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Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease

Draft

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This guideline replaces 'Note for guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease' (CPMP/EWP/563/98).

Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu

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Executive summary

Venous thromboembolism (VTE) is the third leading cause of death due to circulatory diseases, only behind of myocardial infarction and stroke [1]. Since the publication of the *CPMP guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease [CPMP/EWP/563/98]* in 2000 [2], there has been intense research in this field. An update of the mentioned guideline is considered necessary to adapt its content to current scientific knowledge and to harmonise it with the content of new or revised EMA guidelines related to clinical investigation with antithrombotics. The update includes: a) the distinction between initial and extended treatment of VTE, and between treatment of deep vein thrombosis (DVT) and superficial vein thrombosis (sVT), with a discussion on the need for specific studies in each of these situations and in certain special populations (e.g.: VTE associated to cancer and/or central venous catheters, VTE during pregnancy or childhood); b) current place of alternative imaging techniques for diagnosis of VTE; c) suitable control drugs that may be used in comparative trials; d) standardized definition of bleeding events and its assessment, as well as detailed description of methods for measuring blood loss and timing for collection of data; e) inclusion of additional secondary safety outcomes of clinical importance for new antithrombotics, like hepatic events or arterial thromboembolism.

1. Introduction (background)

The reported annual incidence of VTE in Western countries is estimated to be approximately 1-2/1,000 [3]. VTE clinically manifests as deep vein thrombosis (DVT) and pulmonary embolism (PE). A transient or permanent risk factor for VTE is demonstrable in a large fraction of patients.

There is good evidence that DVT and PE may be considered as expressions of one and the same disease, as in different studies, patients presenting with documented DVT have been shown to have evidence of silent PE or perfusion defects on ventilation/perfusion lung scan in 30-70% of cases [4,5], while about 70% of patients with documented symptomatic PE will have DVT [6].

Since the basic treatment strategy for patients with DVT and PE is similar, it is considered relevant that efficacy and safety studies of new treatment modalities in this area should include patients with DVT and PE (either in the same study with appropriate stratification or in separate studies). There are, however, some important differences between patients who present with PE and those who present with DVT that justify separate consideration of some aspects of the treatment of PE. First, the risk of recurrent VTE, including early death (within 1 month) from VTE is greater after presenting with PE than after DVT. These differences may justify more aggressive, or more prolonged, long-term therapy for PE than for DVT [7].

The choice of treatment in VTE should be based on the clinical impact of the disease. Therapy aims are to prevent extension of the thrombus, (fatal) pulmonary embolisation and early recurrence. In addition, the duration of therapy should be adapted to the risk for VTE recurrence in the patient population under study.

It is important to distinguish between initial treatment of VTE (usually 3-6 months), and extended treatment (secondary prevention of recurrences) of VTE (once initial treatment has finished, to indefinite). For acute DVT or haemodynamically stable PE, current guidelines recommend initial treatment with a parenteral anticoagulant for at least 5-7 days and a vitamin K antagonist for at least 3 months, started together [7]. For a first proximal DVT or PE that is provoked by transient risk factors (e.g. recent surgery, trauma, immobilisation), or in patients with unprovoked VTE and high risk of

bleeding, 3 months of therapy may suffice. For acute VTE that is unprovoked and bleeding risk is low or moderate, extended therapy beyond 3 months is recommended. In acute VTE associated with active cancer, extended therapy (beyond 3 to 6 months) with LMWH over vitamin K antagonists is recommended. Some patients with VTE and chronic risk factors for recurrence may be candidates for life-long anticoagulant prophylaxis.

Trials submitted to support a marketing authorisation are not expected to address if the benefit in preventing recurrent VTE also extends to the long-term sequels of VTE (i.e.: the post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension). However, long-term trials are encouraged to be conducted post-authorisation to address this.

Finally, superficial vein thrombosis (sVT) is closely linked to DVT and PE. DVT is diagnosed in 20-30% of sVT patients. Moreover, clinically relevant symptomatic VTE events complicate isolated sVT in 4-8% of patients [8]. Anticoagulant treatment is usually needed in extensive sVT (≥ 5 cm in length), but of lower intensity and duration than for VTE, generally comprising the use of a parenteral anticoagulant at prophylactic doses for 1-2 months [7,9].

2. Scope

The aim of this guideline is to provide guidance to industry when performing trials to develop medicinal products in acute treatment and extended treatment of VTE (DVT and PE). Recommendations for the clinical investigation of medicinal products in the treatment of sVT are also provided, as it shares some methodological features with clinical investigation in VTE. The revised guideline does not deal with the development of medicinal products for patients with haemodynamically unstable PE, considered to be candidates for thrombolysis or pulmonary embolectomy.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles and parts I and II of the Annex I to Directive 2001/83 as amended.

