20 July 2017
EMA/CHMP/760125/2016
Committee for medicinal products for human use (CHMP)

Guideline on clinical investigation of new medicinal products for the treatment of acute coronary syndrome

Draft agreed by Cardiovascular Working Party	February 2016
Adopted by CHMP for release for consultation	1 April 2016
Start of public consultation	27 April 2016
End of consultation (deadline for comments)	31 October 2016
Agreed by Cardiovascular Working Party	July 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	1 March 2018

This guideline replaces 'Points to consider on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome (ACS) without persistent ST segment elevation' (CPMP/EWP/570/98).

Keywords	***Acute coronary syndrome, STE-ACS, NSTE-ACS, guideline, CHMP***

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

Table of contents

Executive summary

Two CHMP Guidelines have been previously developed to address clinical investigations of new medicinal products for the treatment of acute coronary syndrome (ACS): (I) the *CHMP points to consider (PtC) on the clinical investigation of new medicinal products for the treatment of acute coronary syndrome without persistent ST-segment elevation (CPMP/EWP/570/98)*, published in 2000 [1], and (II) the *CHMP PtC on the clinical development of fibrinolytic products in the treatment of patients with ST segment elevation myocardial infarction (CPMP/EWP/967/01)*, published in 2003 [2]. Since their finalisation, major developments have taken place in the definitions, diagnosis, interventions and management of ACS, as reflected in the relevant European Society of Cardiology (ESC) clinical practice guidelines [3, 4]. Currently, an update of the above mentioned CHMP Guidelines is considered necessary to take these new developments into consideration based on literature review and experience gained with medicinal products intended for treatment during the acute phase and beyond. The present update includes the following changes: 1) guidance addressing both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), as well as unstable angina (UA), 2) update in their definitions, 3) risk stratification using different scoring systems, 4) to be investigated endpoints, and 5) clinical developments of new medicinal products beyond the acute stage, including agents other than antiplatelets and anticoagulants.

1. Introduction (background)

Cardiovascular diseases are currently the leading cause of death in industrialized countries and also expected to become so in emerging countries by 2020 [3, 4]. Among these, coronary artery disease (CAD) is the most prevalent manifestation and is associated with high mortality and morbidity. ACS has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischemia. It encompasses STEMI, NSTEMI, and UA.

ACS represents a life-threatening manifestation of coronary atherosclerosis. It is usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow. In the complex process of plaque disruption, inflammation was revealed as a key pathophysiological element. Non-atherosclerotic aetiologies are rare e.g. arteritis, coronary embolism, and dissection.

The leading symptom of ACS is typically chest pain. Patients with acute chest pain and persistent (>20 min) ST-segment elevation have ST-elevation ACS (STE-ACS) that generally reflects an acute total coronary occlusion; most patients will eventually develop ST-elevation myocardial infarction (STEMI). Patients with acute chest pain but without persistent ST-segment elevation (NSTE-ACS) have rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-normalization of T waves, or no ECG changes. At presentation, based on the measurement of troponins, it is possible to further discriminate between the working diagnosis of non-ST-elevation myocardial infarction (NSTE-MI) and unstable angina.

NSTE-ACS is more frequent than STE-ACS [5] with an annual incidence around 3 per 1000 inhabitants, but varying between countries [6]. Hospital mortality is higher in patients with STEMI than among those with NSTEMI (7% vs. 3–5%, respectively), but at 6 months the mortality rates are very similar in both conditions (12% and 13%, respectively) [5,7,8]. Long term follow-up shows that death rates were higher among patients with NSTE-ACS than with STE-ACS, with a two-fold difference at 4 years

[8]. This difference in mid- and long-term evolution may be due to different patient profiles, since NSTE-ACS patients tend to be older with more co-morbidities, especially diabetes and renal failure.

2. Scope

The aim of this guideline is to provide guidance when performing trials to develop medicinal products in the management of ACS. The focus in this Guideline concerns mainly the pharmacological treatment of ACS, including:

1. The prevention of major adverse cardiovascular events like cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke and those with a need for urgent revascularization.
2. The reduction in the amount of myocardial necrosis that occurs in patients with AMI, thus preserving left ventricular (LV) function, preventing heart failure (HF), and limiting other cardiovascular complications.

The treatment of acute, life-threatening complications of ACS, such as serious arrhythmias, pulmonary oedema, cardiogenic shock and mechanical complications of acute myocardial infarction (AMI) [9], which is one of the goals of therapy for patients with ACS is addressed in other guidelines. The choice of interventional procedures [percutaneous coronary intervention (PCI) or coronary artery bypass graft CABG)] also falls outside the scope of this guideline.

