29 April 2024

Draft Guideline on the clinical requirements for non-replacement therapy in haemophilia A and B – EMA/CHMP/136018/2023

1. General comments

	Stakeholder name (*to be repeated in all rows*)	General comment
1	EFPIA	There are several statistical considerations under the specified section and others section in the guideline (detailed in the following comments) that should illustrate the pitfalls to avoid and suggest strategies to implement in the statistical testing – please consider elaborating with illustrative examples for sponsor and/or developer clarity.
2	EFPIA	The guidance could benefit from a general discussion on the combination of phase 2 and phase 3 studies as outlined in the 'REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN' given the rarity of the patients within these disease areas as mentioned in the beginning of section 4.3. The agency could consider including an additional sentence on combination of phase 2 and phase 3 studies and refer to the reflection paper mentioned in the comment
3	EFPIA	A non-inferiority analysis is proposed for the comparison of the non-replacement therapy and the prophylaxis treatment regimen. Yet in a nonrandomized design the adequacy of a non-inferiority conclusion can be problematic even if the proposed statistical analysis fulfils the non-inferiority criteria. The 'GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN' provides several cases where the use of a non-inferiority trial is more suitable than a randomized superiority trial. It would be helpful if the guidance could provide justification of the non-inferiority trial with offset in these cases, or if referring to this guideline
4	EFPIA	Collection of "all bleeds" is recommended in the draft guidance. That implies collection of untreated bleeds (bleeds that do not require infusion/injection of coagulation factor containing products). Such bleeds are common and could for example be marks and bruises, small cuts that bleed for a few minutes,

		traces of blood after brushing of teeth, or short-lived nose bleeds. This type of bleeds is common in the general population. Collection of such (all) bleeds may not be adding scientific value in a clinical trial setting. Assessment of what to report/collect may be highly subjective introducing a level of uncertainty. Please consider recommending defining or setting a "threshold of significance" for "untreated bleed" collection in the study protocol as that could alleviate the problem. The confirmatory efficacy test should preferably only be based on ABR for bleeds requiring treatment with factor containing products.
5	EFPIA	The choice of NI margin has briefly been discussed. Given that non-inferiority trials are the preferred choice of design for the clinical development of non-replacement therapies in this guidance, the NI margin should be discussed. Please consider implementing the general considerations under 'GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN', including but not limited to a discussion of statistical reasoning and assay sensitivity, if possible
6	EFPIA	While some elements of the estimand in terms of population of interest and endpoint is discussed in other sections of the guidance, a more detailed elaboration on the other aspects from the estimand framework would be appreciated. Here a reflection like the one given in 'Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus' would be appreciated. A discussion on handling of intercurrent events such as surgery as mentioned in section 4.3.4 and missing data as mentioned under section 4.3.5 is needed, is possible please elaborate on the agency position. Furthermore, as a great deal of importance is put on the non-inferiority framework, the discussion should offset from the current EMA paper 'Concept Paper for the Development of a Guideline on Non-Inferiority and Equivalence Comparisons in Clinical Trials' – please consider referencing in this section.
7	EFPIA	Most special circumstances are mentioned but for future there should some consideration moving forward on how we handle assessment of treatments in women. The EMA (the agency) should consider some guidance in evaluating women with HA (or carriers). There is nothing in this document relating to this and this guidance is likely to be active for the foreseeable future (consideration such as is no consensus on trials including women at this stage could be seen as sufficient at this stage)

8	EFPIA	In the lack of an independent control and suggested stratification by disease severity, the proposed intra patient comparisons can be subject to a 'regression to the mean' issue.

(Add more rows as needed)

2. Specific comments on text

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1				

Executive summary

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.1 Introduction (background)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 35-37	EFPIA	Recommend specifying in the summary that the guideline pertains to HA and HB irrespective of inhibitor status, i.e. with and without inhibitors	For line 37 please consider adding "with and without inhibitors"
2	Line 45-36	EFPIA	Prophylaxis is the primary treatment strategy for hemophilia A patients with inhibitor. For 'primary treatment strategy' - if referring to severe haemophilia - 'on demand' is no longer standard of care as evidenced by most recent WFH guidance. If the agency were to include non-severe HA, particularly mild haemophilia, then on demand is still the SoC for many. This description needs to be updated e.g. severe haemophilia, or non-severe presenting with a severe bleeding phenotype require regular haemostatic treatment to prevent bleeding (prophylaxis~~).~~ The primary treatment strategy for severe haemophilia of non-severe haemophilia with a severe bleeding phenotype is prophylaxis with either factor replacement or non-factor	The primary treatment strategy includes on-demand treatment of bleeding or prophylactic treatment with factor or non factor replacement to prevent bleeding

