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Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation

Draft

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Executive summary

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. AF confers a 5-fold risk of stroke, and one in five of all strokes is attributed to this arrhythmia.
Current Note for Guidance on Antiarrhythmics (CPMP/EWP/237/95) and its addendum on atrial fibrillation and flutter (EMA/CHMP/EWP/213056/2010) do not cover stroke prevention. The aim of this guideline is to provide guidance to industry when performing trials to develop drugs in prevention of stroke and systemic embolic events (SEE) in patients with AF.

1. Introduction (background)

AF is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population [1]. The prevalence of AF increases with age from 0.5% at 40–50 years to 5–15% at 80 years [2]. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages [2,3]. Based on the presentation and duration of the arrhythmia, AF is classified as: first diagnosed, paroxysmal, persistent and permanent AF [2]. Ischaemic strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. Current recommendations for antithrombotic therapy are based on the presence (or absence) of risk factors for stroke and thromboembolism [2,4]. The simplest risk assessment scheme in non-valvular AF is the $CHADS_2$ score [cardiac failure, hypertension, age, diabetes, prior stroke or TIA (transient ischaemic attack) (doubled)] [1]. The original validation of this scheme classified a $CHADS_2$ score of 0 as low risk, 1–2 as moderate risk, and >2 as high risk. In patients with a $CHADS_2$ score of ≥2, chronic anticoagulation therapy with a vitamin K antagonist (VKA) in a dose adjusted manner to achieve an International Normalised Ratio (INR) value in the range of 2.0–3.0, or with other oral anticoagulant approved for this indication (e.g.: oral direct factor Xa inhibitors or direct thrombin inhibitors) is currently recommended [2]. In these patients, antiplatelet therapy could be considered as alternative therapy only when oral anticoagulation is unsuitable. In patients with a $CHADS_2$ score of 0–1, or where a more detailed stroke risk assessment is indicated, it is recommended to use a more comprehensive risk factor-based approach (e.g. CHA_2DS_2-VASc score) [5]. Bleeding risk has also to be assessed at the time of deciding to start antithrombotic therapy in patients with AF (e.g. using HAS-BLED score) [2].

2. Scope

The aim of this guideline is to provide guidance to industry when performing trials to develop medicinal products in prevention of stroke and systemic embolic events (SEE) in patients with non-valvular AF. Heart valve disorders, (i.e.: presence of prosthetic valve or haemodynamically relevant valve disease), with or without concomitant AF, represent a particular high-risk situation in which specific preclinical and phase II and III studies may be required and adequate advice should be requested on a case by case basis.

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).
- 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)
- Note for guidance on antiarrhythmics (CPMP/EWP/237/95).
- Addendum to the Guideline on antiarrhythmics on atrial fibrillation and atrial flutter (EMA/CHMP/EWP/213056/2010).

4. Assessment of efficacy criteria

4.1. Primary efficacy outcome

The main objective of phase III clinical studies will be to demonstrate that the drug decreases the number of thromboembolic events, i.e. ischaemic strokes and SEEs in patients with AF who are either already using anticoagulant agents or are suitable candidates for treatment initiation with anticoagulant agents. The composite primary efficacy endpoint of time to first stroke (including ischaemic and undefined strokes) and SEEs from randomisation is therefore recommended.

4.2. Secondary outcomes

A mandatory secondary analysis should include the individual components of the recommended primary efficacy endpoint i.e. ischaemic and undefined strokes, separately and other non-central nervous embolic events.

Other recommended clinically relevant secondary efficacy outcomes are the occurrence of:

- Disabling stroke
- Transient ischaemic attack (TIA)
- Myocardial infarction
- Vascular death
- All-cause death
- Pulmonary embolism

Net clinical benefit endpoints, combining both efficacy and safety endpoints, can be of value in the risk-benefit assessment of the studied anticoagulant agents. A clinically relevant net clinical benefit secondary endpoint consisting of "all strokes (i.e. ischaemic, undefined and haemorrhagic stroke) and other non-central nervous embolic events" is therefore recommended. All major bleedings, all-cause death or vascular death may also be acceptable for inclusion as a part of a net clinical benefit secondary endpoint. In addition, composite secondary endpoints have been used in clinical trials in AF and may be of interest, e.g., composite of the primary efficacy endpoint with myocardial infarction and either vascular death or all cause mortality. The evaluation of QoL by standardized form comparing the results between the experimental and control drugs may be of interest.

