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Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)

Draft

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This guideline replaces Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) (EMA/CHMP/BPWP/410415/2011 rev 1).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)

Table of contents

Executive summary

This guideline describes the information to be documented when an application is made for a marketing authorisation for a human normal immunoglobulin for subcutaneous and/or intramuscular use (SCIg/IMIg). The guidance covers clinical trials and patient follow-up.

This is the second revision of the Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg). It replaces version 1 and updates the guideline to be consistent where applicable with the revised guideline for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 current version). It clarifies the indication wording of secondary immunodeficiencies (SID) and includes the indication for maintenance treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

1. Introduction (background)

The purpose of this guideline is to provide applicants and regulators with harmonised guidance for applications for marketing authorisation for SCIg/IMIg.

The first use of polyvalent immunoglobulin preparations was applied as replacement therapy in humoral immunodeficiency situations. As human normal immunoglobulin for subcutaneous and intramuscular use (SCIg/IMIg) is prepared from plasma collected from a high number of healthy blood and plasma donors, the idiotypic diversity expressed by the IgG is significant. Therefore, SCIg/IMIg recognise many bacterial, viral and other infectious agent antigens, and also a large number of self-antigens. SCIg/IMIg, as IVIg, have also a recognised immunomodulatory activity, and are therefore used in clinical practice for several diseases based on literature. However, the only currently authorised immunomodulatory indication for SCIgs, based on phase III clinical trials conducted with several SCIg products, is Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). The other immunomodulatory indications for IVIgs are not yet approvable for SCIgs as no clinical data are available.

Although IgG replacement therapy was initially administered intramuscularly, this route of administration can now be considered outdated for replacement therapy, with few exceptions, as the required doses to achieve adequate trough levels cannot be administered safely or without excessive and unnecessary discomfort for the patient.

2. Scope

This guideline describes the information to be documented when an application for a marketing authorisation for SCIg/IMIg is made, including biological data, pharmacokinetics, clinical trials and patient follow-up.

These data are required for:

1. products for which an application for a marketing authorisation is to be submitted, referred to as "new products" in the text and;

2. authorised products where a significant change in the manufacturing process has been made (e.g. additional viral inactivation/removal steps or new purification procedures).

This guideline covers normal human immunoglobulin for subcutaneous and/or intramuscular administration defined by the relevant European Pharmacopoeia monographs.

It does not apply to products intentionally prepared to contain fragmented or chemically modified IgG.

Quality aspects except relevant biological data are outside the scope of this guideline such as where a significant change in the manufacturing process has been made.

3. Legal basis and relevant guidelines

This Guideline should be read in conjunction with the introduction and general principles of Annex I to Directive 2001/83/EC, as amended, and all other relevant EU and ICH guidelines. These include, but are not limited to:

- Core SmPC for human normal immunoglobulin for subcutaneous and intramuscular use (EMA/CHMP/BPWP/143744/2011 current version).
- Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 current version).
- Guideline on plasma-derived medicinal products (EMA/CHMP/BWP/706271/2010).
- Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products (EMA/CHMP/BWP/360642/2010 current version).

4. Indications

Biological data, pharmacokinetic (PK) data and clinical evidence of efficacy and safety in primary and secondary humoral immunodeficiencies (PID, SID) are key elements required for the licensing of SCIg/IMIg. This guideline outlines the general principles for the design of clinical trials which support the following indication at the time of Marketing Authorisation.

Indications for subcutaneous use (SCIg)

SCIg can be used in all age ranges; however, potential safety issues for the excipients used for a particular product, limiting the use to defined age ranges, have to be evaluated.

Replacement therapy 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.

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

Immunomodulation in:

- chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as maintenance therapy after stabilisation with IVIg.

Indications for intramuscular use (IMIg)

Hepatitis A prophylaxis

If the SCIg/IMIg has a minimum antibody content for hepatitis A virus (HAV) of 100 IU/ml, it is also used in adults and children and adolescents (0-18 years) for:

- Pre-exposure prophylaxis, preferably in combination with vaccination, in unvaccinated individuals travelling in less than 2 weeks to areas at risk of hepatitis A.
- Post-exposure prophylaxis in unvaccinated individuals within 2 weeks of hepatitis A virus (HAV) exposure.

For long term hepatitis A prophylaxis, vaccination is recommended.

Other indications

In other indications, relevant clinical data are required, see 5.3.5.

5. Products for which an application for a marketing authorisation is to be submitted: "New products"

Biological and pharmacokinetic data are the key elements to evaluate activity and safety of SCIg preparations.

5.1. Biological data

Adequate documentation with regards to batch-to-batch consistency is provided in Module 3 of the dossier and should adhere to the Ph. Eur. Monograph 2788 requirements.

