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Guideline on the clinical requirements for non-replacement therapy in haemophilia A and B

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Table of contents

Executive summary

This guideline describes the main clinical data needed to support an application for a marketing authorisation for non-replacement therapy for use in prevention of bleeding in patients with haemophilia A and/or haemophilia B.

1. Introduction (background)

The purpose of this guideline is to provide applicants and regulators with harmonised requirements for applications for marketing authorisation of non-replacement therapies for haemophilia A and/or B. Haemophilia A and B (HA, HB) are hereditary X-linked recessive disorders caused by mutations in the genes encoding factor VIII (FVIII) and factor IX (FIX), respectively. The genetic defect results in disruption of the blood clotting pathway. Severe haemophilia is associated with frequent spontaneous bleeds into muscles, joints and soft tissues which can result in debilitating arthropathy and severe impairment in the patient's quality of life. The primary treatment strategy includes on-demand treatment of bleeding or prophylactic factor replacement to prevent bleeding, with plasma-derived or recombinant FVIII or FIX products. The occurrence of inhibitors (neutralising antibody, nAB) against FVIII or FIX, is the most important complication in haemophilia treatment.

Non-replacement therapies are already approved such as an antibody with FVIII-mimetic activity or are in development such as e.g. antibodies directed against the Tissue Factor Pathway Inhibitor (anti-TFPI), or a siRNA (small interfering RNA) targeting Anti-Thrombin (AT). In contrast to factor replacement therapies given intravenously, these therapeutic agents are mostly to be administered subcutaneously. Furthermore, due to their mode of action, non-replacement therapies will mainly be developed for prophylaxis.

For anti-TFPI products and siRNA targeting AT, the independence from FVIII and FIX activity potentially enables a broad indication encompassing prophylactic treatment of both HA and HB patients with and without inhibitors.

Gene therapies for HA and for HB have recently been authorised.

2. Scope

The Guidelines on Clinical Investigation of recombinant and plasma-derived FVIII and FIX products, are product-specific guidelines and do not cover the clinical requirements for approval of non-replacement HA and HB therapy. As there are several types of products in development, it is considered necessary to reflect on considerations on general principles of the clinical development programme of these products. However, specific considerations depending on the mode of action are also required. Gene therapy for treatment of haemophilia as well as clinical development of products intended for acquired haemophilia are not in the scope of this guideline.
An integrated view is aimed for by aligning scientific advice, Paediatric Investigations Plans (PIPs) and post-authorisation requirements.

This guideline will focus on the confirmatory phase III trials investigating safety and efficacy and serving as the main basis for benefit/risk (B/R) assessment of these products.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/83/EC as amended, as well as the Paediatric Regulation (EC) 1901/2006 as amended.

4. Overall clinical development programme

4.1. Considerations for Exploratory Studies

The clinical development programme of non-replacement therapies usually starts with a first-in-human (FIH) study, followed by exploratory phase I or phase II studies, or combined phase I/II studies, investigating safety and tolerability, pharmacology, optimal dosing and aiming to demonstrate proof of concept.

4.2. Dosing

A thorough characterisation of the relationship between dose, pharmacokinetic (PK) parameters, exposure and pharmacodynamic (PD) response parameters is considered necessary for an appropriate dosing decision. The PD, safety and efficacy of the intended dosing regimens should be comprehensively studied. In particular, a potential impact of haemophilia subtypes (HA/HB) and disease severity on dosing need to be addressed. There should be a rationale for either fixed or body-weight adjusted dosing.

Further on, dosing regimens for adults as well as for the whole age range of the paediatric population need to be well justified. This should take into account age related differences in coagulation and haemostasis particularly in very young paediatric patients. For dose response evaluation, *"ICH E4 guidance Dose-Response Information to Support Drug Registration"* should be considered. Due to the mechanisms of action of non-replacement therapies, a thrombogenic risk cannot be excluded. Therefore, a comprehensive dose-finding is of particular importance before initiating phase III trials.

