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Guideline on similar biological medicinal products containing interferon beta

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Executive summary

This guideline lays down the non-clinical and clinical requirements for interferon beta (IFN- β) containing medicinal products claiming to be similar to another interferon beta already marketed. The non-clinical section addresses the pharmaco-toxicological requirements and the clinical section the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as pharmacovigilance aspects.

1. Introduction (background)

Three different medicinal products containing recombinant IFN- β are currently approved in the EU for the first-line treatment of multiple sclerosis (MS); they differ with respect to their molecular structure, injection route, recommended posology, and MS indications.

Recombinant IFN- β -1a is a single glycosylated polypeptide chain containing 166 amino acids. Two products are available, one is administered subcutaneously and the other intra-muscularly.

Recombinant IFN- β -1b is produced as a single non-glycosylated polypeptide chain of 165 amino acids with no methionine at the N-terminus and an amino acid substitution at position 17 and is administered subcutaneously.

Medicinal products containing recombinant IFN- β are currently indicated for patients with relapsing MS including those at high risk of developing MS after a single demyelinating event. The mechanism of action of IFN- β in MS is not well established but it has been hypothesized that it acts as an immunomodulator by 1) interfering with T-cell activation in several ways, including downregulating the expression of Type II MHC molecules, inhibiting the production of pro-inflammatory cytokines by T_h1 cells, promoting the production of anti-inflammatory cytokines by T_h2 cells, activating suppressor T-cells and 2) inhibiting permeability changes of the blood brain barrier and the infiltration of T-cells into the central nervous system (CNS).

The clinical effects of recombinant IFN- β in relapsing MS (RMS) are modest with decreases in the frequency of exacerbations by approximately 30% as compared with placebo and inconsistent results on the progression of disability.

All products are associated with similar adverse reactions which may affect patient adherence to therapy; the most frequent are influenza-like symptoms (fever, chills, arthralgia, malaise, sweating, headache, and myalgia). Injection site reactions and asymptomatic liver and white blood cell abnormalities occur more frequently with the subcutaneous products at the recommended dose regimens. Less common adverse reactions include depression and autoimmune disorders manifested as thyroid or liver dysfunction. All products induce the development of antibodies, and in particular neutralising antibodies (NAbs); in clinical trials, the incidence of NAbs has been shown to range widely, from 5% for intramuscular IFN- β -1a given weekly to 45% for subcutaneous IFN- β -1b given every other day. Most Nabs develop in the first year of therapy and they have the potential to impact clinical outcomes after 18-24 months of treatment.

2. Scope

The Marketing Authorisation application dossier of a new IFN- β claiming to be similar to a reference medicinal product already authorised is required to provide the demonstration of comparable quality, efficacy, and safety of the product applied for to a reference medicinal product authorised in the EU.

This product specific guideline presents the current view of the CHMP on the non-clinical and clinical requirements for demonstration of comparability of two medicinal products containing recombinant IFN- β and should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with other relevant CHMP guidelines (see point 3. Legal basis).

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83/EC as amended as well as all other pertinent EU and ICH guidelines and regulations, especially the following:

- Guideline on Similar Biological Medicinal Products - CHMP/437/04;
- Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals - EMA/CHMP/ICH/731268/1998 (ICH S6(R1));
- Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical issues - EMEA/CHMP/BMWP/42832/2005;
- Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis - CPMP/EWP/561/98 Rev. 1;
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **);
- Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004);
- Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins - EMEA/CHMP/BMWP/14327/2006;
- Biologics Working Party Report to the CHMP Beta-interferons and neutralising antibodies (in multiple sclerosis) - EMEA/CHMP/BWP/580136/2007;
- Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems – EMA/838713/2011.

4. Main guideline text

4.1. *Non-clinical studies*

As regards non-clinical development, a stepwise approach should be applied to evaluate the similarity of the biosimilar and reference medicinal product.