2.2 Scope

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text

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2.3 Legal basis

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.4 Overall clinical development programme

2.4.1. Considerations for Exploratory Studies

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.4.2. Dosing

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 82-84	EFPIA	Consider adding "and efficacy" as the dose-exposure-bleeding	A thorough characterisation of the relationship between dose,

			relationship is key for Ph III dose selection	pharmacokinetic (PK) parameters, exposure pharmacodynamic (PD) response parameters and efficacy parameters is considered necessary for an appropriate dosing decision.
2	Line 85	EFPIA	Current text: 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. Comment: This does not consider biomarker-based dosing that is used in some novel approaches which is not related to either weight or a fixed dose.	
3	Line 94	EFPIA	Consideration for the agency to clarify which biomarkers it values as surrogate marker of VTE risk. There is scientific debate about 'normalisation' of thrombosis risk equivalent to the non-haemophilic population versus abnormal thrombogenesis specific to molecules	

2.4.3. Considerations for Confirmatory Studies

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 101-106	EFPIA	The justification of a proposed single arm (or rather single	

			sequence crossover) trial suggested is lacking. As outlined in ICH E9 randomisation will reduce bias in the associated analyses. Therefore it is not clear why a randomized cross over trial is not to be preferred to a single arm trial. This will of course require a careful consideration of the wash out period as also partly discussed in section 4.3.2. In the absence of randomization an adequate evaluation of before and after treatment will not provide an adequate intra-patient evaluation as stated in the same paragraph – please consider adding the argument	
2	Line 116	EFPIA	Current text: 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. Comment: what is the rationale for 12 months at steady-state? This would delay the development of novel therapies and several studies have historically used a 6-month period to capture sufficient efficacy period	The active treatment period should be at least 6 months at steady PD state to characterise efficacy and identify safety risks associated with these novel medicinal products

2.4.3.1. Patient population

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 124	EFPIA	Current text: 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. Comment: Historically safety pool consists of patients with and without inhibitors and this was agreed with EMA and FDA. What is the scientific rationale for not allowing extrapolation given that the pathophysiology is comparable across Hem A and Hem B, especially when clinical data confirm a similar response regardless of the hemophilia type? Statistically powered subgroup analyses in this rare disease are limited by the availability to enroll sufficient numbers of patients for each subgroup.	Pooling and/**or** Extrapolation between HA and HB may be acceptable when scientifically justified.
2	Line 126-128	EFPIA	By definition – non-factor replacement therapies are inhibitor insensitive/agnostic. Enrolling patients into a single study should be acceptable, but subgroup analyses should still be performed as populations may be different	In contrast, depending on the mode of action, including patients with and without inhibitors in one study would be acceptable.
3	Lines 130-132	EFPIA	If possible, please provide further clarification on what is required to request approval for moderate and mild severity	Depending on the mechanism of action and the intended indication, patients with severe, moderate or mild haemophilia (according to International

			Depending on the mechanism of action of the non replacement therapy (eg lack of additive procoagulant effect on top of residual FVIII or FIX), patients with mild hemophilia could be enrolled. De facto, emicizumab is approved and safely used in mild hemophilia A patients (acknowledging this is outside of EU)	Society on Thrombosis and Haemostasis, ISTH, definitions) can be included into the clinical studies.
4	Line 139	EFPIA	The draft guidance should not state that "'it currently remains unclear whether TFPI levels are comparable in HA and HB patients" Propose to delete this statement as it is not relevant - as the guidance in line 248 and 249 states a combined analysis of HA and HB patients is not deemed acceptable.	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. This issue as well as any potential impact on dosing needs to be addressed by applicants.
5	Line 143	EFPIA	Current text: 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. Comment: There is limited data to support this conclusion on a difference in thrombin generation between Hem A and Hem B, and contradictory to following paragraph.	