Pertinent elements outlined in current and future EU and ICH guidelines, should also be taken into account, especially those listed below:

- Dose-Response Information to Support Drug Registration (ICH E4);
- Statistical Principles for Clinical Trials (ICH E9);
- Choice of Control Group and Related Issues in Clinical Trials (ICH E10)
- Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99);
- Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99);
- Investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013);
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A);
- Pharmacokinetic Studies in Man (3CC3A);
- Studies in Support of Special Populations: Geriatrics (ICH E7 CHMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009);

- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95);
- Reporting the Results of Population Pharmacokinetic Analyses (CHMP/EWP/185990/06);
- Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population (EMEA/CHMP/EWP/692702/2008).

4. Selection of patients

Inclusion and exclusion criteria in clinical trials should ensure adequate representativeness of the population studied across the entire clinical development, in reference to the population who will be treated with the new drug in standard clinical practice, while keeping the necessary assay sensitivity of individual studies. Special mention is made to the need for inclusion of a sufficient number of older patients (see section 8.3). Clinical trials may include patients with acute VTE (DVT and/or PE) or sVT (see also section 5.1 for the diagnostic criteria of DVT, PE or sVT).

It is expected that clinical trials in patients with acute VTE will focus on patients with symptomatic, usually proximal (extending above knee level) DVT and/or symptomatic PE. Stratification of the study population regarding the presence of symptomatic PE at baseline as well as by intended treatment duration should also be undertaken. If the claim treatment of PE is intended but supported with a pivotal trial recruiting patients with both types of index VTE (DVT and/or PE), it is sufficient to prove non-inferiority for the overall study population, provided that there is a sufficient representation of patients with PE and the effect is homogeneous in both subpopulations. However, patients with PE could also be studied in separate clinical trial/s.

The population encountered in clinical practice will be heterogeneous with regard to the presence of identifiable risk factors for VTE and comorbidity. This has major impact on the risk for recurrences during and after therapy, as well as all-cause mortality. To increase assay sensitivity, only patients with reasonable remaining life expectancy should be included. It is also important that studied patients are well characterised and that treatment groups are comparable regarding risk for recurrent VTE.

Factors that should be taken into consideration related to the initial VTE event and risk factors for recurrence include:

1) Clinical presentation: Unprovoked versus provoked VTE;

2) Risk factors for recurrence: a) Temporary risk factor (e.g.: recent surgery or trauma, immobilisation, estrogen therapy); b) Previous episodes of VTE;

3) Presence of known prothrombotic states (e.g. deficiencies of AT III, resistance to activated protein C, lupus anticoagulant, antiphospholipid antibody, hyperhomocysteinemia, factor V Leiden, prothrombin mutation G20210A, etc.).

Patients with VTE associated to active cancer or central venous catheters (CVC) and VTE occurring in children or during pregnancy have particular characteristics related to clinical presentation, treatment and outcome. Before a claim of use can be granted in these populations, separate studies are needed using an appropriate comparator (see also section 7.4, subsection “choice of control group”).

Finally, in the particular case of clinical trials in the treatment of sVT, it should include patients with symptomatic lower limb extensive (at least 5 cm long) superficial-vein thrombosis, as confirmed by standardized CUS [9,10]. In sVT, it is crucial for the external validity of the study that DVT is effectively excluded at baseline.

5. Methods to assess efficacy

5.1. Primary efficacy outcome

5.1.1. Methods for documentation of DVT/PE

The following diagnostic methods are considered acceptable for documentation of DVT and PE. It is considered that the diagnosis of VTE should be now included in a diagnostic strategy including clinical probability and the use of D-Dimers to rule out VTE. It is recommended to use the same methods for diagnosis of index and recurrent events across all the trial.

Established methods for diagnosing DVT

- Bilateral compression ultrasonography (CUS) examination is a non-invasive method that is well accepted by patients and currently the most frequent method used in clinical trials due to its adequate sensitivity and specificity to detect symptomatic, proximal DVT [12], but is less adequate for distal DVT and asymptomatic DVT. Video recordings of CUS examinations can be adjudicated centrally, but all sonographers have to receive CUS training to ensure a high quality of standardized CUS, particularly if a quantitative evaluation of thrombus burden is to be conducted. Not infrequently, CUS imaging may be technically difficult, or the abnormality is more suggestive of old rather than recent thrombosis. If the CUS examination is inconclusive, venography is indicated to confirm or refute the diagnosis of DVT.
- Ascending venography is regarded as the gold standard method due to its high sensitivity and specificity. For this method a quantitative system has been reasonably validated [11] and it allows (blinded) centralised reading or reading by several observers. However, the method may be of low acceptability to the patient, especially for repeated examinations and for these reasons is less and less performed in clinical trials.