Additional specific data may be needed to support the pharmacodynamic and therapeutic activities as well as the safety profile of the SCIg preparation. The relevant data should be summarised in Module 5 of the dossier along with the cross-reference to Module 3.

For example immunomodulatory and anti-inflammatory activities for auto-immune diseases, depending on the claimed indications and the relevance of ***in vitro*** and/or ***in vivo*** models such as:

- Ability to inhibit auto-antibody activity ***in vitro*;**
- Experimental autoimmune models.

5.2. Pharmacokinetics

Pharmacokinetic (PK) data are essential to support the pharmacological activity and efficacy of the product, and may differentiate one product from another. Therefore, PK data must be provided in each application dossier (see PK study chart).

5.2.1. PK population

Pharmacokinetic data set can be derived from patients with primary immunodeficiency syndromes (PID) who are either already stabilised on SCIg treatment **(Group A)** or on IVIg treatment **(Group B)** or are naïve to Ig treatment **(Group C)** or the set can contain patients from the various groups. **Groups A - C**)

Group A and B) Patients already stabilised on SCIg or IVIg treatment.

- In patients already stabilised with another SCIg or an IVIg preparation, trough levels and treatment intervals should be documented for at least two previous infusions, prior to the introduction of the new SCIg preparation. After a period of approximately 5-6 administrations of the new SCIg product, trough levels and treatment intervals should be measured.

Group C) Patients naïve to Ig treatment.

- In patients naïve to Ig, the pharmacokinetic profile should be assessed when the steady state (Tss) is reached.

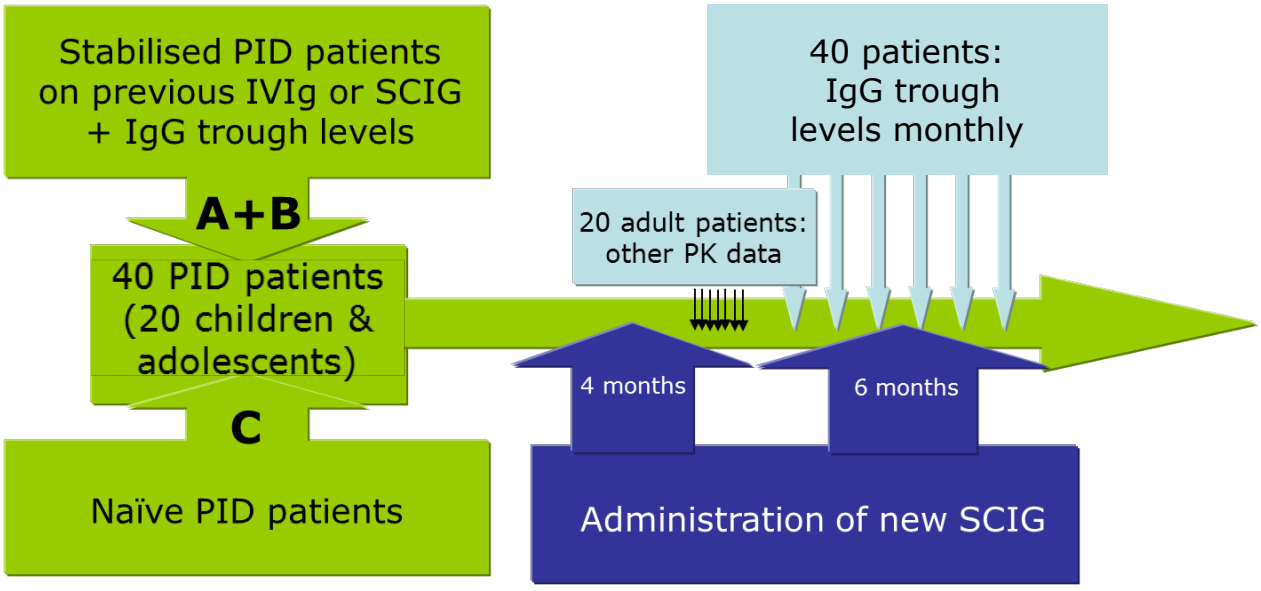
5.2.2. PK parameters

1. IgG trough levels should be studied in 40 PID patients, whereby 20 of these should be children or adolescents with an age distribution representative of this patient population. The IgG trough levels of the investigational product should be assessed prior to each infusion over a period of 6 months, starting after 4 months treatment on the new SCIg product. The monthly IgG trough levels obtained should be compared to trough levels of at least two previous infusions of the former SCIg or IVIg product (Group A + B). For Group C, a descriptive comparison to published literature (if available) is requested.

2. Other PK parameters including plasma concentration-time curve, area under the curve, Cmax, and Tmax should be measured in a sub-set of 20 adult PID patients assessed by repeated blood sampling after approximately 4 months of the product until immediately before the next infusion. The other PK parameters obtained should be discussed by the applicant in the light of the literature data.

