25 February 2016
EMA/129183/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease ' (EMA/CHMP/41230/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Bayer Pharma AG
2	Pfizer Inc.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
99	2	Comment: This is the first time low weight molecular heparin (LMWH) is mentioned in the document, however it is not spelled out nor defined. Proposed change (if any): Suggest spelling out LMWH and adding any applicable definitions.	**Accepted.**
104	2	Comment: While 'long-term trials' are mentioned, there is no guidance on the duration of the trials. Proposed change (if any): Suggest adding information related to length of 'long-term trials'.	**Not accepted.** Long-term sequels of VTE (post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension) can start after several months or years after the acute episode. Therefore, it is difficult to guide on the exact duration of the trials. On the other hand, the term "long-term" is already coined in the ICH guidance, and refer to "*chronic or repeated intermittent use for longer than 6 months*" (ICH E1). Paragraph was moved to section 7.4.2.
172 and 183	2	Comment: Compression ultrasonography (CUS) was first mentioned on line 172, but is not defined until line 183. Proposed change (if any): Suggest moving the definition from line 183 to line 172.	**Partly accepted.** We have spelled out "CUS" the first time it appears in line 172 " Compression ultrasonography (CUS)". However, the definition fits better in section 5.1.1 as it reads now.
207-208	1	Comments: Guidance regarding central adjudication is	**Not accepted.**

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		provided regarding CUS. What about other modalities?	An explicit mention to central adjudication is made in the guideline for CUS and venography. In section 6.1.1 is also stated that all major endpoints should be adjudicated by a blinded clinical events committee. Therefore, there is no need to refer to central adjudication each time we mention an imaging technique. It is implicit that, if the imaging technique is used for the diagnosis of a major endpoint, it has to be adjudicated centrally.
296	1	Comments: It is not clear why non-inferiority versus superiority is driven by clinical rather than statistical considerations.	**Not accepted.** The only difference in the main efficacy endpoint for non-inferiority vs. superiority is the consideration of VTE-related death (in non-inferiority trials) or all-cause death (in superiority trials). This is because "*in non-inferiority trials, it is generally recommended to choose an endpoint reflecting as much as possible the effect of a drug; therefore, a VTE related death (or a death considered to be due to VTE, such as fatal PE and sudden death, as autopsy findings may not be always available) is recommended. For superiority trials, a death form any cause is recommended as a part of a composite endpoint.*" (Doc. Ref. CPMP/EWP/707/98 Rev. 1)
300-301	1	Comments: “Recurrent DVT and PE should be objectively verified (see section 3). Deaths should be carefully characterised regarding their relationship to VTE, according to criteria specified in the study protocol” – this might require further details.	**Partly accepted.** The intention of the phrase is that the criteria to consider the death as related or not to VTE have to be pre-specified in the study protocol, in order to allow the central adjudication committee to take a evidence-based decision. In other words, the definition of VTE-related death included in section 5.1.2