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; CPMP/ICH/378/95).*
- *Statistical Principles for Clinical Trials (ICH E9; CPMP/ICH/363/96).*
- *Choice of Control Group and Related Issues in Clinical Trials (ICH E10; CPMP/ICH/364/96).*
- *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; CPMP/ICH/375/95).*
- *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/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).*
- *Draft Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure (EMA/392958/2015)*
- *Guideline on clinical investigation of medicinal products for the treatment of acute heart failure (CPMP/EWP/2986/03 Rev. 1)*

4. Choice of efficacy criteria (endpoints)

Definitions of clinical endpoints in confirmatory trials should be in line with the relevant clinical guidelines [3, 4, 10, 11 and 12] to facilitate interpretation of the results, to allow comparisons across clinical studies and to extrapolate to clinical practice. The following endpoints are relevant to the investigation of efficacy in patients with ACS.

4.1. Mortality

As one of the goals of treatment of ACS is reduction of mortality, this is an important endpoint to measure. Assessment of mortality in confirmatory trials should include both all-cause mortality and cardiovascular mortality (see section 5.1).

4.2. New myocardial infarction

New onset MI is a relevant endpoint in studies of ACS and should always be investigated. The definition of MI has evolved through the years; at the time of drafting of this Guideline, the third universal definition of MI is applicable [10]. Criteria of MI are the same as those used to define the index event (see below).

4.3. Non-fatal stroke

Stroke accounts for a small proportion of events in ACS trials. Non-fatal stroke should be investigated only if there is a biological rationale suggesting a beneficial or detrimental treatment effect on risk of stroke [13]. Otherwise, including non-fatal stroke as part of the composite endpoint may add complexity and noise rather than clarity.

Assessment of non-fatal stroke in confirmatory trials should include all types of strokes(see section 5.3).

4.4. Revascularisation

Some clinical trials have included revascularization endpoints (PCI or CABG) as part of the primary composite with conflicting results [14, 15]. Such endpoints are considered more relevant to PCI/CABG interventional studies, and in the scope of this Guideline, their inclusion as a primary endpoint should be clearly justified and their assessment pre-defined and systematically assessed. Independent adjudication of these endpoints is necessary.

4.5. Unstable angina pectoris necessitating hospitalisation

Unstable angina has been investigated in ACS clinical trials but due to the varying definitions used, the associated subjectivity and the influence of local clinical practice, this endpoint is not encouraged to be included in the composite primary endpoint.

4.6. Stent thrombosis

Stent thrombosis is a rare event that can have fatal consequences. Stent thrombosis has been captured in some registration studies, but not consistently in the primary endpoint (PEP). The investigation of stent thrombosis as part of the primary endpoint is not encouraged due to the uncertainty of the clinical relevance of all captured events, except for the "definite" subcategory which could be of more clinical relevance than the other subtypes. Another category identified by the timing is intra-procedural stent thrombosis, which is a rare event indicating the development of occlusive or non-occlusive new thrombus in or adjacent to a recently implanted stent before the PCI procedure is completed. Some recent studies [16, 17] show that these events may be of prognostic value. As such they should also be collected and presented as secondary endpoint but not included in the analysis of stent thrombosis.

4.7. Left ventricular function and heart failure

Some medicinal products such as modulators of reperfusion injury or inflammation, or gene/cell therapy are developed to improve myocardial function and reduce the occurrence of HF. In these cases, measurement of myocardial function could be relevant to investigate the mechanism of action; the occurrence of heart failure can be investigated as a secondary endpoint. Occurrence of HF should be considered as an endpoint in phase III studies aimed at showing benefit in cardiovascular outcomes.

4.8. Composite endpoints

Due to the rather low incidence of cardiovascular events during the follow-up period after the acute phase of the ACS, composite endpoints consisting of relevant components are acceptable, both as primary and secondary endpoints. The composite of CV death, non-fatal MI and non-fatal stroke (Major Adverse Cardiovascular Events, [MACE]) has commonly been used in registration studies, with non-fatal strokes showing limited contribution to the results in most studies. As such, it is preferred to investigate the composite of (cardiovascular) death and non-fatal MI in confirmatory studies; non-fatal stroke could be included in the composite if justified. Different definitions of MACE have been used in the evaluation of novel therapies [17]. Such a choice should be justified if chosen in place of MACE. The inclusion of subjective outcomes in the same composite is generally not encouraged, as they may either drive the efficacy or dilute the results. In case these endpoints are included they have to be stringently defined, and adjudicated. Each component of the primary composite endpoint should be analysed as secondary endpoint.