4.3. Considerations for Confirmatory Studies

HA and HB are rare diseases which causes limitations in patient availability for clinical studies. Moreover, haemophilia patients are heterogeneous with regards to clinical signs and symptoms, such as bleeding phenotype, bleeding risk due to different lifestyle and individual treatment history, target joints, risk for inhibitors etc. In consequence, feasibility of sufficiently informative, randomized, controlled trials to estimate efficacy and safety of a novel therapeutic agent is challenging in this disease setting. While a randomised-controlled study would be the preferred option, a single-arm study with an intra-participant comparison relative to a prospectively captured baseline is considered acceptable (non-inferiority and/or superiority comparison, depending on the patient population, see further below). Data on bleeding events, factor consumption, prophylaxis medication use, and other relevant parameters should be collected prospectively during a run-in phase of the study of at least 6 months prior to start of treatment, allowing for an adequate intra-patient comparison.

Considering that non-factor replacement therapies represent a novel approach for long-term treatment of HA and HB patients with and without inhibitors, an adequate number of patients should be included to permit a meaningful evaluation of efficacy and safety. Importantly, the sample size should not only be determined based on statistical considerations concerning the efficacy endpoint(s), e.g. to demonstrate non-inferiority in terms of annualised bleeding rate (ABR) of prophylaxis with a new non-replacement product vs prophylaxis with conventional factor replacement therapy (or superiority against on-demand treatments), but also justified from a safety perspective. In the case high heterogeneity is anticipated, representativeness of clinically relevant subgroups should be also taken into consideration in sample size evaluation.

The active treatment period should be at least 12 months at steady PD state to characterise efficacy and identify safety risks associated with these novel medicinal products. Further data collection beyond

12 months (at steady PD state) might be necessary and could be done post-marketing, see also section 5.

4.3.1 Patient population

General

Several non-replacement therapies, with varying modes of action, are in development for HA and HB patients with and without inhibitors. Inclusion of both HA and HB into one study may be appropriate. However, a sufficient number of patients for each disease needs to be enrolled in order to allow meaningful subgroup analyses. Extrapolation between HA and HB is not acceptable.

In contrast, it is not considered meaningful to include patients with and without inhibitors into one study or to pool data from patients with and without inhibitors as these patients are not comparable concerning baseline characteristics and standard of care.

Severity

Depending on the intended indication, patients with severe and moderately severe haemophilia (according to International Society on Thrombosis and Haemostasis, ISTH, definitions) can be included into the clinical studies. However, for primary analyses of (annualized) bleeding rates patients should have a clinically severe phenotype (definition needs to be justified by literature and laid down in the study protocol). Of note, B/R considerations might differ between disease severity by e.g. weighing the benefit of a prophylactic treatment against (potential) safety concerns. In any case, stratification according to severity is required. Furthermore, the intended posology needs to be well justified for each disease severity. It is important to avoid overdosing in patients with moderate haemophilia and higher endogenous factor VIII/IX levels to prevent a potentially increased risk of thrombosis.

As regards anti-TFPI products, it currently remains unclear whether TFPI levels are comparable in HA and HB patients. This issue as well as any potential impact on dosing needs to be addressed by applicants. Nevertheless, it is considered meaningful to include both HA and HB patients into one study, taking into account the considerations above on subgroup analyses.

Although both haemophilia subtypes are characterised by a defect in thrombin generation, differing results in thrombin generation assays between HA and HB have been described in literature (Maseide *et al* 2021). Therefore, treatment effect of anti-AT products should be demonstrated in both haemophilia types. As mentioned above, inclusion of both HA and HB patients into one study is appropriate, provided a sufficient number of patients of each type is included allowing meaningful subgroup analyses. In order to be able to evaluate the clinical effect of different doses, an analysis of the AT activity, efficacy (bleeding) and safety per separate dose and the dosing regimen should be performed.

