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POINTS TO CONSIDER ON THE CLINICAL INVESTIGATION OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF ACUTE CORONARY SYNDROME (ACS) WITHOUT PERSISTENT ST-SEGMENT ELEVATION

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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CLINICAL INVESTIGATION OF NEW MEDICINAL PRODUCTS FOR THE TREATMENT OF ACUTE CORONARY SYNDROME (ACS) WITHOUT PERSISTENT ST-SEGMENT ELEVATION

PREAMBLE

These notes are intended to provide guidance for the evaluation of drugs which are administered in patients with unstable angina pectoris (UAP) or non-Q-wave myocardial infarction (NQWMI) also called acute coronary syndrome without persistent ST-segment elevation.

These notes consider the clinical evaluation of - usually short-term (e.g. 1 - 7 days) administered - drugs which are intended to be used in the acute symptomatic phase of ACS without persistent ST-segment elevation but not those intended for long-term prevention of cardiovascular events in stabilised patients after UAP/NQWMI or other patients at high cardiovascular risk. Presently these "Points to Consider" relate especially to antithrombotic drugs, the majority being antiplatelet or antithrombin acting agents.

These notes should be read in conjunction with the Directives 75/318/EEC, as amended, as well as in conjunction with other pertinent elements outline in current and future EU and ICH "Notes for Guidance", especially those on:

- Pharmacokinetic Studies in Man
- Investigation of Drug Interactions
- Dose Response Information to Support Drug Registration (E4)
- Statistical Principles for Clinical Trials (E9)

1. INTRODUCTION

The ACS without persistent ST-segment elevation is characterised by severe or worsening angina (e.g. prolonged or repetitive angina pectoris at rest) with or without elevations of specific biochemical cardiac markers diagnostic of myocardial infarction (MI).

The pertinent electrocardiographic changes include ST-segment depression, transient ST-segment elevation and/or T-wave inversion in at least two contiguous leads but no clear-cut electrocardiographic signs of suspected MI with persistent ST segment elevation which usually requires reperfusion therapy.

ACS without persistent ST-segment elevation is a medical emergency and patients require urgent hospital admission. If untreated, ACS without persistent ST-segment elevation can lead to large and/or fatal myocardial infarction. Accordingly, the major complications are cardiac death, new myocardial infarction (MI) and refractory angina frequently requiring urgent coronary intervention procedures.

Though in the acute phase NQWMI and UAP are associated with a lower mortality/morbidity than Q-wave MI (QWMI), in particular patients with NQWMI have a comparable cardiovascular event rate within the following 6 months as those with QWMI.

One of the difficulties in the management of ACS without persistent ST-segment elevation is the identification of those patients most at risk of progression to complications. Although there are no absolute predictive factors, a higher incidence of cardiovascular events has been associated with increased age and heart rate and low systolic blood pressure. Co-morbidities like heart failure, persistent/recurrent ischaemic cardiac pain, as well as ischaemic ECG changes (in particular ST-segment depression) and raised specific cardiac biochemical markers (e.g. CK-MB, troponins) are also associated with a higher incidence of cardiovascular events.

The pathophysiology of ACS without persistent ST-segment elevation relates to variable thrombotic obstruction at a site of a complex atherosclerotic plaque. The plaque is typically fissured, ulcerated or ruptured with superimposed non-occlusive thrombus resulting in emboli from this thrombus to distal coronary vessels. Frequently, an increased vascular tone is associated with the thrombotic occlusion. Angiograhic observations are rather consistent in patients with UAP/NQWMI. The culprit lesions in the coronary arteries are often associated with complex, excentric atheromatous coronary luminal narrowing, frequently greater than 70 % in at least one vessel.

Consequently, the main objective of treatment for this condition is the prevention of (new) myocardial infarction and its sequelae by attempting to control platelet activation/ aggregation, coagulation and vascular spasm and thus, to prevent complete thrombotic occlusion.