Established methods for diagnosing PE

- Pulmonary angiography is the gold standard, but is now rarely performed.
- Spiral computed tomography (sCT) is currently the most frequent method used for the diagnosis of PE in clinical trials so far.
- Ventilation-perfusion lung scan (VPLS). A normal VPLS or perfusion lung scan (PLS) is considered adequate to rule out PE. Only so-called “high probability” findings on VPLS are specific enough to allow a positive diagnosis of PE. Other types of findings should be regarded as “non-diagnostic” and should be verified through pulmonary angiography or positive CUS in patient with symptomatic PE (see below).
- In the presence of symptoms indicative of PE in a patient with demonstrated DVT, nondiagnostic” findings on VPLS are sufficient for a diagnosis of PE.

New methods for diagnosing DVT/PE

Computed tomography venography (CTV) or magnetic resonance venography (MRV) are validated methods for diagnosis of DVT/PE and could complement current established techniques. CTV has similar sensitivity/specificity to ultrasound in the diagnosis of proximal DVT and also offers assessment of the pelvic and deep femoral veins [13]. CTV leads to the detection of an additional 3% of cases of VTE when combined with pulmonary CT angiography in the assessment of PE [14]. MRV can be highly

accurate, easy to perform and successful in many situations where other imaging techniques yield ambiguous results [15].

5.1.2. Diagnostic criteria of outcome events

The diagnosis of "acute" recurrent VTE (i.e. during the first 3-6 months of treatment) should be based on the comparison of objective tests compared to baseline test performed for the initial diagnosis of acute VTE.

The diagnosis of recurrences during an extended study after the initial 3 to 6 months of treatment should be compared to a new baseline test (i.e. CUS for VTE or sCT or VPLS for PE) performed at the end of the initial treatment. A recurrence during the extended treatment should be defined in comparison to this new baseline test.

The following diagnostic criteria are considered acceptable for confirmation of recurrent DVT and PE in studies of drug efficacy and safety:

Suspected (recurrent) DVT may be confirmed in the presence of at least one of the following findings*:

- Abnormal CUS where compression had been normal or, if non-compressible during screening, a substantial increase (4 mm or more) in diameter of the thrombus during full compression;
- An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of non-visualization of veins in the presence of a sudden cut-off on venography;
- An extension of an intraluminal filling defect , or a new intraluminal filling defect on sCT of the leg.

Suspected (recurrent) PE may be confirmed in the presence of at least one of the following findings:*

- A (new) intraluminal filling defect in segmental or more proximal branches on sCT scan;
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram;
- A (new) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on VPLS;
- Inconclusive sCT, pulmonary angiography, or VPLS with demonstration of DVT in the lower extremity.

**Diagnosis of symptomatic recurrent DVT or PE based solely on clinical signs and symptoms is discouraged. The number of such episodes, especially if leading to changed or renewed therapy, must, however, be noted and accommodated for in the analyses.*

VTE-related death:

- PE based on objective diagnostic testing, autopsy;
- Death which cannot be attributed to a documented cause and for which DVT / PE cannot be ruled out (sudden unexplained death).

Asymptomatic deterioration of thrombus burden (Phase II trials):

Asymptomatic deterioration in thrombotic burden may be assessed by comparison of the CUS (DVT) and/or PLS (PE) (or any other validated technique allowing for quantitative measurement of thrombus burden) at the study endpoint (e.g.: at the end of acute VTE treatment and at the end of long-term treatment) with baseline. The definition of "deterioration" has to be pre-specified in the protocol and may include:

Deterioration of DVT: increase of 4 mm or more in the residual diameters of at least one of the veins (common femoral, superficial femoral, and popliteal) under full compression at study endpoint as compared to baseline [16,17];

Deterioration of PE: decrease by more than 0.25 (25%) in lobe score for any individual lobe at study endpoint as compared to baseline [18].

Symptomatic extension of sVT (sVT trials only):

Downstream (i.e., proximally) symptomatic progression of the initial sVT by at least 2 cm AND to within 3 cm or less from the sapheno-femoral junction confirmed by CUS [9,10], or extension to the deep venous system.

Symptomatic recurrent sVT (sVT trials only):

New episode in any other superficial venous location, confirmed by CUS, meeting at least one of the following criteria:

- The new symptomatic sVT was in a different superficial vein and not directly contiguous upstream (i.e., distally) with the index sVT, or
- The new symptomatic sVT was in the same superficial vein but clearly distinct from the index sVT with an open venous segment of at least 10 cm in length [9,10].

5.2. Secondary outcomes

All secondary efficacy endpoints should be defined by generally accepted definitions and diagnostic criteria should be clearly predefined in the study protocol.