The net clinical benefit that includes both benefit and safety issues of the studied drug may be used as a secondary endpoint to be evaluated if it contributes to the discussion on the benefit-risk balance of the studied drug.

4.9. Angiographic endpoints

In studies of fibrinolytic medicinal products, angiographic studies using the TIMI (Thrombolysis in Myocardial Infarction) perfusion grades as evaluation criteria are often used. However, complete recanalization cannot be considered as a surrogate for survival when assessing fibrinolytic drugs, as some medicinal products providing higher complete recanalization rates than alteplase, failed to demonstrate additional survival benefit. For this reason, all-cause mortality is the most relevant endpoint or a combined endpoint as previously discussed (see 4.1). Secondary endpoints such as heart failure hospitalisations, change in left ventricular function, the occurrence of ventricular arrhythmias, and the need for rescue recanalization (emergent and/or planned) should also be considered and justified.

5. Methods to assess efficacy (how to measure the endpoints)

Precise descriptions of the effects of treatment that the trial seeks to quantify should be documented. These should, in turn, inform choices related to trial design and statistical analysis. The manner in which the treatment effect will be measured and quantified should be clearly specified, in particular concerning events occurring post-randomisation such as non-CV death if this is not part of the endpoint definition (see section 5.1). The statistical analysis plan should be closely tailored to the specified treatment effects of interest.

5.1. Mortality

Even though cardiovascular death is an adequate clinical outcome that reflects the disease process targeted by treatments for ACS, all-cause mortality may in many cases be the preferred choice. The use of all-cause mortality as an endpoint (or as a component of a composite endpoint) simplifies statistical analysis since all deaths are treated as events rather than non-CV deaths needing to be handled through a statistical model with associated assumptions and risks of bias. This is of specific importance in trials when the expected incidence of non-cardiovascular mortality is difficult to predict.

In situations when the incidence of non-cardiovascular death is expected to be negligible (e.g based on previous knowledge from similar products and or patient populations) and hence the possibility of important bias in the estimated treatment effect can be assessed as being small, CV death can be used as a primary endpoint (or as a component of a composite endpoint) provided that the study population is representative of the target population with respect to baseline risk of non-CV death. In this case, all-cause mortality should be planned and presented as secondary endpoint (or as a component of a composite endpoint).

It is mandatory to report and centrally adjudicate all mortality data in all studies in patients with ACS. Efforts should be made to define the specific cause of death occurring in the studies (e.g. sudden cardiac death, pump failure, acute coronary events).

5.2. New myocardial infarction

The diagnostic of MI is based on the detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL). All MIs should be collected and also classified by their different sub types (i.e.,

spontaneous, secondary to an ischemic imbalance, related to PCI, related to ST or CABG) [10]. This is particularly important considering the different prognostic values of each type of MI. For the same reason and to support the clinical relevance of post procedural MIs, these events should be presented with higher cut-off values (≥ 5 and ≥10x upper level of normal ULN, in case of CK-MB or ≥70x ULN of cTn) [19]. These higher cut-off values can also help in diagnosing MIs in the setting of elevated baseline biomarkers, which is a problematic situation. In such cases, serial measurements of the biomarkers are necessary, in addition to new ECG changes or signs of worsening of cardiac function, e.g. HF or hypotension [19].

5.3. Stroke

Even though ischemic stroke may be an adequate clinical outcome in order to reflect the disease process targeted by treatments for ACS, the use of all-cause stroke as part of the composite endpoint is recommended. If ischaemic stroke only is used, continuation of data collection in patients experiencing hemorrhagic stroke under the assigned treatment regimen is in principle required but may not be feasible, resulting in the need to handle this missing data through a statistical model with associated assumptions and risks of bias To differentiate between effects on efficacy and safety, rates of ischemic and haemorrhagic strokes should be presented separately (see also section 8.1).

Diagnosis of stroke (i.e.: signs and symptoms of acute episode of focal or global neurological dysfunction suggestive of brain, spinal cord, or retinal vascular injury as a result of infarction or haemorrhage) should be confirmed by brain imaging. Brain imaging with CT or MRI can localize the regions of brain infarction and haemorrhage. According to current updated definitions, an ischemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal or retinal infarction [20], while haemorrhagic stroke is caused by a collection of blood in the same areas not attributable to trauma.