2. SELECTION OF PATIENTS

2.1 Inclusion criteria for the therapeutic studies

Patients should present with acute (e.g. within the last 24 hours) symptoms suggesting severe or worsening angina pectoris (e.g. according to class III of the Braunwald classification) and ECG changes suggesting myocardial ischaemia (e.g. transient ST-segment elevations, ST-segment depressions of > 0.05 mv and/or acute T-wave inversion in at least two contiguous peripheral or three precordial leads) and/or elevated specific cardiac biochemical markers.

NQWMI can be defined by the presence of an elevated CK-MB activity ≥ 2 times the upper limit of normal, in addition to symptoms and ECG changes. In case the CK-MB values were initially normal (up to 8 hours after enrolment) but rise subsequently (between 16 to 24 hours), a diagnosis of MI should still be made in the presence of recurrent angina. Serial measurements of the specific biochemical cardiac markers are strongly recommended as an increase in their levels may sometimes be delayed.

In addition, new definite Q-waves (e. g. ≥0.04 seconds with an amplitude >0.25 % of the R-wave or QS complexes in at least two contiguous leads) recorded up to 24 hours after enrolment can indicate a (QW-)MI at inclusion.

Subgroup analyses from large scale trials indicate that the length of the time period between symptom onset and inclusion in the study/initiation of study drug could be relevant for the results in terms of death/MI reduction, i. e. the shorter the better.

2.2 Exclusion criteria for the therapeutic studies

The patients should not fulfil the criteria for reperfusion therapy (e.g. fibrinolysis or direct PTCA), i.e. should not be suspected to suffer from ACS with persistent ST-segment elevation.

If drugs interfering with the haemostatic system are tested, patients with active or a recent history of significant bleeding (e.g. stroke, major trauma or surgical intervention) and/or a propensity to bleed (e.g. thrombocytopenia, clotting disturbances, intracranial vascular diseases, peptic ulcers) should be excluded from participation in the clinical studies.

Attention should be paid to the time elapsed between a previous application of antiplatelet/antithrombin acting agent beforehand and the administration of study drug (e.g. the pharmacokinetic and even more importantly, the pharmacodynamic 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 be excluded from the main therapeutic clinical trials.

3. EFFICACY CRITERIA

Since the goal of treating acute ACS without persistent ST-segment elevation is to prevent associated morbidity and mortality, death and myocardial infarction (MI) are considered to be the clinically most meaningful endpoints in therapeutic studies, whereas refractory angina is of more uncertain clinical relevance.

In particular the diagnosis of refractory angina pectoris but also that of myocardial infarction are subject to considerable inter-individual variability of the treating physicians/investigators. Since the key issue is to get unbiased event documentation, it is strongly recommended to establish blinded event adjudication committees for the additional verification of these events in the pivotal clinical trials.

3.1 Individual efficacy criteria

Some of the following definitions are based on - widely accepted and/or frequently used - published criteria, but in some studies small variations have been applied to the criteria mentioned below . However, it should be born in mind that the ACS without persistent ST-segment elevation is a rapidly evolving field. Accordingly, these criteria could be subject to modifications or changes in the near future.

Nevertheless, different definitions of the efficacy criteria mentioned below can only be accepted when their robustness and clinical relevance have been proven.

3.1.1 All cause mortality

The preferred approach to the analysis of death is to consider all deaths regardless of cause since the classification of the mode of death is fraught with difficulties. All cause mortality is the most important endpoint in clinical trials for the estimation of the risk/benefit ratio of a drug. This is true whether death is considered on its own or as a component of a composite endpoint.

According to published literature, approximately only 2 - 4 % of the patients die 30 days following the acute phase of the ACS without persistent ST-segment elevation, mostly due to MI. Therefore, the disadvantage of this endpoint is its rather low incidence in UAP/NQWMI particularly, if all cause mortality is measured after a short-term treatment and follow-up period. This is also true if patients resuscitated from sudden (cardiac) death are counted for all cause mortality.