Given the extensive literature for immunoglobulins, a separate paediatric PK study is not deemed necessary and children included should only be assessed for trough levels and not for other PK parameters including area under the curve, Cmax, and Tmax.

5.2.3. PK study chart



5.3. Efficacy

5.3.1. Replacement therapy in primary immunodeficiency syndromes

Efficacy should be demonstrated in an open-label, single-arm clinical trial of one-year duration in primary immunodeficiency (PID).

The recommended primary endpoint is the number of serious bacterial infections per subject per year. The protocol should prospectively provide specific diagnostic criteria for each type of serious infection to be included in the primary efficacy analysis. Serious bacterial infections include:

- bacteraemia or sepsis
- bacterial meningitis
- osteomyelitis / septic arthritis
- bacterial pneumonia
- visceral abscess

Secondary endpoints are PK parameters, e.g. IgG trough levels (see section 5.2), all other infections, antibiotic treatment, days lost from school/work, hospitalisations and fever episodes.

The study primary efficacy objective should be to demonstrate that in treated patients, the rate of acute serious bacterial infections is less than 1.0 per person per year.

The Applicant should justify the sample size estimate and the power calculation; however the number of subjects to be included into the study is expected at least to exceed 40 patients as the study should provide at least 80% power to reject the null-hypothesis of an acute serious bacterial infection rate (infection per patient per year) greater or equal 1.0 by means of a one-sided test and a Type I error of 0.01. Approximately half of these patients should be children and adolescents with an age distribution representative of this patient population The patients should be followed over 12 months to avoid a seasonal bias due to a greater rate of infections in the winter months.

The secondary endpoints should be prospectively defined and their statistical analyses provided in the study protocol.

The efficacy results from this study would apply to all types of primary immunodeficiency syndromes due to deficiency of functional IgG.

5.3.2. Replacement therapy in secondary immunodeficiencies

Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic 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.

If efficacy has been proven in primary immunodeficiency syndromes (see 5.3.1 no further studies are required to demonstrate efficacy in SIDs. Dosage regimens different from the standard dosages stated in the core SmPC should be supported by clinical data.

5.3.3. Chronic inflammatory demyelinating polyradiculoneuropathy as maintenance therapy (CIDP)

If the efficacy in primary immunodeficiency syndromes is established, then an extrapolation to maintenance therapy for CIDP after stabilisation with IVIg might be possible without the need to perform separate clinical trials in this indication, if adequately justified.

The dosage regimen should, however, be justified. If other dosage regimens than the ones provided in the guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration (SCIg/IMIg) are requested, they should be supported by relevant clinical data.

5.3.4. Hepatitis A prophylaxis

Clinical data are not required. The Monograph for Human normal immunoglobulin (0338) should be adhered to.

5.3.5. Other Indications

Other possible indications cannot be granted without relevant specific clinical data.

Biological and pharmacokinetic data alone are not sufficient to support clinical efficacy.

Controlled clinical trials comparing the SCIg preparation with placebo or with an established therapy are thus required to substantiate marketing authorisation in other indications, following the relevant guidelines where available.

The required extent of clinical data and the type of trial design may vary according to the proposed indication(s) thus, it is recommended to seek scientific advice (SA).

5.4. Safety

Product safety is evaluated based on all pertinent safety findings. A comprehensive risk management plan (RMP) has to be submitted as part of the dossier.

5.4.1. Adverse Events

All adverse events (AE) in clinical studies must be recorded, reported and analysed with regards to causality, seriousness, severity, outcome and expectedness. Safety data from trials in indications not claimed in the application can be used as supportive data.

Comprehensive baseline data and patient histories are essential to compare the safety signals arising from the studies. The safety signals should be compared with data and frequencies described in the literature. Any deviation from known signals and rates should be discussed. Adverse events and serious adverse events (SAEs) from all patients followed through the clinical studies should be recorded and reported, regardless of whether the AE is determined to be related to the product or not.

Safety evaluation should include monitoring of short term and local tolerance (blood pressure, heart rate, temperature, and monitoring of other adverse events, skin reactions) at repeated intervals following the infusion of the new product. Local reactions should be evaluated with regards to the anatomical localisation, infusion rate and infused volume per site of injection.

All safety data should include a separate evaluation of the safety dataset in children and adolescents. This should be compared to the adult dataset and relevant discrepancies listed in the SmPC.

Post-marketing safety data collection in children should be required in the Risk Management Plan.

A separate safety evaluation of the excipients should be provided (e.g. for new excipients, new route of administration, considerably higher quantities administered compared with previous uses); this should encompass a summary of the non-clinical and literature data.