5. Methods to assess efficacy

5.1. Primary efficacy outcome

Stroke should be defined by a generally accepted definition [i.e. Standardized Data Collection for Cardiovascular Trials (SDCCT Initiative) definition; World Health Organisation (WHO) definition]. All efforts should be made to classify strokes as "primary ischaemic" (component of the primary endpoint) or "primary haemorrhagic" (not a component of the primary endpoint). An ischemic stroke with hemorrhagic conversion should be considered as "primary ischaemic". The subgroup of "undefined strokes" should be as small as possible in order to be able to properly assess the effect of the study treatment. It is therefore recommended that the classification of stroke subtype is based on clinical symptoms and results from neuroimaging (computed tomographic and/or magnetic resonance scanning) and/or autopsy.

Subdural or epidural haematoma are not considered as strokes and should thus not be part of the composite stroke endpoint. These intracranial haemorrhages should only be assessed as safety endpoint (major bleedings).

It is recommended to adjudicate suspected strokes and TIAs as a group. A suspected TIA should be adjudicated as stroke if there is positive neuroimaging confirming a cerebral infarction, even if the duration of symptoms is of less than 24 hours [American Heart Association (AHA) and American Stroke Association (ASA) definition of TIA; Standardized Data Collection for Cardiovascular Trials (SDCCT) Initiative definition]. This definition will modestly alter stroke and TIA incidence rates, but these changes are to be encouraged, because they reflect increasing accuracy of diagnosis. The occurrence of a TIA (transient episode of focal neurological dysfunction without positive neuroimaging) should not be part of the composite stroke endpoint, instead it is recommended to assess this as a secondary efficacy endpoint. Appropriate sensitivity analysis with different definition of ischemic stroke (including or excluding TIA with positive neuroimaging as being an ischaemic stroke) is encouraged. For this purpose, the investigators have to collect data regarding symptom duration.

The diagnosis of SEEs should be defined by a generally accepted definition. The diagnosis should be confirmed by findings from angiography, surgery, scintigraphy, and/or autopsy. The location of the vascular occlusion should also be specified.

The occurrence and classification of the components of the primary endpoint should be adjudicated by an independent and blinded committee in order to limit the introduction of bias caused by differences in diagnostic sensitivity and local standards of care.

5.2. Secondary outcomes

All secondary efficacy endpoints should be defined by generally accepted definitions and diagnostic criteria should be clearly described "a priori".

Deaths should be classified using all available methods, including autopsy results, physicians' reports, and read-outs of ICDs, Holter ECGs or other monitoring devices. All deaths should preferably be categorised as "non-vascular", "vascular" or "unknown etiology". Vascular deaths should include deaths caused by bleeding, stroke and other thromboembolic events and all cardiac deaths

Final stroke outcome should be assessed at 3-6 months after stroke onset using a validated stroke outcome scale, preferably the widely used modified Rankin scale. A disabling stroke should be defined

as a score on the modified Rankin scale of 3-5, whereas a non-disabling stroke should be defined as a score of 0-2. Other validated stroke outcome scales (e.g. Barthel Index) could be used in sensitivity analyses.

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

6. Selection of patients

6.1. Study population

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).

6.2. Inclusion criteria

1) Atrial fibrillation criteria: Patients to be included should have non valvular atrial fibrillation (i.e. with documentation of both atrial fibrillation and absence of haemodynamically significant valvular disease or prosthetic valve). Atrial fibrillation may be paroxysmal, persistent or permanent, but not secondary to a reversible disorder such as myocardial infarction, pulmonary embolism, recent surgery, pericarditis or thyrotoxicosis. Atrial fibrillation has to be documented on two separate occasions by ECG evidence, Holter monitoring, pacemaker or cardiac defibrillator read outs.

2) Thrombo-embolic risk and bleeding risk factors: Patients should present at inclusion with a level of thrombo-embolic risk justifying anticoagulant therapy, as recommended by current guidelines. $CHADS_2$ score [1] should be included in the categorisation and description of the patient population. Generally, in clinical trials, patients at high risk of bleeding complications should be excluded. The estimation of bleeding risk is rendered difficult since many of the known factors that increase bleeding risk overlap with stroke risk factors [7]. New validated cardiovascular and bleeding risk scores (e.g.: CHA_2DS_2-VASC, HAS-BLED) [5,8], may be useful.

3) VKA use: If the study is intended to include patients with contraindications to VKA or unsuitable for VKA, clear definitions of contraindications/unsuitability for VKA treatment should be provided. In the same line, if the clinical trial is intended to include VKA-naïve and VKA-experienced patients, VKA naïve may be defined as VKA use for < 6 weeks immediately before entry into the trial [9]. As a sensitivity analysis, in order to be able to compare with other studies, additional accepted definitions may be used (e.g.: patients not on a VKA at randomization; patients who had never been on a VKA; patients who previously had received a total of ≤ 2 months of VKA therapy).