Consequently, studies primarily aiming at all cause mortality alone would have to include very large sample sizes, which is a relevant obstacle for the performance of such studies. However, as a component of a combined efficacy endpoint, all cause mortality provides very valid information about the clinical usefulness of a new agent.

3.1.2 New myocardial infarction (MI)

The definition of new MI should have proven to be clinically relevant for the individual patient. In general, a new MI should be diagnosed on the basis of acute symptoms (e.g. typical prolonged severe chest pain and related symptoms), ischaemic ECG changes (e.g. persistent ST-segment elevation with progressive T-wave inversion and/or progression from non Q-wave to a definite Q-wave in at least two contiguous leads) and a rise of specific cardiac biochemical markers followed by a subsequent fall.

For example, an increase (to ≥ twice **u**pper **l**imit of **n**ormal [ULN] in activity) and subsequent fall of CK-MB is considered to be a valid criterion for the diagnosis of myocardial infarction. Thus, serial measurements of biochemical markers should be performed for the confirmation of (new) MI. If fibrinolytic therapy is administered for suspected ACS with persistent ST-segment elevation, this could be counted as (aborted) MI even though no typical patterns of biochemical markers had been recorded.

Presently, study sites should preferably use CK-MB to diagnose the occurrence of MI. Although CK-MB is less tissue-specific than troponin I/T, the data documenting its specificity for irreversible injury are more robust.

Though an increase in troponins in addition to ischaemic symptoms and ECG changes is highly specific for myocardial necrosis, a definition of a clinically relevant MI according to solely elevated troponin I/T has not been established yet. Moreover, troponins have a long half-life and can remain elevated for approx. 1 week in case of large infarcts. Consequently, in case of elevated troponins alone it can be difficult to differentiate between index MI and early re-infarction. In order to validate troponin I/T as a diagnostic marker for acute MI, it is recommended to measure the latter and CK-MB simultaneously in large clinical trials.

If an alternative definition of MI (other than the WHO standard criteria) is used in the confirmatory clinical trial(s), the sensitivity of this new definition should be evaluated in relation to the standard WHO criteria. Additionally, the results of the specific cardiac biochemical markers should be robust enough to support the alternative definition of MI. Furthermore, it is recommended to evaluate various levels of biochemical cardiac marker elevations in order to get an estimate on the size of MIs (e.g. > 3 ULN, > 5 ULN, > 10 ULN).

In patients enrolled with NQWMI the differentiation between index MI and re-infarction can be problematic. Such a decision should be based on the total amount of clinical data including symptoms, the pattern of protein release from the myocardium and results of repeated ECGs. Definitions in the protocol must assure a clear differentiation between key event and new MI. For example, the occurrence of definite Q-waves - without information on enzyme values - should only be counted as a new MI if the time-span between index-MI and subsequent MI is approx. 24-hours and characteristic symptoms had occurred. Optimally, CK-MB increases to values > 50 % of the previous ones.

In addition, the diagnosis of new MI after revascularisation procedures is problematic. A frequently used definition requires that the increase in CK-MB activity, is more than 3-times above normal after percutaneous coronary interventions (PCI) and more than 5-times above normal after coronary artery bypass graft (CABG) surgery. Depending on the setting (e.g. PCI or CABG), ECG and symptomatic criteria (see above) are considered to be supportive, as well (e.g. significant Q-waves).

Though in the literature published on ACS without persistent ST-segment elevation the incidence of new MI is usually higher than that of death (depending on the inclusion criteria, approximately 6 - 8 % 30 days after initiation of study drugs), a confirmatory trial aiming primarily at new MI alone - measured after a short-term treatment and follow-up period - would miss a part of the fatal MIs but would still require a very large sample size.

Since a large proportion of acute MI is immediately fatal, additional information regarding the effect of the new drug on mortality is necessary. The occurrence of death may prevent a MI being diagnosed (i.e. censoring). If this happens to a different extent in the different treatment arms, bias could result. Furthermore, a reduction in new MI cannot outweigh an increase in mortality. Accordingly, new MI is considered to be a hard component of a combined primary efficacy endpoint (in addition to all cause mortality) and - on its own - a clinically relevant secondary endpoint for confirmatory clinical trials.

