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Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in non-surgical patients (formerly CPMP/EWP/6235/04 Rev.1)

Draft

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This guideline replaces the 'Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients' (CPMP/EWP/6235/04).

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

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Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in non-surgical patients

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Executive summary

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cause of death due to circulatory diseases, only behind myocardial infarction and stroke, and it is an important source of morbidity in acutely ill medical patients [1].A key element in the benefit risk assessment of drugs used for prophylaxis of venous thromboembolism (VTE) is balancing their antithrombotic effect versus the risk of bleeding. Since the publication of the *CHMP guidance on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic disease [CPMP/EWP/6235/04]* in 2006 [2], a number of new EMA guidelines related to clinical investigation with antithrombotics have been released [3,4] or are being revised [5]. The present update of the CPMP/EWP/6235/04 guideline on non-surgical patients includes the following changes: a) clarifications regarding imaging tests to be used in dose-finding and confirmatory trials; b) discussion on the need for dedicated studies depending on the claimed indication, target population (e.g.: acutely ill non-surgical patients at high risk of VTE, outpatients with cancer, etc.) and treatment duration (e.g.: acute versus extended prophylaxis); c) updated definition of bleeding events (e.g.: major bleeding and clinically relevant non-major bleeding) and its assessment, according to recent CHMP guidelines, in order to provide an objective and standardised definition of bleedings as well as a detailed description of methods for measuring blood loss and timing for collection of data; d) inclusion of additional secondary safety outcomes of clinical importance for new antithrombotics, like hepatic events or arterial thromboembolism.

1. Introduction (background)

Venous thromboembolic disease (VTE) is a common condition, with clinically recognised deep vein thrombosis (DVT) and/or Pulmonary Embolism (PE) and with a reported annual incidence of 2 per 1000 general population. The majority of patients developing VTE are non-surgical, accounting for 3 out of 4 fatal pulmonary emboli. VTE is associated to significant morbidity-mortality and long-term sequels, such as post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension. The primary aim of prophylaxis and/or treatment in the setting of thromboembolism, in clinical practice, is the prevention of PE, both fatal and non-fatal, usually resulting from proximal DVT of the lower limb venous system. Distal DVTs are considered less serious unless propagating proximally.

Medical patients have a significantly heterogeneous risk for VTE. Current clinical practice guidelines [1] recommend routine thromboprophylaxis with low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (UFH) or fondaparinux in acutely ill hospitalized medical (non-surgical) patients at high risk of thrombosis during the period of risk (usually no more than 10 days). Thromboprophylaxis (with LMWH or low-dose UFH) is also recommended in critically ill patients [those who are admitted to an Intensive Care Unit (ICU)] at high risk of thrombosis [1].

There is no strong evidence available about the need for routine thromboprophylaxis in acutely ill hospitalized medical patients at low risk of thrombosis, or in outpatients, like long-distance travelers, in chronically immobilized patients (e.g. nursing home or rehab residents, immobilized persons living at home), in outpatients with cancer receiving chemotherapy or in those with an indwelling central venous catheter [6,7] or in asymptomatic outpatients with thrombophilia [1]. Specific recommendations, requirements and/or dedicated studies may be needed depending on the claimed indication and treatment duration (e.g.: acute versus extended prophylaxis) and target population (e.g.: acutely ill non-surgical patients at high risk of VTE versus outpatients with cancer, etc.). As a result, active drugs or placebo may be suitable as control in comparative trials, depending on VTE risk of the included population and period of risk.

Despite venography being the gold standard for diagnosis of DVT [1], it is an invasive method that has been replaced by mandatory bilateral compression ultrasonography (CIS) in recent trials in non-surgical patients [8-11] (see also section 5.1.1).

2. Scope

The aim of this guideline is to provide guidance to industry when performing trials to develop medicinal products in the prevention of venous thromboembolism in non-surgical patients. The revised guideline does not deal with the development of medicinal products for prevention of long-term sequelae of VTE, such as post-phlebitic syndrome or chronic thromboembolic pulmonary hypertension.