An ischaemic stroke with haemorrhagic conversion should be considered as "primary ischaemic". The subgroup of "undefined strokes" (i.e.: those without sufficient evidence to be classified as ischemic or haemorrhagic) should be as small as possible in order to be able to properly assess the effect of the study treatment. A suspected transient ischemic attack (TIA) should be adjudicated as ischaemic stroke if there is positive neuroimaging confirming a cerebral infarction, even if the duration of symptoms is of less than 24 hours duration.

5.4. Need for revascularisation

The underlying cause of revascularization should be identified: restenosis, stent thrombosis or disease progression. In the latter case target vessel revascularization (TVR) could be included. Early target lesion events after revascularization (before 30 days) are more likely to be caused by an angiographic complication and should preferably be included as safety endpoint. Reference should also be made to the scope of the intervention e.g., single or multiple vessels.

5.5. Unstable angina pectoris necessitating hospitalisation

When investigated, robust definitions should be employed. In order to support the clinical relevance of the event it should preferably be shown that it has led to a revascularisation procedure. Since a medicinal product that prevents death and/or new MI might result in more patients suffering from UA, the analysis of this endpoint should take into account censoring issues as well.

5.6. Stent thrombosis

Stent thrombosis (ST) should be collected and classified as definite, probable and possible in line with acceptable definitions [21]. In addition, the timing of ST should be documented (acute, sub-acute, late and very late), as risk factors and clinical sequels differ with timing.

5.7. Ventricular function and heart failure

Investigation of cardiac function should follow state of the art methods. This can include among others measurement of ventricular function by isotopic method and/or by cardiac magnetic resonance imaging and/or echocardiography. Investigation of HF should follow the relevant CHMP guidelines.

5.8. Angiographic endpoints

Angiograms should undergo central blinded reading. In principle, the rate of TIMI 3 flow (complete revascularization) of the infarct related artery at 90 minutes is considered the most relevant angiographic endpoint, as it has been shown to correlate with an improved outcome in terms of mortality and left ventricular function. An earlier evaluation of the patency pattern (i.e. 30 and 60 minutes) may provide important information on the speed of recanalization. Whatever is the time-point selected as primary outcome, it must be properly justified and pre-specified in the clinical trial. Graft vessel thrombosis should also be reported, if relevant.

6. Selection of patients

6.1. Study population

The definition of the different ACS subtypes should be based on current guidelines/universal definition of MI including STEMI and NSTEMI as well as UA [3, 4, 10].

6.1.1. STE-ACS (ST elevation acute coronary syndrome)

In patients with acute chest pain and persistent (>20 min) ST-segment elevation on ECG the diagnostic of STE-ACS is made [3]. This condition generally reflects an acute total coronary occlusion. Most patients will ultimately develop an ST-elevation myocardial infarction (STEMI) with the criteria of acute myocardial infarction described before [see 5.2].

6.1.2. NSTE-ACS (Non-ST elevation acute coronary syndrome)

In patients with acute chest pain but no persistent ST-segment elevation the diagnostic of NSTE-ACS is made [4]. ECG changes may include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves or the ECG may be normal. The clinical spectrum of non-ST-elevation ACS (NSTE-ACS) may range from patients free of symptoms at presentation to individuals with ongoing ischaemia, electrical or haemodynamic instability or cardiac arrest. The pathological correlate at the myocardial level is cardiomyocyte necrosis (NSTEMI) or, less frequently, myocardial ischaemia without cell loss (UA). Currently, cardiac troponins play a central role in establishing a diagnosis and stratifying risk, and make it possible to distinguish between NSTEMI and UA [4]. Among NSTE-ACS population, the higher sensitivity of

troponin has resulted in an increase in the detection of MI [4]; the diagnosis of UA is less frequently made.

6.2. Inclusion criteria for the therapeutic studies

Inclusion of both STE-ACS/ STEMI and NSTE-ACS/NSTEMI patients in the same clinical trial (or not) should be justified based on the mechanism of action of the investigated product and the proposed time of intervention. If both subgroups are investigated in the same trial, both subgroups should be well represented. For interventions aimed at post-acute and longer term phases (secondary prevention or plaque stabilisation) it may be justified to address both conditions in the same clinical trial. Time of inclusion of the patients in relation to the index event should be set and adequately discussed *a priori*.