Deaths should be classified using all available methods, including autopsy results, physicians' reports, and other clinical data available. All deaths should preferably be categorised as "non-vascular", "vascular" or "unknown aetiology". Vascular deaths should include deaths caused by thromboembolic events (PE, stroke), all cardiac deaths (e.g.: due to myocardial infarction, heart failure or arrhythmia) and bleeding.

All secondary efficacy endpoints should be adjudicated by an independent and blinded committee in order to limit the introduction of any bias.

6. Assessment of efficacy criteria

6.1. Primary efficacy outcome

6.1.1. Confirmatory trials

The main efficacy outcome recommended in Phase III trials in the treatment of VTE is the composite of:

- Documented symptomatic recurrent DVT;
- Documented symptomatic recurrent non-fatal PE;
- VTE-related death (non-inferiority trials) or all-cause death (superiority trials).

All major endpoints should be adjudicated by a blinded clinical events committee. Definitions of recurrent DVT, PE and VTE-related death are provided in section 5.1.2 (Diagnostic criteria of outcome events).

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.

Subgroup analyses are strongly encouraged according to index event (together with stratified randomization in trials recruiting both types of index VTE, DVT and/or PE, see section 6.1) and are encouraged to illustrate outcome in relation to: a) presence/absence of a history of previous episodes of VTE; b) level of extension of index and/or recurrent DVT; c) severity of index and/or recurrent PE: *e.g.* as indicated by clinical or echocardiographic evidence of right ventricular failure;

In studies evaluating medicinal products intended for the acute treatment of VTE, the study period for primary evaluation should be at least three months up to 12 months. In trials assessing different durations of study treatments (e.g.: due to the inclusion of patients at different risk of recurrence), a stratified randomisation should be made depending on intended treatment duration (e.g.: 3, 6 or 12 months). As patients with acute VTE may be heterogeneous regarding risk factors for recurrence, it is recommended that the intended treatment duration should be decided according to objective criteria pre-specified in the protocol depending on the baseline risk for recurrent VTE. The time point for primary evaluation must be related to the presence of non-transient risk factors for recurrent VTE in the population under study. Unless otherwise justified, controlled data on a sufficient number of patients at high risk for recurrent VTE (idiopathic proximal DVT), treated for at least six months should be presented, with appropriate follow-up of at least 1 month. For medicinal products intended for chronic/indefinite use, safety data extending beyond this period should also be presented.

Regardless of treatment duration, an appropriate follow-up of at least 1 month after treatment discontinuation should be included to assess a possible rebound effect.

In the particular case of Phase III trials in the treatment of sVT, the recommended endpoint is the composite of:

- Documented symptomatic DVT
- Documented symptomatic non-fatal PE
- Symptomatic documented extension of sVT (see section 5.1.2 for definition)
- Symptomatic documented recurrent sVT (see section 5.1.2 for definition)
- VTE-related death (non-inferiority trials) or all-cause death (superiority trials).

In sVT, the primary endpoint events are expected to be driven by symptomatic extension or recurrence of sVT. Such a reduction of extension and recurrence of sVT could be regarded as clinically meaningful if it is shown to result in reduced pain and symptoms related to the inflammatory process [10].

6.1.2. Exploratory trials

For proof-of-concept and dose-ranging studies aiming to document the effects of treatment on thrombus extension and/or recurrence, an objective primary efficacy outcome with sufficient sensitivity (e.g.: including symptomatic and asymptomatic VTE) is recommended.

The following composite endpoint may be appropriate:

- Documented symptomatic recurrent DVT
- Documented symptomatic non-fatal PE
- VTE-related death
- Asymptomatic deterioration in thrombotic burden (see section 5.1.2 for definition).

Repeat examinations should be undertaken at baseline and after the end of treatment. If the dosing of the new compound is more intense during the first 1-3 weeks than hereafter, a repeat examination should be undertaken at the end of this initial acute treatment as well.

As the dose to be tested in confirmatory studies will depend on the efficacy in preventing VTE versus bleeding risk, the effects on thrombus extension and/or recurrence during phase II trials should be complemented with the use of a sensitive safety endpoint to assess bleeding risk, like the sum of major and clinically relevant non-major bleeding (see section 8.1 for definition)

6.2. Secondary outcomes

A mandatory secondary analysis should include the individual components of the recommended primary efficacy endpoint.

Other recommended clinically relevant secondary efficacy outcomes, relevant for antithrombotic drugs, are the occurrence of:

- Stroke
- Myocardial infarction
- Vascular death
- Components of “VTE-related death”
    - Fatal PE documented by objective methods
    - Sudden unexplained deaths in which a fatal PE could not be ruled out.