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).
- Guideline on the choice of the non-inferiority margin (CPMP/EWP/2158/99).
- 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).
- Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2).
- 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. Patients characteristics and selection of patients

4.1. Patients characteristics

4.1.1. Predisposing risk factors for VTE

There are a number of factors that are considered important predisposing risk factors for VTE to be considered in clinical trials in hospitalized medical patients [12]. The strength of association for each of the factors is variable, with the first 4 factors being the more important ones. These include:

- Reduced mobility, defined as bed rest with bathroom privileges (either due to patient's limitations or on physicians order) for at least 3 days (level 2 immobility). It is not the same as "immobilisation", which is defined as requiring total bed rest or being sedentary without bathroom privileges for at least 3 days (level 1 immobility).
- Active cancer, including patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been performed in the previous 6 months.
- Previous VTE, with the exclusion of superficial vein thrombosis.
- Already known thrombophyilic condition: carriage of defects of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin mutation, antiphospholipid syndrome.
- Recent (≤ 30 days) trauma and/or surgery.
- Demographic factors such as elderly age (≥70 yrs) or obesity (BMI≥30).
- Heart and/or respiratory failure.
- Acute myocardial infarction or ischemic stroke.
- Acute infection and/or rheumatologic disorder.
- Iatrogenic causes such as ongoing hormonal treatment with contraceptives or hormone replacement therapy (HRT).
- Presence of central venous catheter.

In the particular case of clinical trials in outpatient cancer patients receiving chemotherapy, there are a number of important characteristics of the underlying condition predisposing for VTE that should be taken into account in clinical trials in this specific subset of patients [13]. These include:

- Site of cancer: stomach, pancreas, primary brain tumor (very high risk), lung, lymphoma, gynecologic, bladder, testicular, renal tumors (high risk).
- Pre-chemotherapy platelet count ≥350,000 per microL.
- Hemoglobin level < 10 g/dl and/or use of red-cell growth factors.
- Prechemotherapy leukocyte count > 11,000 per microL.
- Body mass index ≥ 35 kg/m^2.

It is important that the trial population is reflective of the variety of predisposing risk factors. Stratified randomisation may be needed to account for prognostic risk factors that may significantly influence the primary outcome (see also section 6.4).

4.1.2. Patient care and other factors

In addition to the predisposing factors inherent in the clinical status and demography of the patient population to be studied, the risk of development of VTE and efficacy/ safety of the test product in development can be further confounded by a variety of factors such as investigator and site specific standards of care and concomitant illness and/or treatment:

- Practice of early immobilization and physiotherapy; use of mechanical prophylaxis measures (elastic compression stockings, intermittent pneumatic compression).
- Use of medicinal products which could interfere with platelet function such as aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs).
- Diseases which could impair coagulation such as liver disease.
- Potential interaction by medicinal products used to treat underlying diseases such as cancer.
- Poly-pharmacy in case of elderly patients with multiple pathology.

The potential for any of these to affect the efficacy and safety (through effects on pharmacodynamics and/or pharmacokinetics) of the product under evaluation should be prospectively identified.

4.2. Patient selection

Patients should be selected on the basis of target population and intended indication. If a 'general indication' for acutely-ill medical patients is intended, it is important that the trial population has adequate representation of several applicable subgroups e.g., stroke, cardiac disease, cancer and infection/inflammation, due to the heterogeneous nature of predisposing factors.

It is recommended to include in the studies patients at high risk of thrombosis, as assessed by available risk scores in hospitalized medical patients, like the Padua Score [12], Improve Score [14] and Geneva score [15]. In addition to immobilisation or reduced mobility, there should be preferably at least one additional risk factor present in the patients in clinical trials. Extended thromboprophylaxis after discharge can be studied (versus placebo) in a separate study or in a single study after completion of initial inpatient thromboprophylaxis (versus standard of care) (see also section 6.4, "choice of comparator").

Critically ill patients have an increased risk of bleeding. The risk of VTE depends on their acute illness (e.g., sepsis), chronic illnesses (e.g., congestive heart failure), prehospital diagnoses (e.g., prior VTE), and ICU-specific exposures and events (eg, immobilization, surgery, and other invasive procedures [such as central venous catheterization], mechanical ventilation, and drugs such as vasopressors. However, there are no validated risk assessment models to stratify VTE risk in critically ill patients.

In outpatients with cancer and central venous catheters receiving chemotherapy [6,7], the inclusion of high-risk patients as assessed by validated scores, like the Khorana score [13] in separate studies is recommended.

Other patients in whom thromboprophylaxis is not routinely recommended comprise chronically immobilized patients (e.g. nursing home or rehab residents, immobilized persons living at home) or patients with asymptomatic thrombophilias (e.g., deficiencies of antithrombin, Protein C, Protein S; Factor V Leiden, and the prothrombin gene mutation G20210 A; antiphospholipid antibody syndrome) [1]. Specific studies may be needed in these situations where long-term treatment can be anticipated. The methodology for assessing efficacy and safety is essentially the same as for hospitalized medical patients, with logical differences related to the choice of comparator (placebo may be allowed if thromboprophylaxis is not an established treatment) and study duration (longer than for an acute medical illness) (See section 6.4).