4.3.2. Objectives and Endpoints

The main treatment goal of non-replacement therapies in the treatment of HA and HB is to prevent or reduce the frequency of bleeding episodes and minimise disease-related complications. This should be reflected by the primary objective.

The variable for the primary endpoint should be ABR of all bleeds, i.e. both spontaneous and traumatic bleeds. However, it remains open if only treated or also untreated bleeds should be counted for the primary analysis of the ABR. Inclusion of only bleeding episodes requiring treatment might present a more objective and less variable endpoint. If only treated bleeds are included in the primary analysis, incidence of total bleeds irrespective of need for treatment should be captured as a secondary endpoint. Bleeds due to surgery/procedure should not be included in the primary analysis but should

be captured by the study protocol. Definition of bleeds e.g. severity, should be laid down in the study protocol and should follow scientifically established definitions. Furthermore, bleeding events counting for the analysis of ABR should be well defined with regards to their duration and how individual bleeding events occurring in close proximity to each other can be discriminated. Of note, the same definitions should be used during the run-in phase as well as the active treatment phase.

The primary efficacy assessment should be based on intra-patient comparisons between the observational (run-in) and the treatment phase of the study.

In HA and HB patients without inhibitors prophylactic treatment with a new non-replacement therapy should be compared to the pre-study prophylaxis treatment regimen. The primary endpoint for the treatment of non-inhibitor patients with novel non-factor replacement therapies will assess non-inferiority of prophylaxis in terms of ABR with the investigational medicinal product versus pre-study prophylactic treatment. Intra-individual comparison of prophylactic treatment with a new non-replacement therapy to on-demand treatment with factor products is considered less meaningful in those patients, as it does not reflect the standard of care in most EU countries and hence demonstration of superiority of a new non-replacement therapy used prophylactically over on-demand treatment is not considered sufficient.

In HA and HB patients with inhibitors intra-individual comparison of prophylaxis treatment with the investigational medicinal product against standard on-demand treatment may be considered acceptable. Prophylactic treatment in patients with inhibitors is not yet standard of care. Nevertheless, prophylactic treatment of patients with inhibitors might become more important with approval of novel non-factor replacement therapies and for HA patients with inhibitors the use of FVIII mimicking bispecific antibody as prophylactic treatment became a relevant treatment option. Therefore, intra-individual comparison of patients with inhibitors who received pre-study prophylaxis treatment with bypassing agents or non-factor replacement therapies is considered to be of interest and applicants are encouraged to gather at least some supportive data in this respect. Hence, in inhibitor patients, the primary endpoint will assess either superiority of prophylaxis relative to pre-study on-demand treatment or non-inferiority of prophylaxis versus pre-study prophylactic treatment depending on the therapy that inhibitor patients received during the run-in period of the study.

The choice of the margin(s) will be dependent on the baseline characteristics of the study population and whether the patients receive on-demand treatment or have well controlled prophylaxis therapy. The bleeding rate would be very different in the two populations of prophylactic and on-demand treatment. The choice of a clinically meaningful margin should be well justified.

Subgroup analysis to assess consistency of the treatment effect should be provided for relevant subgroups (e.g., haemophilia subtypes, age).

A washout period between run-in phase and active treatment phase to avoid a carryover effect of prior treatment should be considered. By defining the length of such a wash-out period it needs to be taken into account that the half-life of authorised factor replacement and non-replacement products may strongly vary. If a sufficiently long washout period is not feasible due to increased risk of bleeding events and hence active treatment is started before complete washout of previous therapy, the start timepoint of evaluating efficacy needs to be justified.

The run-in period should be long enough to provide adequate data to allow a comparison between the recorded ABRs with those recorded during the treatment phase. Although seasonal effects and related changes in physical activity of the patients could have an impact on treatment effect, a lead-in period of at least 6 months is considered acceptable for intra-patient comparison. The distribution of the enrolment across the year, however, would somewhat reduce the risk of this potential bias on a study level. Considering that non-factor replacement therapies represent a novel approach, the overall

treatment phase with the investigational medicinal product is recommended to be at least 12 months to allow reliable conclusions on the efficacy and identify safety risks associated with these new medicinal products.