5.4.2. Safety with respect to transmissible agents

Compliance with CHMP recommendations (EMA/CHMP/BWP/360642/2010 rev. 1) with regard to viral safety and other transmissible agents is necessary for all plasma-derived products and it is verified by information supplied in Module 3 of the dossier.

A pre-treatment serum sample from each patient included in the clinical trials should be stored at -70°C for possible future testing.

5.4.3. Viral safety

Manufacturers of plasma-derived products, including SCIg/IMIg, are obliged to optimise viral safety by selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective steps for the inactivation/removal of viruses in the manufacturing processes. Similar principles to those outlined for viral safety should apply for all transmissible agents including TSE and other emerging pathogens. Manufacturers should follow the respective guidance documents and position statements. Information can be found in the guidelines on the EMA website (under *Biologicals – Drug Substance - Plasma-derived Medicinal Products*).

The above-mentioned procedures are now considered to be highly effective and demonstrative of the viral safety of the product with respect to enveloped viruses. These procedures may be of limited value against non-enveloped viruses, such as hepatitis A virus and parvovirus B19. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

The applicant is nevertheless required to provide all available data gathered on patients treated with the product in clinical trials. Investigators should continue with their normal clinical practice of monitoring patients. The applicant should demonstrate that there are systems in place to collect information on patients treated with the product and to respond rapidly to any reports of infection with a full investigation.

For products with an entirely novel manufacturing process other principles may apply. These applications should be discussed with the Regulatory Authorities prior to submission.

5.4.4. Other transmissible agents

Similar principles to those outlined for viral safety should apply for all transmissible agents including Transmissible spongiform encephalopathy (TSE) and other emerging pathogens.

Manufacturers should follow the respective guidance documents and position statements.

5.4.5. Other safety issues

The effect of passive transmission of haemagglutinins (anti-A/anti-B), and anti-D should be evaluated in patients receiving high doses of SCIg by searching for haemolysis and performing a Direct Antiglobulin Test (DAT – Direct Coombs Test) in the patient.

5.5. Special populations

Where a paediatric investigation plan is required in order to comply with the Paediatric Regulation (EC) No 1901/2006, the applicant should provide a plan that includes the recommendations described in this guideline for the paediatric population.

Elderly Patients: specific data in the elderly are not needed as the benefit/risk can be extrapolated from the available data in adult patients.

6. Change in the manufacturing process of authorised products

Changes in the manufacturing procedures may lead to significant changes in the product and may thereby alter the structure of the immunoglobulin and/or its activity or the safety of the product.

6.1. General aspects

When a change is introduced to the manufacturing process of a given product, the marketing authorisation holder will have to demonstrate that the "post-change" and the "pre-change" product are comparable in terms of Quality, Safety and Efficacy. This will be a sequential process, beginning with investigations of quality and supported, as necessary, by non-clinical and/or clinical studies.

The extent of clinical data to be provided has to be judged on a case-by-case basis depending on the anticipated impact of the changes and could vary from a pharmacokinetic trial comparing "pre-change" versus "post-change" product up to the full clinical data set as outlined for a new product.

Consequently, applications should be accompanied by assessment of the potential impact of a change on efficacy and safety of a given product and the rationale behind the clinical development plan should be outlined and justified.

If a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics and safety in PID patients is required.

If the biological data and/or pharmacokinetics data are significantly different from the parent preparation, then the product should comply with the requirements for a new product as defined in section 5.

6.2. Biological data

The effects of changes in the manufacturing process (e.g. viral inactivation steps, changes in pH, changes in dimer content or new purification procedures) on the biological characteristics and activity of the product should be investigated.

Thus, it is important to provide full data on antibody integrity and function as for new product (see section 5.1).

6.3. Pharmacokinetics

If a PK study is needed, plasma concentration-time curve, area under the curve, Cmax, Tmax, and trough level should be measured in 20 adult PID patients assessed by repeated blood sampling after

approximately 4 months of the product until immediately before the next infusion. These PK parameters should be compared to data obtained with the "pre-change" product.

PID patients included in the PK study should be evaluated for safety according to the principles outlined in 5.4.

7. References

European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision Peter Y. K. Van den Bergh *et al* First published: 30 July 2021
https://doi.org/10.1111/ene.14959

Glossary

AE	Adverse event
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
HAV	Hepatitis A virus
IgG	Immunoglobulin G
IMIg	Human normal immunoglobulin for intramuscular administration
IVIg	Human normal immunoglobulin for intravenous administration
PID	Primary Immunodeficiencies
PK	Pharmacokinetics
PSAF	Proven specific antibody failure
SA	Scientific advice
SAE	Serious adverse event
SCIg	Human normal immunoglobulin for subcutaneous administration
SID	Secondary immunodeficiency
TSE	Transmissible spongiform encephalopathy
Tss	Time to steady-state