The proportion of ACS patients with unstable angina (UA) (i.e. myocardial ischaemia at rest or minimal exertion in the absence of cardiomyocyte necrosis) is estimated at 20–30% of ACS admissions although the proportion is decreasing with the introduction of high-sensitivity troponin assays. For this reason many of the patients previously included in trials as 'unstable angina' would now be classified as NSTEMI. This reclassification raises the question of whether the diagnosis of UA should be reconsidered [13]. Patients with unstable angina represent a different risk category and prognosis that necessitates different interventions than NSTE-ACS/NSTEMI patients. However, during the acute presentation of NSTE-ACS it may still be difficult to discriminate NSTEMI from UA so both groups have been included in some clinical studies. In general, the investigation of interventions in these patients should preferably be performed in separate clinical trials.

If fibrinolysis is considered, inclusion criteria should be in line with the current treatment guidelines concerning the inclusion for fibrinolysis [3].

6.3. Exclusion criteria for the therapeutic studies

If the patients do not fulfil the above criteria for ACS they should be excluded from participation in the ACS studies. Other life-threatening conditions presenting with chest pain, such as dissecting aneurysm, myopericarditis or pulmonary embolism may also result in elevated troponins and should always be considered as differential diagnoses [4].

If the test drug is interfering with the haemostatic system, patients with a significant risk of bleeding (e.g. recent stroke, recent bleeding, major trauma or surgical intervention) and/or a propensity to bleed (e.g. thrombocytopenia, clotting disturbances, intracranial vascular diseases, peptic ulcers, haemophilia) should be excluded from participation in the clinical studies. Attention should be paid to the time elapsed between a previous application of antiplatelet or anticoagulant acting agent and the administration of study drug (e.g. the pharmacokinetic [PK] and even more importantly, the pharmacodynamic [PD] half-life of these previously administered drugs).

For reasons of generalisability of the study results to the future target population it is strongly advised not to define the exclusion criteria too narrow, i.e. polymorbid patients (e.g. renal and/or hepatic impairment, heart failure), should not automatically be excluded from the main therapeutic clinical trials.

6.4. Risk Stratification

In clinical trials, the ability of the therapy to demonstrate a treatment effect may depend on the underlying risk and expected event rates. Enrichment strategies are sometimes used in trials to obtain the required number of events within a reasonable time frame by performing studies in specific subgroups which are likely to exhibit a higher event rate than the overall target population. If such a strategy is used, it should be discussed further within the context of the external validity for the claimed indication.

In addition to traditional risk factors, phase III studies may recruit a broader patient population in whom risk scores are evaluated to identify signals of differential/consistent treatment (or safety) responses across levels of the risk score. International guidelines recommend the use of risk scores such as the Global Registry of Acute Coronary Events (GRACE) or TIMI in the clinical care of patients with ACS. These scores can be used to predict the risk of major cardiovascular events (MACE), and they are useful to guide treatment decisions. In addition, there are scores to characterise the bleeding risk e.g. CRUSADE in NSTEMI [4]. The use of biomarkers other than troponins for risk stratification necessitates further investigation (e.g., markers of ischemia and inflammation (ischemia-modified albumin, heart fatty acid binding protein)) [22]. From a regulatory perspective, risk scores should either be reported or adequate data should be provided in the study files to enable risk score calculations. Risk-based analyses can contribute to the interpretation of study results, especially in highly heterogeneous populations, although such analyses may not always be conclusive given the recognized limitations of subgroup analyses. Analysis among different risk setting using risk scores should be pre-defined and foreseen in the protocol. The assessment of subgroups formed by the categories of the risk score may reveal the need for further prospective studies or post-marketing surveillance priorities in specific subgroups.

6.5. Special populations

6.5.1. Older patients

Adequate representation of older patients (above 70 years) in the clinical trials should be ensured. The overall database of the dossier should be examined for the presence of age-related differences, e.g., in adverse event rates, in efficacy, and in dose-response. If these relatively crude overview analyses show important differences, further evaluation may be needed.

Special attention should be given to the frequently associated comorbidities in the ACS population in general and older patients in particular (diabetes mellitus, COPD, renal failure, anaemia), also in relation to possible drug-drug interactions.

7. Strategy and design of clinical trials

7.1. Clinical pharmacology

The objectives of studies related to clinical pharmacology are the investigation of the PD and PK properties of the medicinal product in healthy volunteers, stable patients of both sexes and in patients with different degrees of renal and hepatic impairment as relevant. Furthermore, interactions of the new substance especially with mandatory/probable co-medications which are routinely used in the management of ACS (e.g. platelet inhibitors, anticoagulants as well as other CV medications) should be

investigated. Comprehensive advice on interaction studies is provided in the *CHMP Note for Guidance on the Investigation of Drug Interactions* (CPMP/EWP/560/95).