Net clinical benefit endpoints, combining both efficacy and safety endpoints (e.g.: symptomatic recurrent VTE, major bleeding and all-cause death), can be of value in the risk-benefit assessment of the studied anticoagulant agents. The evaluation of QoL by standardized form comparing the results between the experimental and control drugs may be of interest.

7. Design strategy

The initial studies should determine the general safety of the compound and should provide an indication of doses of potential clinical relevance and of their effects on clinically useful monitoring variables for anticoagulant effect. Therapeutic studies should determine the efficacy and safety of the

drug under investigation in comparison with standard of care or placebo if no standard of care is established in a particular clinical situation.

7.1. Pharmacodynamics

Pharmacodynamic trials should investigate the mechanism of action of the product and the correlation between the PK and PD in healthy subjects and in patients, by using the appropriate human models of thrombosis, in the presence of drugs known to affect haemostasis and coagulation time assays. Effect on thrombus formation, thrombin generation, global clotting tests or specific tests relevant for the individual drug under investigation should be assessed as appropriate. The timing of performing coagulation time assays after drug intake should be considered when studying pharmacodynamics.

7.2. Pharmacokinetics

Pharmacokinetics trials should be performed in healthy volunteers and in patients following applicable guidelines (see section 3) in order to obtain information on the absorption, distribution, metabolism and excretion of the product following its proposed route of administration.

In addition, pharmacokinetic profile of the product in development should also be studied in the following specific patient populations: patients with impaired renal function, impaired liver function, extreme body-weights, and older patients (see also section 8.3).

7.3. Interactions

All potential clinically relevant drug-drug or drug-food interactions derived from the pharmacokinetic or pharmacodynamic characteristics of the investigational drug should be specifically investigated following applicable guidelines (see section 3), preferentially before approval. The potential clinical impact of these interactions should be further investigated in the planned phase 3 studies as appropriate (see also section 8.3 for special populations).

7.4. Therapeutic studies

7.4.1. Dose-response studies:

These studies should allow choosing the selection of an appropriate dosing of the medicinal product in terms of total dose and the dosing interval, in order to find an appropriate dosing of the new drug in terms of the balance between efficacy and safety

The major dose-finding studies should test several doses of the medicinal product. The studies should be conducted in a limited number of patients by dose-groups or dose-interval groups (once-daily, twice-daily) and with a limited duration (about 3 months) in order to minimise under-treatment, and should normally include an active comparator arm with an oral anticoagulant approved for this indication (for more details see “Choice of control group” subsection). These studies will be usually underpowered to detect differences in hard efficacy endpoints, but may allow detecting differences in clinically relevant bleeding (the composite of major bleeding and/or clinically relevant non-major bleeding) as well as coagulation and laboratory parameters (i.e.: drug plasma concentrations, APTT, D-dimer, etc.). Dose-response data from other indication/s (e.g.: prophylaxis of DVT), as well as population PK/PD approaches may also help to establish dose-response in the treatment of VTE.

7.4.2. Confirmatory trials:

Design

For confirmatory trials a prospective, double-blind randomised, controlled, parallel group clinical trial is recommended.

Data from open label studies using VKA as comparator might be acceptable if the outcomes are blindly adjudicated, the methodology is robust and the results are clinically and statistically meaningful. However, even under these conditions treatment allocation awareness could result in bias in a clinical setting where coagulation monitoring is critical for the treatment success and treatment outcomes are strongly influenced by the quality of the INR control. Therefore, a double-blind design is preferable.

Stratified randomisation may be needed to account for factors that may significantly influence the primary outcome (e.g. index DVT or PE, study centre, etc).

In controlled clinical trials with VKA, the INR has to be monitored as appropriate in the beginning of the study and at least every 4 weeks thereafter. Double-blinding can be implemented using sham INRs [19, 20]. In case of a medical emergency, unblinded INR measurements may be necessary. The protocol has to pre-specify the necessary instructions to ensure that these unblinded INRs do not come to the attention of the Clinical Endpoint Committee (CEC), in order to ensure a blinded assessment of outcomes. In these trials using VKA the measure of TTR (time spent in the therapeutic range) is highly recommended.

The study should include a follow-up of at least 30 days after last day of study drug, and a plan for safely transitioning subjects in case of premature discontinuation of study medication if continued anticoagulation is needed should be properly addressed.

Choice of control group

The choice of control group will depend on the clinical setting and patient population. An active control group is normally required in pivotal studies due to the severity of the disease to be treated (DVT and/or PE) unless justified.

For the initial treatment of VTE, an oral vitamin K antagonist, dose-titrated to an International Normalised Ratio (INR) of 2.0-3.0, overlapped with a parenteral anticoagulant (e.g.: LMWH or fondaparinux) for at least 5 days and until the INR is within therapeutic range , is an accepted comparator. Direct oral anticoagulants approved in this indication are considered valid comparators in this clinical setting as well.