5. Evaluation of efficacy

5.1. Methods for diagnosing venous thromboembolism

It is considered that the diagnosis of VTE should be based on a diagnostic algorithm including clinical probability and the use of D-Dimers to rule out VTE. However, since heparins are known to affect D-dimer results, such results may not be useful in excluding thrombosis in patients receiving heparins. In older people, rising levels of D-dimer are frequent due to the high prevalence of pro-inflammatory conditions and increasing burden of lipid abnormalities, anemia and obesity. These factors compromise the specificity of D-dimer levels as a diagnostic aid to thrombosis in older individuals. It is recommended to use the same methods for diagnosis of VTE across all the trials. The following diagnostic methods are considered acceptable for documenting DVT and PE.

5.1.1. 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 DVT and asymptomatic proximal DVT of the lower limbs [16], but is less adequate for asymptomatic distal 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. CUS is also recommended in patients suspected of having upper extremity DVT [17]. Not infrequently, CUS imaging may be technically difficult, or the abnormality may be 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 [18] 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.

5.1.2. Established methods for diagnosing PE

- Spiral computed tomography (sCT) is currently the most frequent method used for the diagnosis of PE in clinical trials so far.
- Pulmonary angiography is the gold standard, but is now rarely performed.
- 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 patients 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.

Since sudden death may be the first sign of PE and is the most important complication of it, ruling out PE as the cause of death without diagnostic confirmation can have important implications for efficacy assessment. In cases of ‘suspected fatal PE,’ effort should be made to obtain an autopsy to confirm the diagnosis. Unless PE has been excluded, it will be difficult to attribute any death to non-PE causes.

5.1.3. 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 [19]. CTV leads to the detection of an additional 3% of cases of VTE when combined with pulmonary CT angiography in the assessment of PE [20]. MRV can be highly accurate, easy to perform and successful in many situations where other imaging techniques yield ambiguous results [21].

5.2. Primary efficacy outcome

Confirmatory trials

Efficacy assessment should take into consideration the intended target population and the duration of treatment, taking into account that benefits may be seen for a variable period after completion of

treatment. Since the main objective will be to prevent symptomatic/fatal PE, evaluation of efficacy will need to focus on confirmation of diagnosis of proximal DVT and non-fatal/fatal PEs and document the clinical impact on morbidity/mortality.

The main efficacy outcome recommended in Phase III trials in the prophylaxis of VTE in non-surgical patients is the composite of:

- Documented asymptomatic proximal DVT
- Documented symptomatic DVT (proximal and distal)
- Documented symptomatic non-fatal PE
- VTE-related death (non-inferiority trials) or all-cause death (superiority trials)

The difference in endpoints between superiority and non-inferiority trials is based on the need for a more sensitive endpoint in the latter. In both cases, a supportive analysis of the composite endpoint should be provided using the alternative group of deaths i.e. VTE-related death for a superiority trial and all-cause death for a non-inferiority trial.

All major endpoints should be adjudicated by a blinded clinical events committee.

Mandatory routine bilateral lower extremity CUS should be performed after the last dose of study medication or matching placebo. In subjects prematurely discontinuing their treatment and/or developing symptoms of DVT, bilateral CUS should be performed at that time and at the initially programmed day of end of treatment.

Although it is expected that most DVTs will occur in the lower limbs, some symptomatic DVTs may occur in the upper extremity. As most cases of upper extremity DVT are specific complications associated with central venous catheters (CVCs), devoted studies are recommended. The incidence of CVC-associated thrombi is particularly high in patients with indwelling CVSs for cancer chemotherapy, varying from 27% to 66% in different series when routine screening with venography is performed. However, even in the presence of an extensive, occlusive thrombus in the proximal veins, only one third of cases are symptomatic. Symptoms of CVC-associated thrombi include swelling, pain, redness, discoloration, and even cyanosis, which have to be documented by objective testing.

Diagnosis of symptomatic 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. Deaths should be carefully characterised regarding their relationship to VTE, according to criteria specified in the study protocol.