Non-clinical studies should be performed before initiating clinical trials. *In vitro* studies should be conducted first and a decision then made as to the extent of what, if any, *in vivo* work will be required. The approach taken will need to be fully justified in the non-clinical overview.

In vitro studies

In order to assess any differences in biological activity between the biosimilar and the reference medicinal product, data from a number of bioassays/pharmacological studies should be provided (e.g. receptor-binding studies; assays for characterisation of antiviral, anti-proliferative and immunomodulatory effects), some of which may already be available from assays submitted as part of

the quality dossier (for IFN- β -1a, the requirements of the European Pharmacopoeia monograph *Interferon beta-1a concentrated solution* apply).

These studies should be comparative in nature and should be designed to be sensitive enough to detect differences in the response between the biosimilar and the reference medicinal product and should not just assess the response *per se*. They should be performed with an appropriate number of batches of product representative of that intended to be used in the clinical trial.

Wherever possible, analytical methods should be standardised and validated according to relevant guidelines (e.g. evaluation of antiviral effects in cell culture in accordance with the provisions of the European Pharmacopoeia, general chapter 5.6 *Assay of interferons*).

***In vivo* studies**

Generally, *in vivo* studies in animals are not recommended.

Only when the outcome of the quality evaluation and/or the *in vitro* bioassays/pharmacological studies leave uncertainties about the comparability of the biosimilar and reference medicinal product, the need for additional studies should be considered.

In vivo studies should be designed to specifically address the remaining uncertainties identified. These could include an *in vivo* pharmacological study and/or a general repeated dose toxicity study in a relevant species.

Further studies in a pharmacologically responsive animal species should only be considered when it is expected that such studies would provide relevant additional information.

4.2. Clinical studies

The clinical comparability exercise should follow a stepwise approach starting with pharmacokinetic and pharmacodynamic studies (PK & PD) and continuing with efficacy and safety studies.

Pharmacokinetics

The pharmacokinetic properties of the biosimilar and reference products should be compared in a crossover study using the route of administration applied for. Healthy volunteers are considered an appropriate study population. The selected dose should be in the linear part of the dose-concentration curve; if available information on the reference product is too scarce, more than one dose should preferably be tested. The choice of a single or repeated dose (e.g. three doses over a week) regimen should be justified; a single dose is preferred as long as the bioanalytical method is sufficiently sensitive to characterise the full PK profile. Although antibody development is not expected after a few doses of IFN- β , their determination should be carried out before/after each treatment course in order to exclude any potential interference with the PK profile.

Serum concentrations of IFN- β are very low after the administration of therapeutic dosages and their measurement is technically difficult. Possible methods of detection include a cell-based myxovirus resistance protein A (MxA) induction assay, which measures the biological activity of IFN- β in serum samples, and ELISA assays, which determine the IFN- β protein mass. The Applicant should justify the rationale for the choice of assay.

The design of the study should take into account the recommendations as outlined in the Guideline on the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004). In particular, the pharmacokinetic parameters of interest should include AUC, C_{max} and also T_{1/2} or clearance. The equivalence margin has to be defined *a priori* and appropriately justified, especially given the high variability of the relevant PK parameters. A two-stage design may be planned in the protocol provided

adjusted significance levels are used for each of the analyses in accordance with the Guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1 Corr).

Pharmacodynamics

Pharmacodynamics should preferably be evaluated as part of the comparative pharmacokinetic studies using validated assays. There is currently no identified biological marker related to the mechanism by which IFN- β influences the clinical evolution of MS. However, a number of markers of the biological activity of IFN- β are well known and a comprehensive comparative evaluation of some of these markers could be used to support the similarity of the biosimilar and reference medicinal products ("fingerprint approach"). MxA induction can be measured from peripheral blood leukocytes both at the protein and mRNA level; it is currently considered as one of the most sensitive markers of the biological activity of type I interferons and should be one of the selected markers. Neopterin, which was found to show a consistent and robust dose-response relationship, should also be investigated. Other possible markers include serum (2'-5')oligo-adenylate-synthetase activity, interleukin 10, or TNF-related apoptosis inducing ligand (TRAIL).