The use of placebo may be appropriate when the new antithrombotic is given on top of standard of care, or when the study is aimed to extend prophylaxis of recurrent VTE (secondary prevention of recurrences) in patients in which extended prophylaxis of recurrence is not established according to scientific knowledge (i.e.: in patients with VTE who had completed an initial anticoagulation therapy

and for whom there is clinical equipoise regarding the continuation or cessation of anticoagulation therapy)..

LMWH is currently the drug of choice in VTE associated to cancer [21] and pregnancy [22]. Therefore, LMWH instead of VKA is recommended as active comparator in VTE clinical trials in these situations.

Concomitant medications/procedures

Concomitant medications: The trial should allow patients to receive concomitant medications usually recommended by guidelines for prevention of cardiovascular diseases. These drugs may include low-

dose acetylsalicylic acid (ASA) and/or other antiplatelets. The use of other concomitant drugs will depend on the risk for interactions of the investigational drug with other compounds (i.e.: other drugs that alter haemostasis, P-glycoprotein inhibitors/inducers, CYP inhibitors/inducers, etc.). In pivotal trials it is preferred not to exclude common medications used in the target population, unless a clear contraindication exists, in order to avoid too much exclusion of a representative population.

Concomitant procedures: the protocol has to describe the management of anticoagulant therapy during the clinical trial in case of elective and urgent surgical procedures as well as major trauma.

Quality of oral anticoagulation

When VKA is used as comparator, the quality of oral anticoagulation should be based on the time in therapeutic range (TTR) calculated by the Rosendaal method [23]. The calculation of the TTR should include the total time on and off drug in all patients. As sensitivity analysis, the TTR may be calculated as the average of TTR values for individual patients (Method of Connolly) [24], which does not include the first 7 days after treatment is started or restarted, time > 5 days from temporary discontinuation and time after permanent discontinuation.

The TTR should be shown as mean and median values in the overall population as well as by centers and regions, since the site highly influences the quality of anticoagulation.

The impact of quality of oral anticoagulation on the main efficacy and safety outcomes has to be shown:

- By quartiles of centre time in therapeutic range (cTTR): below 1st quartile, between 1st and 2nd quartile, between 2nd and 3rd quartile, above 3rd quartile.
- By cTTR, in the following intervals of cTTR: <50%, 50-65%; >65%.

In addition, the impact of treatment interruptions on the main efficacy outcomes has to be shown in patients after:

- Temporary interruptions < 5 days and ≥ 5 days.
- Permanent interruptions (early discontinuations and end-of-study).

Statistical considerations

Non-inferiority testing (followed by superiority if non-inferiority is demonstrated) is the recommended approach in active controlled trials. The analysis of non-inferiority and superiority should follow general statistical guidelines (ICH E9). In non-inferiority trials, the choice of the non-inferiority margin should be pre-specified and justified (ICH E10). In cases where the confirmatory evidence is provided by one pivotal study only, special attention will be paid, among others, to the degree of statistical significance (CPMP/EWP/2330/99).

The pivotal studies should usually be event-driven studies with a goal of collecting a pre-specified number of primary efficacy endpoints. The analysis to show non-inferiority should include the primary endpoint events while taking study drug including a period of 3 days after study drug discontinuation (on-treatment analysis). Sensitivity analyses should include events occurring 1 week and 1 month after study drug discontinuation in order to investigate a possible early rebound increase in thromboembolism after treatment cessation. The analysis to show superiority should include all primary endpoint events occurring through end of study (from each patient's date of randomisation to the estimated date of attainment of the study's target of primary endpoint events).

Key pre-specified subgroups should include at least oral anticoagulation status at randomisation, TTR quartiles of the INR, age categories, renal function subgroups and geographic region (EMEA/CHMP/EWP/692702/2008). For this purpose, the definition of geographic regions should allow to show the results in patients specifically included within the EU/EEA area.

Additional investigations during pivotal trials

The following investigations may be useful but not essential for further refining the knowledge of the PK/PD, efficacy and safety of the new product:

- **Pharmacokinetics/pharmacodynamics:** Characterize the relationship between exposure and response in terms of PD markers, efficacy and safety to the new drug (i.e.: plasma concentration, coagulation tests, etc.). Particular attention should be paid to the appropriate determination of pharmacokinetics in older patients, as potential increased exposure and/or decreased elimination may pose elderly patients at particularly increased risk of major bleeding, particularly haemorrhagic stroke.
- **Pharmacogenetics:** Identify genetic polymorphisms that identify patients at higher risk for recurrent VTE and bleeding.
- **Biomarkers:** Correlate concentrations of biomarkers of thrombosis, inflammation, endothelium, metabolism, necrosis and hemodynamic status with efficacy and safety profiles of anticoagulant therapy. These biomarkers should be measured at baseline, during treatment and after treatment withdrawal (after the drug has been cleared from plasma, i.e. at least 5 half-lives) in order to investigate a possible rebound hypercoagulation.