The primary efficacy endpoint should also be investigated within a follow-up period after trial drug discontinuation, usually 30 days, in order to rule out a potential rebound effect. As many patients may have permanent/persistent VTE risk factors, additional follow-up efficacy assessment o (e.g.: 3 to 6 months after withdrawal of the prophylaxis) may also be discussed in the initial design of a study.

Exploratory trials

For proof-of-concept and dose-ranging studies, 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 and asymptomatic DVT.
- Documented symptomatic and asymptomatic non-fatal PE.

- VTE-related death.

5.3. Secondary efficacy 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 medicinal products, 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 efficacy and safety endpoints (e.g.: symptomatic 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 (Quality of Life) by standardized form comparing the results between the experimental and control drugs may be of interest.

6. Strategy and design of clinical trials

6.1. 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.

The possibility of a pharmacodynamic interaction, considered important for drugs used in this indication, should also be evaluated. It is not possible to list all the potential interacting drugs in this document. Some common examples to be considered are NSAIDs and anti-platelet agents.

6.2. Pharmacokinetics

Pharmacokinetics trials should be performed 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 sections 6.5, 6.6 and 6.7).

Potential for pharmacokinetic interactions should be investigated both with respect to the effects of other drugs on the investigational drug and the effects of the investigational drug on other medicinal products. Drug-drug interaction studies may include: a) Mechanistic studies with strong and moderate

inhibitors of an enzyme involved in drug metabolism: b) Studies with interacting drugs expected to be commonly used concomitantly with the investigational drug aiming to obtain a specific dose recommendation; c) Studies to verify the suitability of a proposed dose adjustment or to confirm a lack of interaction with a commonly co-prescribed drug in the target population.

6.3. Therapeutic exploratory studies

These studies should allow 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 medicinal products 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 in order to minimise under-dosing, 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 (e.g.: drug plasma concentrations, APTT, D-dimer, etc.). If appropriately justified, dose-response data may be extrapolated from other indication(s) (e.g.: prophylaxis of DVT in surgical patients). Population PK/PD approaches may also help to establish dose-response in the prophylaxis of VTE in non-surgical patients.

In certain cases, where there is strong and confirmed evidence, a laboratory test could support dose-selection; the assay used should be a validated test and should preferably be the same for all participating patients. Such assay results would typically be applicable for efficacy monitoring, although it would be advantageous to have applicability for safety purposes also.

6.4. Therapeutic confirmatory studies

Design

For confirmatory trials a prospective, double-blind randomised, controlled, parallel group clinical trial is recommended. Even if blinding is not possible, the trial should be controlled and randomised. In such trials, evaluation of efficacy and safety should be carried out by independent adjudication committees. In multicentre trials, stratified randomisation by important prognostic factors measured at baseline e.g. study centre, type of index disease targeting thromboprophylaxis, type of chemotherapy, etc. may sometimes be valuable in order to promote balanced allocation within strata.

The possibility of screening the proximal veins at baseline with US to detect old thrombi should be considered in order to increase its diagnostic precision. Old thrombi will often result in non-compressible segments for a long time, and therefore a comparison of the CUS imaging test performed at the scheduled time point (i.e.: end of treatment or earlier if symptoms occur) with a baseline imaging test may be helpful.

Depending on the intended indication, the relevant cross-section of the patient population should be represented in the trials (see also section 4.2 "Patient selection").

An appropriate follow-up of at least 30 days after treatment discontinuation should be included to assess a possible rebound effect.

Choice of comparator

If a medicinal product is already approved or recommended in treatment guidelines, an active treatment should be included in the study design, otherwise it should be fully justified. A placebo-controlled design could in some situations be justified if the patients are followed with repeated US investigations at regular intervals. In situations when no prophylactic methods have yet been registered in the targeted indication superiority over placebo should be demonstrated for the medicinal product combined with an acceptable safety profile. A sequential comparison with standard of care for the first 10 days (non-inferiority), followed by a comparison with placebo for approximately 5 weeks (superiority) may also be acceptable [9-11].

Duration of treatment

The duration of treatment intended for each clinical indication should be adequately reflected in the studies and the duration chosen should be justified. In the case of acute medical illness, when patients have reduced mobility or are immobilised, treatment should be administered until full mobilisation prior to discharge. The duration of treatment in this situation is usually for 7-14 days.

If the indication proposed is for a chronic irreversible condition(s), such as established paralysis due to cerebrovascular disease, or a permanent risk factor, like active cancer, where the treatment may be given indefinitely, the trial duration should be of reasonable length – at least 3-6 months – to be able to provide sufficient reassurance of efficacy and at least 6-12 months for safety.