PD studies should include evaluation of mechanism(s), onset and duration of action, as well as a preliminary investigation of tolerability. The PD activity of the new substance should be defined as much as possible, for example with regard to effects on haemostatic and haemodynamic variables.

7.2. Therapeutic exploratory studies

7.2.1. Objectives

The purpose of this development phase is to identify those patients with ACS who may benefit from the medicinal product and to establish suitable therapeutic dose ranges - usually as adjunctive therapy to existing standard treatment.

These early clinical trials often primarily aim at measuring drug activity. However, it is encouraged to investigate clinical endpoints as secondary or exploratory endpoints. As some medicinal products (e.g. parenteral agents) may be intended for limited duration of administration, investigation of transition from and to other oral agents may be necessary.

Furthermore, initial information on safety should be obtained and dose schedules should be defined for older patients and those with risk factors.

7.2.2. Design

Dose ranging studies should be performed using a randomised, controlled, double-blind design. Different dosages should be tested for the projected duration of the treatment period. Dose schedule selected for pivotal studies should be justified on the basis of the results of the dose-finding studies in the target population.

The duration of these studies is - among other criteria - dependent upon the (primary) target variable(s) and the extent of clinical information they are aiming at. Mostly, it is useful to include a sufficiently long-term follow-up in order to estimate the incidence of significant clinical events and delayed adverse drug reactions (e. g. thrombocytopenia).

7.3. Confirmatory Therapeutic Studies

7.3.1. Objectives

The objectives of these studies are to provide robust evidence of efficacy establishing reduction of clinically relevant cardiovascular events (e.g. death/new MI) at a predefined time justified by the mechanism of action and duration of administration. These studies should also establish the safety of the new substance at the posology proposed for marketing.

The majority of the main therapeutic studies will use composite endpoints as primary efficacy variables. Optimally, all components of the composite will contribute to the positive results. Studies aiming at providing proof of efficacy must have a confirmatory statistical approach. These studies must be controlled, randomised and every effort should be made to maintain double blindness. The statistical approach e.g. a demonstration of superiority, equivalence or non-inferiority, has to be pre-specified in the protocol.

In some cases (e.g. large scale, multicentre, multinational trial) a single confirmatory trial could be sufficient for the proof of efficacy of a new substance if the results are statistically persuading and clinically relevant as discussed in the relevant CHMP guideline (see section 3).

Investigation of all-cause mortality and long term follow-up are mandatory in studies with novel interventions.

7.3.2. Background therapy

In general, background therapy should reflect the standard of care as recommended by current clinical guidelines [3, 4]. Alternatively, EU Registry data can be helpful to determine the standard of practice and can inform the design of pivotal studies. Background therapy is also relevant in the context of the used revascularisation strategy. The degree to which background therapy should be specifically standardized in terms of interventions, timing, drugs, and dosing will depend on the study drug's mechanism of action or the specific question being addressed by the randomized controlled trial. This may eventually have to be reflected in the labelling.

7.3.3. Choice of comparator

Depending on the class of drug tested and its mechanism of action, placebo and/or active controlled trials may be adequate for the late development phases. Whenever plausible and adequate (i.e. different mechanism of action than that of standard therapy) the investigational drug or placebo should be given in addition to standard therapy, unless otherwise justified e.g., when investigating a different treatment strategy. The choice of the comparator should reflect the EU standard of care and should preferably be unified throughout the different regions.

7.3.4. Duration of clinical studies

For medicinal products intended for short-term administration (e.g. hours to 7 days), the primary endpoint should preferably be measured at 30 days following initiation of therapy in the confirmatory studies. Depending on the mechanism of action of the investigated drug, shorter time spans when measuring the primary endpoint may be acceptable if the follow-up data provide evidence of durability of the effect. In any case, further measurements should be performed after longer (e.g. 180 days) but also after shorter duration (e.g. at time of termination of study drugs) as secondary measures of efficacy.

In case of longer duration of administration, an appropriately chosen duration of follow-up should be pre-specified in the protocol in order to estimate longer-term efficacy and safety. The maintenance of an adequate benefit risk balance should be demonstrated. Long term results should preferably also be adjudicated by a blinded clinical event committee.