Evaluation of the treatment effect by comparison against historical data is not recommended for the primary analysis but may serve as supportive evidence for the benefit-risk assessment.

Supportive data should be collected through secondary endpoints such as factor/bypassing agents' consumption, number of target joints, improvement in target joints, annualised joint/traumatic/spontaneous bleeding rate, percentage of patients with no bleeds and health-related quality of life. Furthermore, any relevant information regarding dosing needs to be captured.

Safety-related (secondary) endpoints should specifically capture the incidence and severity of thrombotic events, immunogenicity and infusion/injection site reactions.

There is not yet a laboratory measurement that directly correlates with haemostatic activity of these novel agents suitable to be used as surrogate endpoint. However, evaluation of appropriate, well justified PD–related response parameters showing a relationship to clinically meaningful efficacy outcomes is strongly encouraged.

4.3.3. Estimand

The estimand of primary interest needs to be carefully considered, taking into account the specific setting of the disease and the treatment. The handling of intercurrent events needs to be defined in the study protocol, together with a definition of the primary (and secondary) estimand(s). This applies to both the run-in and the active treatment period.

4.3.4. Treatment of Bleeds

Due to their mode of action and PK/PD profile, most new non-replacement therapies will only be developed as prophylactic treatment. For treatment of breakthrough bleeding events, patients need to use approved standard of care.

Standard treatment for bleeding events in HA and HB patients without inhibitors is on-demand therapy with plasma-derived or recombinant FVIII and FIX products, respectively.

In HA and HB patients with inhibitors, treatment of bleeding events is more difficult to manage than in non-inhibitor patients. In patients with low titre inhibitors (< 5 BU/ml) bleeding events can be treated with high doses of FVIII or FIX products. However, factor replacement is ineffective in patients with high titre inhibitors (>5 BU/ml). In those patients on-demand treatment of bleeding episodes with bypassing agents is the standard of care.

According to their mode of action, bypassing agents and non-factor replacement therapies are potentially associated with a thrombotic risk, in particular concerning the concomitant use with other coagulant products for treatment of breakthrough bleedings. In inhibitor patients, the safety profile of non-replacement therapies is potentially more negatively influenced by the fact that severe bleeds or (emergency) surgeries in those patients would require concomitant administration of bypassing agents with thrombogenic potential. Generating data to support recommendations on how to manage (emergency) surgeries, severe bleeds and trauma with additional haemostatic therapy are considered necessary to adequately address this safety concern (e.g., dosing, patient monitoring) and to support respective information to be included in the Product Information. With regards to thrombogenicity, please also refer to section safety.

4.3.5. Statistical Considerations

Although inclusion of both HA and HB into one study is considered appropriate, combined analysis of HA and HB patients is not deemed acceptable.

Formal sample size calculations are hampered by patient availability. Therefore, the number of patients needed to be enrolled into pre-authorisation clinical trials need to be based on balancing the clinical data package needed to demonstrate efficacy and safety against the availability of patients suffering from a rare disease, or even a subgroup of this disease (e.g., inhibitor patients). Nevertheless, this does not waive the need for formal sample size calculations based on the primary hypothesis to be tested. Sample size should be large enough to provide a reliable answer to the questions addressed, taking into account uncertainty with respect to bias due to lack of an independent control arm and the potential need to demonstrate an effect in relevant subgroups.

Methods for handling missing data should be pre-defined based on the reason for missing data and sensitivity analyses should be planned to assess the robustness of the results.

4.3.6. Safety

Considering that non-replacement therapies represent a novel approach for treatment of HA and HB patients with and without inhibitors, an adequate number of each haemophilia subtype (HA, HB, +/- inhibitors) should be included in the safety database to permit a meaningful analysis of the safety profile. As these new medicinal products are intended for long-term use to prevent and reduce the frequency of bleeding events, the active treatment phase should be at least 12 months (at steady PD state) to characterise the long-term safety and detect potential safety risks (e.g. severe bleedings, thrombotic complications) and increase the likelihood of detecting unexpected complications associated with these therapies.