6	Line 148	EFPIA	Current text: 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. Comment: This approach does not take into account biomarker-based dosing, in which the dose of the IMP is titrated to achieve a prespecified AT activity level, thus making the actual dose (in mg) irrelevant to the analysis. The analysis will need to focus on the efficacy and safety in participants within that prespecified biomarker (AT) range.	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. Alternative approaches including biomarker-based analyses may be considered.

2.4.3.2. Objectives and Endpoints

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 163	EFPIA	Collection of duration of bleeding episodes is challenging as that requires collection of a bleed stop time. The bleed stop time may be difficult to assess from a patient perspective. Patients often struggle in distinguishing between bleed stop and resolution of bleed symptoms, also often patients forget to enter the stop time in the bleed diary. Probably the best	Please consider making collection of bleeding duration (in essence) stop time optional

			indicator of bleed stop is the number of doses needed to treat the bleed and the response to the treatment	
2	Line 174	EFPIA	…standard of care in most EU countries….as the number of patients both to be treated worldwide as well as to be enrolled in clinical trials cannot be based upon EU only there needs to be an acceptance of integration of standards from other parts of the world which includes OD comparison.	Please consider adding on line 174**:** "provided relevant justification, a global inclusion of haemophilia patients receiving other standards of care than that of EU may be considered".
3	Line 179	EFPIA	WFH have recommended that prophylactic treatment is standard of care. Observation with recently recruiting a phase 3 study in HA with FVIII mimetic in development proved challenging to recruit HAwI patients as those wishing to be on prophylactic treatment was already on prophylactic treatment. Only a few countries outside EU/North America/Japan with poor access to treatment were able to enrol such patients, hence it IS standard of care in EU.	Please consider adding for line 179 that "prophylactic treatment in HA patients with inhibitors has become standard of care in most EU countries".
4	Lines 182-188	EFPIA	It is not clear what the guidance is suggesting for inhibitor patients: on one hand it is suggesting to gather additional supportive data and on the other hand it is suggesting to have a primary endpoint in which either superiority relative to pre-study on-demand treatment or non-inferiority of prophylaxis versus pre-study prophylactic treatment is to be demonstrated. Can the	

			agency clarify is it just supportive or primary? In addition the current text may suggest that non-inferiority of prophylaxis versus pre-study prophylactic BPA might be acceptable as primary endpoint. Clarity would be appreciated by the agency in the guidance	
5	Lines 189-190	EFPIA	Previously it was stated in the guidance that only superiority vs on-demand is acceptable. Can the agency clarify why discussing in this section non-inferiority vs. on-demand? Additionally a clarification of what "margin" means, i.e., is it "non-inferiorty margin (NIM)" or also "the targeted difference for surperiority"?	Consider removal rest of sentence after: The choice of the margin(s) will be dependent on the baseline characteristics of the study population. And replacement in line 192 of "margin" by "non-inferiority margin or targeted difference for superiority"
6	Line 195	EFPIA	In this case, it would be very helpful to provide more advice on how to handle the carry-over effect. In addition to move the start timepoint of evaluating efficacy (a lot of data will be excluded if the half-life of the previous therapy is very long), e.g. include all the data on active treatment but implying innovative statistical methodology	

2.4.3.3. Estimand

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.4.3.4. Treatment of Bleeds

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 244	EFPIA	Given the importance of evidence on surgery related procedures more details on the evidence generation would be helpful. Please consider a more detailed description/discussion of the data that might be needed in the context surgical procedures	

2.4.3.5. Statistical Considerations

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Line 249-250	EFPIA	As the guideline says that "combined analysis of HA and HB is not deemed acceptable", Can the agency provide more clarity on the need to control multiplicity between HA and HB? Or is it	

			acceptable to consider multiplicity within HA and HB independently?	
2	Line 249-250	EFPIA	A combined trial with separate analyses for HA and HB is proposed. This appears to follow a basket trial approach with a master protocol. In the statistical section, please consider if a more elaborated discussion is needed with illustrative examples to cover the benefits of such designs.	
3	Line 256-257	EFPIA	The guidance says that the sample size calculation should take into account uncertainty with respect to bias due to lack of an independent control arm (for intra-patient comparison). Can the agency provide more clarity on which type of bias is expected (e.g. time-related bias) and provide guidance on how to assess this bias?	