6.3. Exclusion criteria

General non-inclusion criteria and some drug specific non-inclusion criteria will be added according to each drug's pharmacological properties.

7. Strategy design

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 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, 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

Dose-response studies:

These studies should allow choosing both the appropriate doses(s) of the medicinal product in terms of total daily dose and dose interval, in order to find the optimal dosing of the new drug with the most favourable 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 minimize 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 or treatment of deep vein thrombosis), as well as population PK/PD approaches may also help to establish dose-response in AF [10].

Confirmatory trials:

Design

The more appropriate design for confirmatory trials is considered to be a prospective, double-blind randomized, controlled, parallel group clinical trial.

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.

A stratified randomization may be needed to account for factors that may significantly influence the primary outcome (e.g. CHADS2 score, 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 [9,16]. 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.
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 off of study medication at study termination 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 prevented (stroke and/or SEE). VKA or new anticoagulants approved in this indication (e.g.: oral direct thrombin inhibitor, oral direct FXa inhibitor) are considered valid comparators in this clinical setting.
The use of ASA as control is discouraged in patients with a $CHADS_2$ score of ≥ 2 due to its poorer efficacy in comparison to VKA. The use of placebo may be appropriate when the new antithrombotic is given on top of standard of care, or in patients at apparently low risk of thromboembolism ($CHADS_2$ score = 0), but it is ethically questionable in patients at higher thromboembolic risk.

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.).

Concomitant procedures: the protocol has to describe the management of anticoagulant therapy during the clinical trial in case of cardioversion, catheter ablation, 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 [11]. 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) [12], 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 center 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 approach (followed or not by hierarchical superiority) is recommended in active controlled trials, while superiority approach is mandatory in placebo-controlled trials.

The analysis of non-inferiority and/or 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 end points. 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 randomization to the estimated date of attainment of the study's target of primary endpoint events).

Key specified proper subgroups should include at least oral anticoagulation status at randomization, TTR quartiles of the INR, $CHADS_2$ risk score categories, age categories, creatinine clearance (CrCl), 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.)
- **Pharmacogenetics:** Identify genetic polymorphisms that identify patients at higher risk for recurrent AF, thromboembolism, 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.
- **Continuous and static electrocardiography:** Determine the varying risk associated with

different burdens of AF.

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.

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 in pivotal trials in non-surgical patients [13]. The only difference with the ISTH 2005 definition [14] is that the definition above includes clinically overt bleeding that necessitates surgical intervention as an additional criterion [Ezekowitz et al, 2007].

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 [14]. 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 [13, 15] 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 [14,16] 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 cm^2, or > 100 cm^2 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 bleed or clinically relevant non-major bleed (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 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).

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.

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, as in stroke prevention in AF, 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 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 [13]. Available regulatory guidance on DILI should be followed [17].

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).

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 old older (≥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 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

Stroke: acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Stroke is categorized as ischemic or hemorrhagic or undefined/undetermined (based on computed tomographic or magnetic resonance scanning or autopsy).

Ischemic Stroke: acute episode of focal cerebral, spinal, or retinal dysfunction caused by *infarction* of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

Hemorrhagic Stroke: acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undefined/undetermined Stroke: acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic.

Transient ischemic attack (TIA): transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction on neuroimaging.

Systemic embolism: acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and must be documented by angiography, surgery, scintigraphy, or autopsy.

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.

9. References

1. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. JAMA. 2001; 285: 2864-70.

2. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010; 31: 2369-429.

3. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2011; 42: 227-76.

4. Stroke in AF working group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology. 2007; 69: 546–54.

5. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on Atrial Fibrillation. Chest 2010; 137: 263–72.

6. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133(6 Suppl): 160S-198S.

7. Lip GY, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. Europace. 2011; 13: 723-46.

8. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010; 138: 1093-100.

9. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J. 2010; 159: 340-7.

10. Mueck W, Lensing AW, Agnelli G, et al. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep-vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. Clin Pharmacokinet. 2011; 50: 675-86.

11. Rosendaal F, Cannegieter S, van der Meer F, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69: 236-9.

12. Connolly SJ, Pogue J, Eikelboom J, et al; ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008; 118: 2029-37.

13. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J. 2009; 157: 805-10.

14. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005; 3: 692-4.

643 15. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute
644 coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494–502.

645 16. Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban
646 compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective
647 aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial
648 Infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J. 2010; 160: 635-41.

649 17. Food and Drug Administration. Guidance for Industry. Drug-Induced Liver Injury: Premarketing
650 Clinical Evaluation. Available at: http://www.fda.gov