Claims of chronic administration (following ACS) necessitate support from sufficiently long studies to demonstrate that a positive benefit risk balance is maintained according to the pre-defined hypothesis or to the number of events calculated (in case of events driven design).

7.3.5. Analyses and subgroup analysis

The database for the primary analysis, investigator or - preferably - event adjudication committee adjudicated endpoints has to be pre-specified in the protocol. A primary analysis based on the data

produced by the event adjudication committee is especially important if side effects of the test drug or the comparator may potentially un-blind some of the patients.

Regarding the primary analysis, the total event rates at the pre-specified time points or time-to-event within this period can be chosen. However, in any case survival curves over this period - and also over the-follow-up period - should be provided for the combined endpoint and all its components in order to evaluate whether differences occur or not.

The components of a composite efficacy endpoint should be analysed individually in order to evaluate their contribution to the overall results. The handling of deaths in the analyses of other individual components (e.g. non-fatal MI) needs to be carefully considered and justified: an assumption that censoring is uninformative might not be reasonable. Optimally, the results of all components of the composite endpoint should be consistent. In a hierarchical view, the component "all cause mortality" will be considered as being the most relevant (e.g. an over-mortality cannot be compensated by a decreased rate of angina pectoris).

Randomisation should be stratified for the qualifying condition (STEMI and NSTEMI) and for region (if applicable). Other risk factors (gender, age) may also be considered for stratification of the randomisation. Stratification factors should be reflected in the statistical analysis.

Subgroup analyses for risk score (section 6.4) as well as for revascularisations (e.g. CABG, PCI, fibrinolysis) should be foreseen in the protocol in order to demonstrate consistency of the results.

In addition, subgroup analyses regarding patients with different cut-offs of elevated troponin I/T concentration at enrolment, as well as differences in duration between symptom onset and initiation of study drugs (e.g. < 6 hours, > 6 or 12 hours) may be of interest.

8. Safety aspects

During the course of the clinical trials all adverse events should be carefully documented; the most important being bleeding and all-cause death. Careful consideration should be given to those patients who failed to complete the study per protocol (in particular drop-outs due to adverse events/drug reactions or lack of efficacy) or those who have achieved an endpoint. Follow-up of these patients is important in order to obtain information on long term safety.

Safety in high-risk groups (e.g. patients with organ dysfunction, older age, extremes of body weight) requires special consideration. Furthermore, any information available concerning clinical features and therapeutic measures in accidental overdose should be provided.

Special efforts should be made to investigate potential adverse drug reactions that are characteristic for the class of drug being tested, in particular those listed below.

8.1. Bleedings

Bleeding is the main complication of antithrombotic and antiplatelet therapy. 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 should 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.

Bleedings should be categorised according to an acknowledged classification. Different bleeding definitions have been used in the setting of ACS; this heterogeneity impairs the interpretation of the safety profile across trials. Consensus has not been reached on a unified classification. TIMI (i.e. TIMI major and minor) and GUSTO (The Global Use of Strategies to Open Occluded Arteries) criteria for example, have been previously used and have been shown to be independently correlated with subsequent risk of death. Reporting of bleeding events using two acceptable definitions e.g., GUSTO, TIMI and BARC definitions [23] could be considered for future clinical trials and/or regulatory submissions to improve the comparative assessment of safety endpoints across medicinal products and trials.

In addition, the inclusion of ISTH major bleeding may be helpful to compare major bleeding rates of similar compounds across different indications (e.g., in comparison with stroke prevention in atrial fibrillation and/or treatment of VTE).

It is advisable to use the same classification for bleedings throughout the whole clinical development program. A subgroup analysis of bleedings regarding patients undergoing invasive procedures (e. g. PCI, CABG surgery) - or not - is necessary.

Transfusions of blood, red blood cells, coagulation factors, specific antidotes or modification of co-administered therapy are further indicators of bleeding severity and should thus be documented carefully (number, temporal association to application of study drug and/or procedure).

8.2. All-cause mortality

In addition to being part of the primary endpoint, all-cause mortality is also of importance for the safety assessment throughout the study period. Any observed imbalances in non-cardiovascular deaths should be adequately analysed.

8.3. Thrombocytopenia

In particular heparins and platelet aggregation inhibitors are known to cause (acute and delayed) thrombocytopenia that can be severe and the cause of serious bleedings or other complications (e.g. heparin-induced thrombocytopenia in case of heparins). Consequently thrombocyte values have to be monitored closely during and after therapy. In cases with thrombocytopenia, information on degree, recovery time and outcome should be provided. Moreover, it has to be documented in detail (number, temporal association to study drug/procedure etc.) if transfusions of thrombocytes had become necessary.