3.1.3 Refractory angina pectoris

Refractory angina pectoris usually occurs more frequently than death or MI within 30 days after the onset of the ACS without persistent ST-segment elevation (depending on the inclusion criteria approximately 9 - 12 %).

Since a drug which prevented death and/or new MI might result in more patients suffering from refractory angina, the analysis of this endpoint should take into account censoring issues as well.

If this endpoint (-component) is chosen for confirmatory clinical trials, the protocol has to pre-specify and the investigator is required to document the criteria under which the patient was considered to have reached the endpoint "refractory angina pectoris". In particular, angina pectoris is considered to be refractory, if it occurs despite "optimal" anti-anginal therapy and leads to an urgent invasive intervention - unless inadvisable on reasoned grounds. Urgent invasive interventions include diagnostic catheterisation and/or revascularisation (e.g. PCI or CABG).

However, the inherent weakness of this endpoint is that "optimal anti-anginal therapy" and "urgent revascularisation" are difficult to define, and will depend much on local usual practice patterns and available facilities. Moreover, since it seems possible, that patients can benefit from rather early (i.e. during anti-thrombotic therapy) cardiac interventions on the long run, doubts have been raised about the clinical value of this endpoint (-component) for confirmatory studies.

Nevertheless, presently refractory angina - as defined below - can still be considered as a component of a combined primary efficacy endpoint (in addition to all cause mortality and new MI) and as a clinically rather useful secondary efficacy endpoint if investigated on its own:

3.1.3.1 Refractory angina pectoris during the hospitalisation period:

Severe, prolonged or repetitive anginal pain accompanied by ischaemic ECG changes (e.g. marked ST-segment depression/elevation or T-wave inversion/pseudonormalisation in at least two contiguous ECG leads) occurring despite anti-anginal therapy which is considered to be "optimal" for the patient concerned (e.g. if not contra-indicated, the combined administration of nitrates - in particular i.v. nitrates - and/or ß-blockers and/or calcium channel blockers) and leading to urgent invasive intervention (unless inadvisable on reasoned grounds).

3.1.3.2 Refractory angina pectoris leading to hospitalisation

Despite "optimal" anti-anginal therapy (see 3.1.3.1) occurrence of severe, prolonged and/or repetitive chest pain at rest (e.g. recurrent bouts of chest pain, some of longer duration, within a 24-hour period - preferably accompanied by ischaemic ECG changes - leading to hospitalisation and urgent invasive intervention (unless inadvisable on reasoned grounds).

3.1.4 Cause specific mortality/morbidity

Though the classification of the mode of death and also that of cause specific morbidity is fraught with difficulties, for example cardiac death, cardiovascular death, the development/worsening of heart failure (including the severity) - in particular during 6 - 12 months follow-up - as well as other clinically important events (e.g. stroke) can be recommended as secondary target criteria for the clinical testing of new drugs in ACS without persistent ST-segment elevation.

3.1.5 Measures of drug activity

Depending on the mechanism of action of the test drug, measures of drug activity (e.g. laboratory parameters like for example inhibition of platelet aggregation, bleeding time,

activated partial thromboplastin time, thrombin time) should be performed during the initial clinical development of the new drug according to the state of the art and can be used as target criteria of human pharmacology and initial therapeutic studies.

3.2 Composite efficacy endpoints

Due to rather low incidence of cardiovascular events within the short-term follow-up period after the acute phase of the ACS without persistent ST-segment elevation, combined endpoints consisting of prognostically relevant components are considered to be useful with regard to the performance of confirmatory efficacy studies.

For the time being, combined endpoints used as primary target variables in large-scale efficacy trials in UAP/NQWMI were either the double endpoint "death/new MI" or the triple endpoint "death/new MI/refractory ischaemia or recurrent angina or urgent revascularisation".