Magnetic resonance imaging (MRI) is a useful tool for monitoring CNS lesions in MS. Different MRI derived parameters have been related to clinical activity, e.g. gadolinium-enhancing T1-weighted lesions or new/enlarging T2-weighted lesions have been related to relapses.

Clinical efficacy

Similar clinical efficacy between the biosimilar and reference medicinal product should be demonstrated in an adequately powered, randomised, parallel group, equivalence clinical trial, preferably double-blind. If blinding is technically not feasible, alternative measures should be applied to avoid information bias. The route of administration used in the clinical trial should be the route recommended for the reference product.

According to the Guideline on medicinal products for the treatment of MS (CPMP/EWP/561/98 Rev1) an acceptable primary efficacy variable for a disease modifying agent in RMS is the relapse rate, which has been used in the pivotal trials on medicinal products containing recombinant IFN- β . While in principle this would be the preferred option, such a trial may not be necessary in a biosimilar context, since the focus of this trial is to demonstrate comparable clinical activity of the biosimilar product to the reference product, which then allows bridging to the benefit-risk of the reference product. For demonstrating clinical similarity of a biosimilar and reference product, magnetic resonance imaging of disease lesions in RMS may be sufficient (see Pharmacodynamics). In addition, clinical outcomes such as relapse rate or percentage of relapse-free patients should be used as secondary endpoints in support of the MRI outcomes.

The design of the equivalence trial should ensure assay sensitivity, i.e. the choice of study design, population, duration and MRI endpoints should make it possible to detect a difference between the biosimilar and reference products, if such difference actually exists. Regarding the study design, assay sensitivity could be shown by a three-arm trial including a placebo arm for a short period of time (e.g. 4 months) sufficient to demonstrate superiority of both the biosimilar and reference products over placebo using an MRI endpoint. Patients in the placebo arm could be subsequently switched to the biosimilar product and the trial continued with the two active arms. An alternative design could be a three-arm trial with the reference product and two doses of the biosimilar product, for which differences in MRI and clinical outcomes are expected to be observed over 12 months; if the MRI curves do not differentiate the two doses over time, interpretation of the results would be difficult as the assay sensitivity of the trial would be questionable.

Whatever the design, the duration of the trial should be sufficient to show comparable efficacy on MRI endpoints and provide relevant information on clinical outcomes, i.e. not less than 12 months.

The most sensitive patient population, which would enable to detect differences between the biosimilar and reference products, should be selected. This would be a homogeneous sample of patients with a confirmed diagnosis of relapsing-remitting MS (RRMS) and sufficient disease activity based on relapse frequency and/or MRI criteria to anticipate rapid changes in MRI.

MRI-based variables are acceptable primary endpoints in the context of a biosimilar comparison if backed up by relapse-related clinical outcomes; no formal equivalence test is required for clinical outcomes, which would be expected to show the same trend in effect as the MRI-based variables. A relapse should be differentiated from a pseudo-exacerbation and accurately defined. Repeated MRI scans should be performed during the trial. All possible actions should be taken to ensure high quality MRI data and maximum reliability of measurements. Updated recommendations on appropriate technical facilities and standardized procedures and training should be followed. The reading of the images should be central and blinded. The combined unique active lesions (CUA, defined as new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions without double counting) are the most sensitive documented MRI variable, and therefore, should always be determined; a cumulative estimate over several scans may be calculated. Other MRI variables may also be used as primary endpoint if adequately justified.

The equivalence margin for the primary MRI endpoint should be pre-specified and adequately justified based on MRI data for the reference medicinal product relative to placebo, or if not available, extrapolation from other IFN- β relevant data. Of note, these data are important at the planning stage of the trial but are not essential for the interpretation of the results as assay sensitivity has to be shown within the trial. It should be adequately powered with particular attention paid in the protocol to the potential drop-out rate and the way of handling missing data.