8.4. Rebound effect

The studies should include the evaluation of events which are considered to be characteristic for a possible rebound effect (e.g. clear increase in angina pectoris and/or new MI and/or death and/or other thrombotic events) after termination of the study drug.

8.5. Effects on laboratory variables

The therapeutic clinical studies should include the investigation of effects on the white and red blood cell count and should especially focus on the question whether the observed changes can be explained by former bleeding. In addition, particular attention should be paid to increases in liver enzymes, creatinine concentration and possible antibody formation.

8.6. Effects on concomitant diseases

The studies should include the evaluation of effects of the new drug on the function of diseased organs (e.g. kidneys in case of renal impairment).

References

1. EMA – CPMP - Points to consider on clinical investigation of new medicinal products for the treatment of acute coronary syndrome without existing ST-segment elevation (CPMP/EWP/570/98) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003363.pdf
2. EMA - CPMP – Points to consider on the clinical development of fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial intarction (CPMP/EWP/967/01).
3. Steg PG, James SK, Atar D, et al. (2012) : ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur.Heart.J.: 33, 2569–2619.
4. Roffi M, Patrono C, Collet JP et al. (2015): 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur.Heart.J.: doi:10.1093/eurheartj/ehv320
5. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010; 362:2155–2165.
6. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA (2010): The Global Registry of Acute Coronary Events, 1999 to 2009—GRACE. Heart 2010;96:1095–1101.
7. Savonitto S, Ardissino D, Granger CB, et al. (1999): Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707–713.
8. Terkelsen CJ, Lassen JF, et al, (20015): Mortality rates in patients with ST-elevation vs.non-ST-elevation acute myocardial infarction: observations from an unselected cohort. Eur Heart J 2005;26:18–26.
9. O'Connor, et al. (2010): Acute Coronary Syndromes; 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Robert E. Circulation. 2010; 122: S787-S817.
10. Thygesen, K; Alpert, JS; Jaffe, AS (2012): Definition of Myocardial Infarction Circulation. 184 2012;126:2020-2035.

11. Hicks KA, Tcheng JE, Bozkurt B. (2014): 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). J Am Coll Cardiol. 2014 Dec 29. pii: S0735-1097(14)07484-1.

12. Steg PG, Huber K, et al. (2011) Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 32(15): 1854-64

13. Bueno, H. et al Report of the European Society of Cardiology Cardiovascular Round Table regulatory workshop update of the evaluation of new agents for the treatment of acute coronary syndrome. European Heart Journal. Acute Cardiovascular Care 2016: 1-10

14. Tricoci P, Huang Z, Held C, Moliterno DJ, et al. (2012): Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes. N Engl J Med 2012;366:20-33.

15. Bhatt DL, Stone GW, Mahaffey KW, et al. (2013): Effect of platelet inhibition with cangrelor during PCI on ischemic events. N Engl J Med 2013;368:1303-13

16. Brener, S.J., MD, Cristea, E. and , Kirtane A.J et al. (2013): Intra-Procedural Stent Thrombosis. A New Risk Factor for Adverse Outcomes in Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes. Am Coll Cardiol Intv 2013;6:36–43

17. Xu.Y. , XINKAI, Q.U. , WEIYI, F and HUI C. (2013): Prevalence, Correlation and Clinical Outcome of Intra-Procedural Stent Thrombosis in Patients Undergoing Primary Percutaneous Coronary Intervention for Acute Coronary Syndrome. J Interven Cardiol 2013;26:215–220 2013

18. Cung TT et al. (2015): Cyclosporine before PCI in patients with acute myocardial infarction. N Engl J Med 2015;373:1021-31

19. Moussa et al, (2013): Consideration of a New Definition of Clinically Relevant Myocardial Infarction After Coronary RevascularizationAn Expert Consensus Document From the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol. 2013;62(17):1563-1570.

20. Sacco, RL, Kasner SE, Broderick JP, et al. (2013): An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Jul;44(7):2064-89

21. Cutlip, D.E; Windecker,S. and Mehran, R. et al. (2007): Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation. 2007;115:2344-2351

22. Scirica BM (2011): Acute Coronary Syndrome. Emerging Tools for Diagnosis and Risk Assessment. J Am Coll Cardiol 2010;55: 1403–15.

23. Mehran R. et al. (2011): Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-2747.