovig have been submitted:

- two uncontrolled studies in subjects with PID (studies 160101 (n=22) and 160001 (n=61))
- one open-label, uncontrolled study in adult subjects with ITP (Study 160002, n=23)
- one double-blind, placebo-controlled study in subjects with MMN (Study 160604, n=44)
- one double-blind, placebo-controlled study in subjects with Alzheimer's Disease (Study 160701, n=383).

3.2. Favourable effects

Data from studies 160001 and 160101 demonstrated that the Kiovig doses administered to PID patients were adequate to maintain protective IgG trough levels above the recommended 6 g/L. The total median non-serious infection rates per month over all subjects were of 0.48 (95% CI 0.32 to 0.63) in study 160001, and 0.16 (95% CI 0.08 to 0.23) in study 160101. As no acute serious bacterial infections occurred during the studies (rate: 0.00), the number of serious bacterial infections per patient per year was less than 1.0 per person per year as recommended in relevant guidelines.

Efficacy was also demonstrated in adult ITP patients. 71.4% of ITP patients in the ITT population responded to treatment with Kiovig, as evidenced by the restoration of platelet counts to levels above 50 x 10^9/L at least once prior to Day 15 from onset of the treatment course and who did not require a booster dose prior to Day 15.

Furthermore, Kiovig was shown to improve muscle strength in the upper limbs (grip strength) and reduce the patient-based assessments of disability in patients with MMN. The mean difference in grip strength in the more affected hand was 34.13% (95% CI: 7.35, 60.91) for both treatment sequences. As determined by GNDS scores for the upper limb, 35.7% of subjects worsened during placebo treatment but 10% did not during IVIg treatment, while the opposite was true for 11.9% of subjects (p=0.021). The importance of efficacy was further underlined by the need to switch to open-label Kiovig due to unacceptable deterioration during double-blind placebo infusions in 69% of patients.

As efficacy has been demonstrated for the treatment of PID and ITP, in line with the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg), extrapolation to other established indications for IVIg was granted: SID, CIDP, GBS and Kawasaki Disease.

The demonstrated efficacy of Kiovig is expected to be the same for Deqsiga in the proposed indications, the reduced IgA and IgG4 content is not expected to have a clinically relevant effect on the efficacy of the product.

3.3. Uncertainties and limitations about favourable effects

Due to the comparability of Deqsiga and Kiovig supported by in vivo data in a model of ITP showing comparable efficacy, it is agreed that the clinical efficacy of TAK-880 is supported by the clinical data for Kiovig. Lower IgA content of Deqsiga compared to Kiovig is not expected to impact its efficacy.

In addition, Deqsiga has a reduced content in IgG4 compared to Kiovig. The applicant provided a comprehensive discussion of the impact of the reduced level of IgG4 and the potential effects in an immunomodulation setting. In addition, non-clinical studies have been performed which indicate that

reduced levels of IgG4 do not influence the IVIg immunomodulating effect. Further, the worldwide experience with IVIg with low IgG4 content is growing and does not indicate any influence on the immunomodulating effect, so far. Overall, it is agreed that the low levels of IgG4 in Deqsiga are unlikely to affect the efficacy of Deqsiga, despite that no new clinical studies have been provided by the applicant.

3.4. Unfavourable effects

The safety profile of Deqsiga is based on results from clinical trials with Kiovig, as no new clinical studies were performed with Deqsiga.

The safety profile of Kiovig is consistent with the known safety profile of a typical IVIg. Adverse events are mostly mild to moderate in severity, transient, non-serious and non-severe. The most common related adverse events observed in the clinical trials with Kiovig are in keeping with other IVIg (headache, pyrexia, fatigue, nausea, hypertension, rashes, local reactions). Only very few product-related serious adverse events were reported, of which all are known adverse reactions of IVIg (e.g. hypersensitivity, thromboembolic events, acute kidney disease and aseptic meningitis). These are adequately reflected in the SmPC.

Kiovig has been marketed in Europe since 2006, and spontaneous post-marketing reports do not give rise to any safety concerns. Non-clinical evaluation of the potential for hypersensitivity suggests that it is comparable between Deqsiga and Kiovig.

3.5. Uncertainties and limitations about unfavourable effects

Data in the paediatric and elderly population with Kiovig are limited but do not indicate any safety issues. Overall, the safety profile in paediatric and elderly patients is considered comparable to that in adult patients.

The safety profile is based on results from clinical trials with Kiovig. However, based on non-clinical data, Deqsiga was comparable to Kiovig with regard to anaphylactoid potential in animals and hypersensitivity in human blood in vitro.