8. Safety aspects

8.1. Bleeding events

Bleeding is the main complication of antithrombotic therapy. There should be consistency in the method used for assessing bleeding associated with the medicinal product of interest across the entire development program. A validated and clinically relevant classification of bleedings should be used. Similar to the efficacy evaluation, the adjudication of bleeding events by a central independent and blinded committee of experts, using pre-specified limits and clear terms of reference is strongly encouraged.

In dose-finding studies, the use of a sensitive safety endpoint to assess bleeding risk, like the sum of major and clinically relevant non-major bleeding, is recommended. In pivotal trials, the recommended primary safety endpoint is major bleeding, but the sum of major and clinically relevant non-major bleeding is to be analysed as well (secondary endpoint).

The description of the severity (i.e.: life threatening versus non-life threatening major bleed), localisation (i.e.: intracranial, gastrointestinal, etc.) and temporal pattern (i.e.: time-to-event analysis) is encouraged.

The use of other bleeding definitions (i.e.: TIMI, GUSTO, BARC) in addition to the ones included in this document for the purpose of sensitivity analyses is optional.

8.1.1. Major bleeding

Major bleeding is defined as a bleeding event that meets at least one of the following criteria:

- fatal bleeding
- critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular or intramuscular with compartment syndrome)
- clinically overt bleeding associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L) compared with the pre-randomisation level
- clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells
- clinically overt bleeding that necessitates surgical intervention

The CHMP strongly recommends using the above definition for the primary safety outcome, which is consistent with the International Society of Thrombosis and Haemostasis (ISTH) definition of major bleeding in non-surgical patients [25].

Bleeding warranting treatment cessation is not considered as a sole criterion for qualifying a bleeding as major, because the decision for treatment cessation may be subjective and influenced by a variety of factors other than the severity of bleeding. However, the criterion of “treatment cessation” is still considered valid to qualify a bleed as “clinically relevant non-major bleeding”, because it may be considered as an action taken to control bleed (see below).

In order to describe bleeding severity, major bleedings may be further sub-classified as life threatening [26, 27] if they meet at least one of the following criteria:

- Fatal, symptomatic intracranial bleed;
- Reduction in hemoglobin of at least 5 g/dL;
- Transfusion of at least 4 units of blood or packed cells;
- Associated with substantial hypotension requiring the use of intravenous inotropic agents; or
- Necessitated surgical intervention.

All the remaining major bleeds may be considered as non-life threatening major bleeds.

8.1.2. Clinically relevant non-major bleeding

Clinically relevant non-major bleeding [26,28] is defined as any clinically overt bleeding that does not meet the criteria for major bleed but requires medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy (including discontinuation or down-titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient.

Examples of clinically relevant non-major bleed are: multiple-source bleeding; spontaneous hematoma >25 cm2, or > 100 cm2 if there was a traumatic cause; intramuscular hematoma documented by ultrasonography without compartment syndrome; excessive wound hematoma; macroscopic (gross, visible) hematuria (spontaneous or lasting >24 h if associated with an intervention); epistaxis or gingival bleeding that requires tamponade or other medical intervention, or bleeding after venipuncture for >5 min; hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention.

8.1.3. Other non-major bleedings

Other non-major bleedings include other overt bleeding events that do not meet the criteria for major bleed or clinically relevant non-major bleed (e.g.: epistaxis that does not require medical attention or change in antithrombotic therapy).

8.1.4. Composite bleeding endpoints of interest

The use of the following composite bleeding endpoints is recommended:

- **Clinically relevant bleeding:** defined as the rate of patients experiencing at least one major bleeding and/or a clinically relevant non-major bleeding.
- **Non-major bleeding:** defined as the rate of patients experiencing at least one clinically relevant non-major bleeding or other non-major bleeding.
- **Total bleeding:** defined as the rate of patients experiencing at least one major bleeding, clinically relevant non-major bleeding or other non-major bleeding.

8.1.5. Other parameters related to bleed

As support for the conclusions drawn from the main safety criteria, other bleeding-related parameters are recommended to be recorded during the studies e.g.:

- **Laboratory parameters:** haemoglobin level, haematocrit and red cell count changes during the treatment period.
- **Bleeding index (mean, ±SD)** calculated in each patient as the number of units of packed red cells or whole blood transfused plus the haemoglobin values pre-randomisation minus the haemoglobin values at the end of treatment period.
- **Patients with bleeding index ≥ 2** at the end of treatment period relative to haemoglobin pre randomisation levels (n, %).
- **Patients receiving transfusion of packed red cells (n, %)** (homologous and autologous transfusions need to be distinguished).
- **Transfusion volume (mL; mean, ±SD)** and **transfusion units (U; mean, ±SD)** during the treatment period (homologous and autologous transfusions need to be distinguished).