A composite double efficacy endpoint consisting of all cause mortality and new MI (definition, see 3.1.2), measured after an adequate time interval (e.g. 30 days after initiation of therapy), is considered to be the primary endpoint of choice in confirmatory clinical trials since these events are considered to be the "hardest" objective components representing a clinically relevant drug effect.

However, a triple endpoint could still be acceptable, if it includes all cause mortality and new MI as components with the third component defined very precise (i.e. refractory angina pectoris see 3.1.3) in order to "harden" this component as much as possible. In case that a triple endpoint has been used as primary efficacy criterion, the composite of death/MI should be evaluated as secondary endpoint (in particular 30 days after initiation of study drugs) in the pivotal efficacy trial(s).

4. DEVELOPMENT STRATEGY

4.1 Human pharmacology

4.1.1 Objectives

The objectives of studies related to human pharmacology are the investigation of the pharmacodynamic and pharmacokinetic properties of the new drug in a limited number of volunteers, uncritically ill patients of both sexes and in patients with organ impairments.

Furthermore, interactions of the new substance especially with mandatory/probable co-medications which are routinely used in this indication (e.g. platelet inhibitors, antithrombins) should be investigated.

4.1.2 Design

In the early clinical development phases placebo-controlled trials should be performed, but open uncontrolled studies may be acceptable for certain objectives as well.

Depending on the mechanism of action of a particular drug, subjects/patients who are to be included in the human pharmacology studies should be withdrawn from prior antiplatelet/antithrombin therapy during a wash-out period. The duration of the wash-out period will depend on the half-life of the agent(s) and/or the time necessary for the normalisation of haemostatic parameters to return to pre-treatment levels. An allocation of an individual patient to a human pharmacology study should preferably be performed if the basic bleeding time is normal and no laboratory measures indicate an inhibition of platelet aggregation, thrombin or fibrin formation.

4.1.3 Pharmacodynamics

These studies should include evaluations on mechanism, onset and duration of action, as well as a preliminary investigation of tolerability.

The pharmacodynamic activity of the new substance should be defined as much as possible, for example with regard to effects on haemostatic and haemodynamic variables. Dose response curves should be produced since information on the relationship between dose, plasma-concentration and pharmacological effects is usually helpful for the subsequent clinical development.

For instance, the activity of the new substance on platelet function can be investigated by measuring ex-vivo ADP and/or collagen induced platelet aggregation and bleeding time prolongation. "Antithrombin"-acting agents can often be evaluated by measuring the prolongation of aPTT and/or TT or the extent of inhibition of certain clotting factors.

4.1.4 Pharmacokinetics

The pharmacokinetic data required is listed in detail in the respective EU notes for guidance (see also 1). Special studies should be performed in patients with the target disease, in the elderly and - depending on the way of elimination - in patients with varying degrees of renal and/or hepatic impairment. Pharmacokinetic evaluations should take into account possible differences related to gender, race and bodyweight.

4.1.5 Interactions

Comprehensive advice on interaction studies is provided in the respective EU notes for guidance (see also 1).

Special interaction studies should provide information which may help to define the position of the new drug in the therapeutic scheme used in patients with UAP/NQWMI. For example, attention should be devoted to potential interactions with acetylsalicylic acid (ASA) and heparins which will be frequently used alongside the investigational drug for combined treatment.

It is of note, that unfractionated heparin (UFH) and the different types of low molecular mass heparins (LMMHs) are not considered to be interchangeable in UAP/NQWMI. Thus, depending on the future posology of the test drug, separate interaction studies should be performed for the different types of heparin.

Moreover, symptomatic patients are usually treated with nitrates, ß-blockers and/or calcium antagonists which consequently also have to be considered regarding possible interactions with the test drug. In addition, interaction studies are advised for coumarins and antiplatelet and antithrombin acting drugs possibly administered in connection with PCIs and implantation of stents.