Due to the reduced IgA levels in Deqsiga, better tolerability in IgA-sensitive patients may be expected, therefore relevant information regarding hypersensitivity and the level of IgA has been included in section 4.4 of the SmPC of Deqsiga.

The lower IgG4 content of Deqsiga compared to Kiovig has not been studied in clinical trials, however it is not expected to have a clinically relevant effect on safety. Overall, it is expected that the safety profile of Deqsiga is comparable to Kiovig and other commercially available IVIg products.

3.6. Effects Table

Table 11. Effects table for Kiovig

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Serious bacterial infections	Infection rate per month	n	0.00 (95% CI 0.00; 0.00)	-	Uncontrolled study	Study 160001
			0.00 (95% CI 0.00; 0.00)	-	Uncontrolled study	Study 160101
Non-serious infections	Infection rate per month	n	0.48 (95% CI 0.32; 0.63)	-	Uncontrolled study	Study 160001
			0.16 (95% CI 0.08; 0.23)	-	Uncontrolled study	Study 160101
Treatment response	subjects who i) had a platelet increase to ≥50 x 10^9/L at least once prior to Day 15 and ii) did not require a booster dose prior to Day 15*	n (%)	15/21 (71.4% 95% CI 50.0; 86.2)	-	Uncontrolled study	Study 160002
Treatment response	Improvement of muscle/ grip strength in MMN pt.	Mean difference (95% CI)	34.13% (7.35; 60.91)	Internal	Randomised, double-blinded, cross-over study	Study 160604
Unfavourable Effects						
Aseptic meningitis	Incidence per subjects (Rate per 100 infusions)	%	0.1% (0.02)	-	N=687 (11 clinical studies)	ADR in clinical trial across all indications
Anaphylactic reaction	Incidence per subjects (Rate per 100 infusions)	%	0.3% (0.02)	-	N=687 (11 clinical studies)	ADR in clinical trial across all indications
Hypersensitivity	Incidence per subjects (Rate per 100 infusions)	%	0.6% (0.03)	-	N=687 (11 clinical studies)	ADR in clinical trial across all indications

Notes: * Day 15 referred to the fifteenth day from initiation of treatment (Day 1).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

IVIg treatment is an established standard of care treatment in the intended indications (primary/secondary immunodeficiency, immunomodulation). The IgG trough levels are the main PK parameter of clinical relevance in PID patients, as it has been shown that falling below the critical IgG threshold of 5-6 g/L can lead to increases in serious bacterial infections. Treatment response in ITP patients as defined by the restoration of platelet levels reduces life-threatening complications due to excessive/spontaneous bleeding. For patients with MMN, increased hand grip strength results in reduced disability and thus increased quality of life. Dosing may need to be adjusted or repeated according to the individual clinical response.

The safety profile of IVIg is well known and does not vary significantly from one product to another. Adverse events associated with IVIg are typically mild and transient, and may be alleviated by reducing the infusion rate. The incidence of adverse events during maintenance treatment is usually lower than during induction treatment. Only rarely serious adverse events occur with IVIg. No new safety concerns are expected for Deqsiga due to the high similarity between Deqsiga and Kiovig and the similar manufacturing process. However, the lower levels of IgG4 in Deqsiga compared to Kiovig represent an uncertainty. Nevertheless, given the wide experience with IVIg treatment it is most likely to be minor.

In addition, as Deqsiga contains lower levels of immunoglobulin A (IgA), it may be more suitable for people with IgA deficiency who have a higher risk of hypersensitivity to immunoglobulin products that contain higher levels of IgA. These patients are treated with good tolerability with an IVIg product with very low IgA concentrations that are comparable to those in Deqsiga.

3.7.2. Balance of benefits and risks

The beneficial effects of reducing serious bacterial and other infections in patients with primary and secondary immunodeficiency, reducing the risk of bleeding by restoring platelet levels in patients with ITP, and reducing disability/disease symptoms and slowing deterioration in patients with autoimmune diseases (MMN, CIDP, GBS) outweigh the risks (mainly mild and transient AEs) associated with administration of Deqsiga.

3.7.3. Additional considerations on the benefit-risk balance

None.

3.8. Conclusions

The overall benefit/risk balance of Deqsiga is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Deqsiga is not similar to Strimvelis within the meaning of

Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Deqsiga is favourable in the following indication(s):

Replacement therapy in adults, children and adolescents (0 to 18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production.
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of < 4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Immunomodulation in adults, children and adolescents (0 to 18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease (in conjunction with acetylsalicylic acid; see section 4.2).
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Official batch release

In accordance with Article 114 Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.