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			should be followed. We have rephrased as follows: "Deaths should be carefully characterised regarding their relationship to VTE, according to criteria ***to be pre-***specified in the study protocol ***(see also VTE-related death in section 5.1.2)***."
321	1	Comments: It is not clear what “in particular” means here. This seems to be SVT specific?	**Accepted.** "particular" has been replaced by "specific".
362	2	Comment: The complexity of providing guidance for retrospective observational studies especially for the definitions provided in Section 8 prohibits their inclusion in this guidance. However, prospective observational studies should be covered. Proposed change (if any): Suggest the inclusion of prospective observational studies in ‘Section 7. Design strategy’.	**Not accepted.** The scope of the guideline is the development of drugs for the treatment of VTE and sVT. Prospective observational studies may have a place post-marketing, but its relevance pre-authorisation is limited.
440-441	1	Comment: While this is true as per guideline recommendation, LMWH for a long-term study may lead to more drop-out rates in the comparator arm due to the need for sc application.	**Not accepted.** Subcutaneous LMWH administration is relatively well tolerated by patients, particularly if the situation to be treated is serious, as VTE. Some oral drugs have a significant dropout rate (For example, dabigatran and dyspepsia). Therefore, a priori, it is not clearly evident that a LMWH could be less well tolerated than other drugs. On the other hand, the issue related to withdrawal rates during comparative studies is also further discussed in the "*statistical considerations*" subsection of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
487-488	2	Comment: 'TTR quartiles of the INR' may not be an appropriate subgroup. The novel agents do not influence the INR. INR is an inappropriate marker for activity for those agents. Creating subgroups based on INR or time in therapeutic range as defined by INR levels will produce results that have no valid interpretation. Proposed change (if any): Suggest removing the subgroup of 'TTR quartiles' or clarify to use only if appropriate.	**Not accepted.** It is endorsed that INR is an inappropriate marker for activity of the novel oral anticoagulants. However, it seems to be a misunderstanding in the interpretation of the text of the guideline. The guideline mentions "centre time in therapeutic range", therefore, it refers to subgroups by centres, according to the quality of anticoagulation with warfarin by center. It does not refer to subgroups by TTR in the overall populations by treatment group, because it is already evident that results of subgroups based on INR alone, will produce results that have no valid interpretation, as the INR is not a marker of activity for non-vitamin K anticoagulants.
509	1	Generally: Standardised guidance on how to put patients back on antithrombotic therapy following a bleeding event should be included as new sub analysis from ENGAGE AF-TIMI 48 showed that 60% of patients who stopped therapy following a non-fatal major bleeding event did not receive any other form of antithrombotic therapy thereafter – these patients had substantially worse outcomes than the overall study population.	**Not accepted.** The guideline already includes a recommendation to include *"...a plan for safely transitioning subjects in case of premature discontinuation of study medication if continued anticoagulation is needed"* (last paragraph in subsection "design", in section 7.4.2). The guidance on how to put patients back on antithrombotic therapy following a bleeding event is a rather specific issue that may depend on the type of compound, indication, patients characteristics, etc. Therefore, this guidance for "bridging anticoagulation" or "safe transitioning" should be planned on a case-by-case basis.
530-531	1	Comments: Although the definitions for major bleeding are consistent with the ISTH definitions there is a need for specifications/standardisation of the timeframe for	**Partly accepted.** It is endorsed that in long-term trials in the treatment of VTE,

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		defining major bleeding events (i.e. haemoglobin drop of >= 2g/dl), and the event itself linked to identifiable bleeding (Hb drops could have occurred for other reasons since the first measurement pre-randomisation) -> one option for differentiation between chronic anemia and a genuine acute bleeding event (that are intended to be count in a trial as potentially related to the intervention) could be the introduction of XX-hours timeframe for a Hb drop of >= 2g/dl	there may be a drop in haemoglobin overtime from randomisation that could not be related to acute bleeding. In that case, "pre-randomisation" levels could be different from "pre-bleeding" levels. Therefore, "Pre-randomisation level" has been replaced by "pre-bleeding level". It is implicit that it refers to the last Hb value available before the bleeding event.
546	1	Comments: Fatal **and/ or** symptomatic intracranial bleeds?	**Accepted.**
547	1	Comments: A standardized time frame of the drop of Hb would be desirable to standardize and enable comparison between studies.	**Partly accepted.** "Pre-randomisation level" has been replaced by "pre-bleeding level". It is implicit that it refers to the last Hb value available before the bleeding event.
556-564	1	Comments: CRNM bleeding definitions should be described in a standardised and specific manner otherwise it ends up as very useful information but also very subjective.	**Not accepted.** The definition of CRNMB is included in the first paragraph of section 9.1.2. The second paragraph includes a list of examples, as it is difficult to standardise a definition based on objective measurements (apart from stating that CRNMB must not fulfil with the objective criteria for major bleeding). Unfortunately, there is not a more standardised or specific manner to define CRNMB.
589	1	Comments: Transfusion of platelets, FFPs and other factor concentrates may also be relevant.	**Not accepted.** Although it is endorsed the relevance of the need for transfusion of platelets, FFPs and other factor concentrates, it is transfusion of packed red cells or whole blood what is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			directly relevant for measurement of blood loss.
645	1	Comments: - Impaired renal function is a clear predictor for worse outcomes across the trials, including stroke, bleeding and death - definitions of renal impairment should be standardised across trials / regions based on CrCl - due to different ranges available globally they should be specified in the document	**Partly accepted**. We have included in sections 3 a reference to the "Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal 5 function (EMA/83874/2014)". It includes standardised definitions of renal impairment.
653	1	Comments: Suggest re-phrasing - identify if a different dose is appropriate in the special populations	**Accepted.**