Thrombogenicity, especially in patients who concomitantly receive other coagulant products for treatment of bleeds, is one of the most important safety aspects which needs to be addressed. The thromboembolic risk is potentially higher in haemophilia patients with inhibitors as they may need bypassing agents for treatment of breakthrough bleeds. However, the risk of thrombotic complications due to concomitant use of these novel therapeutics with factor replacement therapies (plasma-derived or recombinant FVIII and FIX products) should also be carefully evaluated. Non-clinical data characterising the potential thrombotic safety of the novel non-factor replacement therapy concomitantly used with bypassing agents or factor replacement products in models that adequately resemble the situation in humans, are prerequisite but do not overcome the need for careful clinical investigation. Thrombotic events should be defined as Adverse Event of special Interest (AESI). Thrombotic microangiopathy and disseminated intravascular coagulation should be specifically named in order to avoid overlooking clinical manifestations of these AEs. Additionally, the risk of thromboembolic complications should be separately evaluated for HA and HB patients as there might be differences due to concomitant medications. A thorough discussion on the most appropriate way to manage the occurrence of a thrombotic event or situations (e.g., sepsis and trauma) in which there may be increased activation of coagulation, should be included. It should be evaluated whether dose adjustments are necessary based on disease severity (e.g., reduced dose in patients with moderate haemophilia).

Adverse events of special interest should further include infusion related reactions and immunogenicity as well as any additional events that could be expected based on the mode of action or non-clinical data.

Immunogenicity for anti-drug-antibodies (ADA) and nAb should be tested in accordance with the respective guidelines.

General guidance regarding assessment of safety needs to be followed.

4.4. Paediatric Population

Children, especially those with inhibitors, have high medical need for a prophylactic treatment to prevent the development of target joints and joint damage. Considering that non-factor replacement therapies are new molecular entities, the clinical development in the paediatric population should follow a stepwise approach in order to have some experience in adults before clinical investigation is started in children. The initial age cohort of haemophilia A and B paediatric patients to be investigated is ≥12 years of age (adolescents). Inclusion of children ≥12 years of age together with adult patients in a phase III study might be acceptable, depending on available data. However, a sufficient number of patients ≥12 years of age should be included for each of the haemophilia subgroups (haemophilia A and B with and without inhibitors). Efficacy and safety data should be separately analysed for adult and adolescents for each of the subgroups. The clinical trial(s) in children <12 years of age should not start before sufficient experience with the new non-factor replacement therapy has been gained in adults and patients ≥12 years of age. The efficacy and safety profile of novel non-factor replacement therapies in patients <12 years of age should be investigated in a dedicated paediatric study. An adequate number of children aged 6 to <12 years of age and <6 years of age should be included to permit for a meaningful benefit risk assessment in all age groups.

In certain cases, extrapolation may be acceptable in some age groups. However, this needs to be well justified by also taking into account the maturity of the coagulation system and needs to follow applicable guidelines (EMA/189724/2018).

Regarding dosing see also section 4.2.

Data to support recommendations on how to clinically manage bleeding events and surgeries in terms of additional coagulation or bypassing agents will also be required for the paediatric population where traumas through falls and acute surgeries (e.g. appendix, teeth, adenoids) are common.

The clinical investigation in children needs to be agreed by an approved PIP.

5. *Post-Authorisation, Registry Data*

Due to the rare nature of the disease and patient availability for clinical studies, safety data will be limited pre-approval. Therefore, additional data may need to be collected post-marketing through registries and/or a dedicated Post-Authorisation Safety Study (PASS)/Post-Authorisation Efficacy Study (PAES). The following table provides an overview on the core data elements required to be collected in registries. The table is part of an agreed outcome of the haemophilia registries workshop from 2018, organised by EMA and with participants of various stakeholder groups (https://www.ema.europa.eu/en/events/haemophilia-registries-workshop).