Clinical safety

Comparative safety data from the efficacy trial are usually sufficient to investigate the more frequent adverse reactions and provide an adequate pre-authorisation safety database for such reactions but not for rarer adverse reactions, which should be addressed post-authorisation.

As IFN- β products are immunogenic, an assessment of immunogenicity by testing of sera from IFN- β -treated patients should be performed according to the principles defined in the Guideline on immunogenicity assessment of therapeutic proteins. Its main objective is the comparison of the immunogenicity profile of the biosimilar and reference products over time since the antibody characteristics and effects change as a result of affinity maturation of the antibody response and/or epitope spreading. A minimum of 12-month comparative immunogenicity data should be submitted pre-authorisation with further assessment to be continued post-approval for at least 6 months for the biosimilar product. A strategy that includes serum sampling at baseline and at regular intervals is necessary for assessing the comparability of the dynamics of antibody development during therapy, e.g., every month in the beginning of the treatment (first 3 months) followed by every 3 months.

The use of a validated, highly sensitive antibody assay, capable of detecting all antibodies (i.e. of different affinities, class and sub-class) is mandatory. Approaches that avoid specific masking of particular epitope(s) should be considered to avoid false negative results. Following confirmation of antibody positive samples, further characterization including determination of the ability to neutralise the biological activity of IFN- β and cross-reactivity is required. It is recommended that the standardised MxA protein NAb assay or a NAb assay that has been validated against the MxA protein NAb assay is used (EMA/CHMP/BWP/580136/2007). The approach used to determine assay sensitivity (e.g., by using different cut-off points) should be described but the distribution of titres should also be presented at each time point for each treatment arm. Finally, patients should be categorised according to the evolution of their immune response over time using predefined criteria. For example, the patient's NAb status may be defined as antibody negative (-ve for all post-treatment samples

according to predefined low/high dilutions or titres) or antibody positive, which can be categorised as 'transiently positive' (1 or more post-treatment samples +ve, followed by –ve samples at all subsequent and at least 2 sampling time points) or 'persistently positive' (2 or more consecutive post-treatment samples consistently +ve). MRI activity and clinical relapses should be compared between these categories for both the biosimilar and reference product. The impact of NABs on clinical outcomes is unlikely to be sufficiently ascertainable before 12 months of therapy and thus will need to be further evaluated post-authorisation as part of the risk management plan.

The immune response to the biosimilar and reference medicinal products is expected to be comparable with regard to the incidence and titres of antibodies (neutralising or not) as well as their impact on efficacy; although the clinical impact of binding, non-neutralising antibodies is not clear, an increased frequency of such antibodies for the biosimilar product relative to the reference medicinal product would contradict the concept of biosimilarity. However, lower immunogenicity alone would have to be explained but may not preclude biosimilarity if efficacy is shown to be comparable in the various categories of patients according to their immune response (as previously defined) and provided all other data (quality, non-clinical, PK, PD, and safety) are supportive of biosimilarity.

4.3. Pharmacovigilance

Within the authorisation procedure a risk management plan should be presented in accordance with current EU legislation and pharmacovigilance guidelines. The RMP should in particular take into account identified and potential risks associated with the use of the reference medicinal product and safety in indications authorised for the reference medicinal product that are claimed based on extrapolation. The risk management plan should further address rare events such as autoimmune disorders, adverse events of special interest such as hepatotoxicity and depression, potential effects of unwanted immunogenicity, and important missing information such as safety in pregnancy (a pregnancy registry for IFN- β containing products is mandatory). This could be managed through routine pharmacovigilance, supplemented by the extension of the pre-authorisation trial (in particular regarding immunogenicity as previously mentioned), a dedicated observational study or the participation in an existing registry.

4.4. Extrapolation of indication

Extrapolation of clinical efficacy and safety in confirmed RRMS to the other indications of the reference medicinal product in MS is possible on the basis of the totality of the evidence provided from the comparability exercise.