8.1.6. Report and collection of bleeding events and related parameters

The population included in the assessment of bleeding events should correspond with those subjects who have received at least one dose of the study drug (either active or placebo) (i.e.: the safety population).

The period for collection of these data should be identical in all treatment groups, starting at the time of the administration of the first dose of study drug (either active or placebo) in any of the treatment groups, until the antithrombotic effect of study drugs is not detectable, and after study drugs have been cleared from plasma.

The decrease in the haemoglobin level ≥ 2 g/dL should be considered relative to the closest haemoglobin level value before the bleeding event.

The use of a fecal occult blood test (FOBT) at screening visit and during treatment at regular intervals is encouraged, since long-term antithrombotic therapy may be associated with unperceived chronic gastrointestinal blood loss.

8.1.7. The need for reversal and laboratory monitoring

The development of a specific antidote or further specific studies with non-specific reversal agent for new antithrombotics when given at high doses for long-term is highly recommended given the potential for life-threatening bleeding events in standard practice. Phase I studies are likely to provide a neutralising dose, but may not address the complex interplay of physiology, concomitant measures (i.e.: blood transfusions, use of plasma expanders, etc) and potential for increased thrombogenicity after administration of the reversal agent in patients who experience life-threatening bleed. This should be followed by a proof-of-principle study pre-authorisation in a small subset of patients to demonstrate the efficacy and safety in the heterogeneous population that may present with life-threatening bleeding (e.g.: spontaneous, associated to trauma, surgical or non-surgical invasive procedures, etc.). A randomised clinical study will be difficult to perform taking into account the heterogeneity of the population and differences in standard of care between the various centres. Furthermore, the potential comparator is difficult to be established, since, up to date, non-specific procoagulant agents are not licensed for reversal of the new agents and may be associated with an increased risk of thrombosis. A post authorisation safety study (PASS) and/or registry will be needed to provide further data. The potential use of the reversal agent in situations other than life-threatening bleeding has to be well justified and supported by specific studies.

The development of a standardised test for laboratory monitoring of the anticoagulant effect of new agents is highly recommended. Even if the new drugs have no monitoring requirements and monitoring has not been applied in pivotal studies, there are potential situations in standard practice where this information might be useful (e.g.: impaired renal function, bleeding, thrombosis, clinically relevant drug-drug interactions, overdose, measurement of treatment compliance, etc.) that will recommend having it.

8.2. Other events

The mechanism of action and pharmacological class of the medicinal product under investigation may suggest specific aspects of safety evaluation (e.g. platelet counts, antibody detection, renal and liver function parameters, hypercoagulability markers to assess a possible rebound hypercoagulation after treatment cessation, etc.) that should be considered for incorporation into the entire development programme.

If there is a potential for drug-induced liver injury (DILI) with the study drugs (experimental and/or control), an algorithm for hepatic monitoring has to be included in the protocol [24]. Available regulatory guidance on DILI should be followed [29].

Special attention should be paid to hypersensitivity reactions of the skin and other organs (especially liver, kidney, lungs), changes in blood cells, and hepatitis.

For biotechnology derived product(s), immunogenicity should be evaluated prospectively. The type of antibody (e.g. neutralising) and incidence of immune mediated adverse events should be assessed and clearly documented.

8.3. Special populations

This should be assessed as dictated by the product and the target population.

In general, the following groups might require specific evaluation:

- older patients
- renal insufficiency (moderate, severe)
- liver disease
- obesity (body-mass index ≥30)

Regarding older patients, it is important to determine whether or not the pharmacokinetic behaviour, pharmacodynamics, disease-drug, drug-drug interactions and clinical response of the drug in this population are different from that in younger adults. Therefore, to assess the benefit/risk balance of a drug that will be used in the geriatric population, patients >65 years and ≥75 years should be appropriately represented in clinical trials (ICH E7 and Clinical Trials Regulation 536/2014, art 6).

There is a need to identify the more appropriate dose in these special populations. A distinction between older patients with and without co-morbidities is to be made. Generating clinical data in older (≥75) and frail oldest older persons (≥85 years) patients with high comorbidity is a matter of utmost importance, as they will represent an important part of the target population in standard practise. Any dose adaptation in these populations should be appropriately explored and justified.

As long as there is a reasonable representation of the above sub-groups of patients in the main therapeutic study/es, a separate study is not considered necessary.

Safety in special populations should be prospectively assessed for inclusion of the sub-groups in SPC.

Description of terms

Cardiovascular death: death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes.

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