Depending on the data and characteristics of a specific product further data to be collected post-marketing might expand the minimum requirements as outlined in this document.

6. *Considerations on significant benefit*

Article 3(1)b in Commission Regulation (EC) 847/2000 states that in the case where satisfactory method(s) of diagnosis, prevention or treatment of the condition exists, the applicant has to establish 'that the medicinal product will be of significant benefit to those affected by that condition'. Significant

benefit is defined as a clinically relevant advantage and/or a major contribution to patient care (please refer to the Commission notice).

Currently there are several products available to patients with haemophilia A and B with and without inhibitors. Therefore, at the time of the orphan designation, the sponsor has to provide a data driven justification based on that the product will be of significant benefit to those within the concerned condition, based on adequate non-clinical and/or clinical data. In case there are already authorised orphan medicines in a specific condition (like in haemophilia A or B), establishing significant benefit based on only non-clinical data could be difficult.

7. *Conclusions*

Based on previous scientific advices and PIPs for new non-replacement therapies, some recommendations for the clinical development can be given and general design principles for clinical studies can be defined. This pertains to a controlled run-in phase allowing an intra-patient comparison against previous (established) treatment, ABR as variable for the primary endpoint, a stepwise approach regarding investigation of safety and efficacy in the paediatric population and the need for collection of additional (safety) data in the post-marketing phase. The risk for thrombotic events is of concern and needs to be carefully investigated. In this context, the optimal posology of non-replacement therapies is not only relevant in terms of efficacy, but also specifically in terms of safety. Also, product-specific design features might be necessary.

References

Applicants should also refer to other relevant European and ICH guidelines (in their current version) including those on (but not limited to that):

Clinical investigation of recombinant and human plasma-derived factor VIII products - Scientific guideline (EMA/CHMP/BPWP/144533/2009 rev. 2)

Clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009 rev. 2 Corr. 1)

ICH E4 Dose response information to support drug registration (CPMP/ICH/378/95)

Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018)

Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (EMA/813938/2011 Rev 3)

ICH guideline E17 on general principles for planning and design of multi-regional clinical trials Step 5 (EMA/CHMP/ICH/453276/2016 Rev 1)

Guideline on strategies to identify and mitigate risks for first-in-man and early clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07 Rev 1)

ICH topic E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)

ICH guideline E8 (R1) on general considerations for clinical studies (EMA/CHMP/ICH/544570/1998)

ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population (EMA/CPMP/ICH/2711/1999)

ICH E7 Studies in Support of Special Populations: Geriatrics Q&A (EMA/CHMP/ICH/604661/2009)

ICH E2A Clinical safety data management: definitions and standards for expedited reporting (CPMP/ICH/377/95)

ICH E2E - Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)

ICH Q2 (R1) Validation of analytical procedures: text and methodology (CPMP/ICH/381/95)

ICH topic E9 Statistical principles for clinical trials – Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017)

Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1)

Guideline on the Choice of the Non-Inferiority Margin (EMEA/CPMP/EWP/2158/99)

Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013)

Points to Consider on Multiplicity Issues in Clinical Trials (CPMP/EWP/908/99)

Points to consider on application of 1. Meta-analyses 2. One pivotal study (CPMP/EWP/2330/99)

Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013)

Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation (EMA/CHMP/564424/2021) (draft published at time of publication of this GL)

Guidance on format of the risk-management plan in the European Union – in integrated format (EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2)

Guideline on Risk Management Systems for Medicinal Products for Human use (EMEA/CHMP 96286/2005)

Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (EMA/876333/2011 Rev 4)

Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations II: Biological medicinal products (EMA/168402/2014 Corr)

Guideline on good pharmacovigilance practices: Module V – Risk management systems (EMA/838713/2011 Rev 2).

Haemophilia registries workshop: https://www.ema.europa.eu/en/events/haemophilia-registries-workshop