Since patients with/after UAP/NQWMI have a high probability to suffer from acute ST-segment elevation MI (QWMI) and thus might undergo fibrinolysis information on interactions between test drug and standard fibrinolytic agents should also be collected (e.g. patients who underwent fibrinolysis shortly after test drug admission) and specifically reported.

Additional pharmacokinetic and pharmacodynamic interaction studies should be performed if pharmacodynamic or pharmacokinetic properties of the drug or its metabolite(s) give reason to suspect particular interaction problems. This is especially true, if a wide range or important subtypes of the P450 enzyme system are involved in the metabolism of the test drug.

4.2 Therapeutic studies

Results of clinical trials, especially with antiplatelet and antithrombin acting agents have shown that inhibition of platelet aggregation and thrombin formation can reduce the complications

associated with coronary artery thrombosis generation in UAP/NQWMI. Presently, the combined administration of ASA and heparin is a widely used pharmaco-therapy for UAP/NQWMI, which for many clinical studies is assumed to be the underlying therapy.

Except if proven by clinical trials, UFH and the different LMMHs are not considered to be equal in their risk/benefit relation in UAP/NQWMI and thus not interchangeable in the clinical setting. This is especially important if the patient has to undergo PCI, a setting where UFH is titrated according to ACT. Of note, LMMHs cannot be monitored by ACT.

4.2.1 Initial therapeutic studies

4.2.1.1 Objectives

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

These early clinical trials will often primarily aim at measures of drug activity (see 3.1.5). However, dose finding studies with a confirmatory approach aiming at clinically meaningful endpoints (see 3.1.1 - 3.1.4 and 3.2) are preferable. It is recommended to identify the minimally effective dose**,** the maximum tolerated dose and that which tends to achieve the maximal efficacy in order to establish the optimal effective dose range and frequency of dosing.

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

4.2.1.2 Design

Dose ranging studies should be performed using a randomised, controlled, double-blind design. Preferably, a placebo group should be included. Different dosages should be tested for the projected duration of the treatment period.

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).

4.2.2 Main therapeutic studies

4.2.2.1 Objectives

The objectives of these studies are to provide unequivocal evidence of efficacy by conducting clinical trials which establish a reduction of clinically relevant cardiovascular events (e.g. death/new MI) after an adequate period of follow-up (e.g. at 30 days following the initiation of therapy) and to confirm the safety of the new substance at the posology proposed for marketing (the dose schedule selected for pivotal studies should be justified on the basis of the results of the dose-finding studies in the target population).

A clinically relevant and statistically significant greater effect compared to placebo or active control or at least the exclusion of inferiority to an approved active comparator should be demonstrated for the proposed posology of the test drug. The majority of the main therapeutic studies will use combined endpoints as primary efficacy variables. Optimally, the treatment effect concerns all components of the combined endpoint. Anyway, the treatment effect must not be accounted solely for a reduction in refractory angina, a reduction in incidences of death and/or MI must contribute to the treatment effect.

4.2.2.2 Design

Studies aiming at the proof of efficacy must have a confirmatory statistical approach - in case of superiority trials on an intention to treat basis and drop-outs should be included by intention

to treat. 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 exceptional cases (e.g. large scale, multicentre, multinational trial) one single confirmatory trial could be sufficient for the proof of efficacy of a new substance if the results are statistically persuading and clinically relevant.

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 it seems 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.

Anyway, it is important to monitor the progress in this therapeutic area, as registration of agents for ACS without persistent ST-segment elevation may necessitate the use of active comparators in pivotal efficacy trials.

4.2.2.3 Timing of measurements

Even if drug therapy is applied short-term (e.g. for 1 to 7 days) in the confirmatory studies, the clinically relevant primary endpoint should preferably be measured 30 days following initiation of therapy (see also 3.2).

Though the measurement of the primary endpoint at 30 days following initiation of short-term therapy is preferred - depending on the mechanism of action of the test drug - shorter time-spans may be acceptable if the follow-up data prove durability of efficacy.