2.4.3.6. Safety

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Lines 263-265	EFPIA	Comment: Given that severe haemophilia is a rare bleeding disorder and the established challenges of recruiting participants in clinical trials investigating novel therapies, can the Agency clarify or define what an 'adequate number of	

			participants' is to facilitate meaningful safety analyses, particularly for Haemophilia B participants with inhibitors? This should be based on historic precedent and clinical safety databases utilized for product approvals to date.	
2	Lines 266-267	EFPIA	Comment: Can the Agency provide the rationale for the recommendation that the active treatment phase should be at least 12 months at steady PD state to characterise long-term safety and detect potential safety risks? This should also account for variability in rebalancing agents' time to achieve steady state PD given differing MOAs.	
3	Lines 265-269	EFPIA	An active treatment period of 6 months is generally considered sufficient to characterise identify safety risk for authorisation. It is acknowledged that as per section 5 that additional data needs to be collected in post-marketing setting that will allow the detection of unexpected complications associated with these therapies.	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 6 months (at steady PD state) to characterise safety profile and detect potential safety risks (e.g. severe bleedings, thrombotic complications).
2	Lines 280-281	EFPIA	Comment: Disseminated intravascular coagulation (DIC) and thrombotic microangiopathy (TMA) represent distinct clinical diagnoses separate from classic arterial or venous thrombotic events. Both conditions can result	Proposed change: DIC and TMA should be incorporated as AESIs if there is an identified or potential risk in the DRMP based on a product's mechanism of action, preclinical, or clinical data.

			in diffuse microthrombi and/or medium vessel thromboses impacting multiple organ systems and eventual multiorgan failure. Both DIC and TMA often occur secondary to an underlying condition; primary diagnoses can include but are not limited to congenital conditions (i.e. congenital TTP), drug-induced TMA, solid tumour or hematologic malignancies, acute infection, sepsis, trauma, organ transplantation, as well as obstetric complications. While DIC and TMA can rarely occur as sequalae of an acute thrombotic event, the Sponsor does not recommend standard incorporation of DIC and/or TMA as AESIs, unless they are an identified potential or established risk in the Development Risk Management Plan (DRMP) associated with a given product based on mechanism of action, preclinical or clinical data obtained from the development program. An example, for reference, would be emicizumab, which carries a labelled risk of TMA. The rationale is that events of TMA and/or DIC may be multifactorial and non-specific to the IMP, hence requiring careful assessment of the conditions leading to the event. This practice should be standard as part of compliant and routine pharmacovigilance practice on behalf of Sponsor oversight.	

3	Line 283	EFPIA	The situations mentioned are acute and severe and specific guidance on management and potential pause of treatment may not be feasible. Patients experiencing such occurrences (trauma, sepsis, DIC etc.) should be managed in accordance with local standard of care.	Suggest rephrasing by instead adding by that "the sponsor could be contacted to discuss such cases, however, not to guide the patient management as such"
4	Lines 286-287	EFPIA	Assumption that mild haemophilia is not included in this assessment and it should be	(…) eg. reduced dose in patients with moderate or mild haemophilia).
5	Line 288	EFPIA	Anti-drug antibodies are usually only analysed at time of primary analysis and will therefore not be reported as adverse events. Hence, does the intended meaning of immunogenicity only refer to hypersensitivity reactions? If so, please consider specifying in the text	
6	Lines 263-265	EFPIA	Comment: Given that severe haemophilia is a rare bleeding disorder and the established challenges of recruiting participants in clinical trials investigating novel therapies, can the Agency clarify or define what an 'adequate number of participants' is to facilitate meaningful safety analyses, particularly for Haemophilia B participants with inhibitors? This should be based on historic precedent and clinical safety databases utilized for product approvals to date.	

2.4.4. Paediatric Population

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	Lines 303-304	EFPIA	Can it be clarified if conducting the primary analysis on the overall population and then showing consistent effect in each subgroup (adults and adolescent) is acceptable?	

2.5. Post-Authorisation, Registry Data

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6. Considerations and significant benefit

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.7. Conclusions

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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Other comments

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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