Concomitant medications/procedures

Concomitant medications: The trials 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 antiplatelet medicinal products. 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 exclusion of a representative population. All drug and non-drug treatment measures should be standardized.

Concomitant procedures: in long-term thromboprophylaxis studies, the protocol has to describe the management of anticoagulant/antithrombotic therapy during the clinical trial in case study subjects have to undergo elective and urgent surgical procedures as well as major trauma.

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 (CPMP/EWP/2158/99). 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).

Statistical analysis should include the primary endpoint events over a fixed duration of follow-up for trials in an acute setting and for the full duration of follow-up to end-of-study for trials in long-term/chronic settings. 'On-treatment' analyses and analyses including events occurring 7 days and 30 days after study drug discontinuation can be conducted in order to investigate a possible early rebound increase in thromboembolism after treatment cessation. For robust conclusions in respect of pharmacological effects, incidence of patient withdrawal and duration of exposure in each treatment arm should be discussed and alternative analyses conducted, in particular where a high incidence of

withdrawal might reduce assay sensitivity. These might include conservative imputation strategies, on-treatment analyses and analyses based on event rates.

Subgroup analyses are strongly encouraged according to demographic characteristics (age, gender) and factors that could result in a differential effect of the new compound versus the control group on efficacy or safety endpoints (e.g.: baseline risk factors for VTE or bleeding, renal function subgroups, and concomitant medications increasing VTE or bleeding risk).

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 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.

6.5. Studies in special populations

This should be assessed as appropriate for the product and the target population.

In general, the following groups might require specific evaluation:

- older patients.
- renal insufficiency (moderate, severe).
- liver disease.

There is a need to identify the more appropriate dose in these special populations. Any dose adaptation in these populations should be appropriately explored and justified.

As long as there is a reasonable representation of obese patients (body-mass index ≥30) in the main therapeutic study/ies, a separate study is not considered necessary.

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

6.6 Older patients

Older patients are more affected by VTE than younger patients and the risk of bleeding related to anticoagulant treatments is high. Therefore, prevention of VTE in this population is particularly challenging [22]. It is important to determine whether or not the pharmacokinetic behaviour, pharmacodynamics, drug-disease or drug-drug interactions and clinical response of the drug in older patients 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).

A distinction between older patients with and without co-morbidities is to be made. Generating clinical data in older persons (≥75) and also in the oldest group (≥85 years) of patients with high comorbidity is a matter of utmost importance, as they will represent an important part of the target population in standard practice.

7. Safety aspects

7.1. 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.

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 [23].

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 bleeding as “clinically relevant non-major bleeding”, because it may be considered as an action taken to control bleeding (see below).

In order to describe bleeding severity, major bleedings may be further sub-classified as life-threatening [24,25] 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.

Clinically relevant non-major bleeding

Clinically relevant non-major bleeding [24,26] is defined as any clinically overt bleeding that does not meet the criteria for major bleeding 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 bleeding 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.

Other non-major bleedings

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

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.

Other parameters related to bleeding

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).

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 (last measured) 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.

7.2. Other events of interest

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. Available regulatory guidance on DILI should be followed [27].

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.

In studies including a parenteral anticoagulant of the heparin class, the inclusion of thrombocytopenia and injection sites hematomas as secondary safety outcomes is also important. The issue of injection

site hematomas may be particularly important for subcutaneous absorption of insulin in acutely ill diabetic patients, since frequently insulin and heparin injection sites overlap.

8. Other information

8.1. 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 bleeding. 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 establish, 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 medicinal products 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.

Definitions

Deep vein thrombosis (DVT): may be diagnosed in the presence of non-compressibility of the common femoral and/or popliteal veins (proximal DVT) or calf veins (distal DVT) on CUS, or intraluminal filling defect on venography if CUS is not conclusive.

Suspected pulmonary embolism (PE): may be confirmed in the presence of at least one of the following findings: a) intraluminal filling defect in segmental or more proximal branches on sCT scan; b) intraluminal filling defect or sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; c) perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on VPLS; d) Inconclusive sCT, pulmonary angiography, or VPLS with demonstration of DVT in the lower extremity.

VTE-related death: may be confirmed in the presence of: a) PE based on objective diagnostic testing, autopsy; b) death which cannot be attributed to a documented cause and for which DVT / PE cannot be ruled out (sudden unexplained death).

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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