Accordingly, if the primary endpoint is measured after a short time period (e.g. 7 days), further measurements should be performed after longer (e.g. 30, 180 days) but also after shorter (e.g. termination of study drugs) time-spans as secondary measures of efficacy.

Except when the primary endpoint is intended to be measured after 6 months, a follow-up of at least 6 months should be foreseen in the protocol in order to estimate longer-term efficacy (in terms of clinically relevant endpoints) and safety. Though it is not mandatory for licensing purposes to demonstrate a statistically significant difference or - depending on the study design - non inferiority to control after 6 -12 months, it should be excluded, that the efficacy seen short-term vanishes early (preferably by a blinded clinical event committee).

4.2.2.4 Analyses

The database for the primary analysis, either 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 could allow for a distinction from the comparator in pivotal clinical trials.

Regarding the primary analysis, the 30 day event rates as well as time-to-event within 30 days can be chosen. However, in any case survival curves over the 30 day period - and also over the-follow-up period - should be provided for the combined endpoint and all its components in order to evaluate when differences occurred.

In addition, the components of a composite efficacy endpoint should be analysed individually in order to evaluate whether efficacy regarding the combined endpoint results from effects on all components. Optimally, the results of all components of the combined endpoint point in the right direction. 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 in refractory angina pectoris).

Subgroup analyses, at least for gender, race, age, region (in case of multicentre /multinational trials*:* an analysis separating sites according to the propensity of coronary revascularisation) and qualifying condition (UAP or NQWMI), as well as for revascularisations (e.g. CABG, PCI) should be foreseen in the protocol in order to demonstrate consistency of the results*.* Moreover, it is advised to separate between a medical treatment effect (prior to or censoring for coronary revascularisation procedures) and a procedure related treatment effect.

In addition, subgroup analyses regarding patients with elevated vs. normal troponin I/T concentration at enrolment, as well as those regarding differences in time-span between symptom onset and initiation of study drugs (e.g. ≤ 6 hours, $> 6 \leq 12$ hours) are of increasing interest.

5. SAFETY ASPECTS

Particularly during the course of the early clinical trials all adverse events should be carefully documented with separate assessment of adverse events and adverse drug reactions.

However, if large scale outcome trials are performed, a hierarchy of safety reporting can be considered. For these trials a differentiation according to unexpected serious adverse not related to usual disease outcomes (expedited reporting) and outcomes related to the disease of interest (non-expedited reporting) could be considered. For example, events like recurrent angina, re-infarction, heart failure, ventricular tachycardia, ventricular fibrillation fall within the criteria of serious adverse events but are usually disease related. Careful collection of such events is definitely required, but they might be reported separately (i.e. non-expedited).

Careful consideration should be given to those patients who died - especially while on therapy - or who failed to complete the study per protocol (in particular drop-outs due to adverse events/drug reactions or lack of efficacy).

High-risk groups (e.g. patients with organ dysfunction) and possible differences in incidence and severity of adverse events/drug reactions according to e. g. sex, bodyweight or age require 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:

5.1 Bleedings

The majority of the bleedings caused by antiplatelet or antithrombin acting agents are of mild to moderate nature. However, special attention must be paid to fatal, and life-threatening (e.g. intracranial, retroperitoneal, pericardial, gastrointestinal) bleedings particularly in the setting of revascularisations.

Bleedings should be categorised according to an acknowledged classification. Though usually used in association with fibrinolytic therapy, the TIMI criteria (i.e. TIMI major and minor: [Bovill 1991, Ann Int Med 115]), for example, are an acknowledged classification for the severity of bleedings.

Anyway, 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. angiography, PCI, CABG surgery) - or not - is considered to be necessary.

Transfusions of blood, red blood cells and/or coagulation factors are considered to be a further indicator for severe bleedings and thus, should be documented carefully (number, temporal association to application of study drug and/or procedure).

5.2 Thrombocytopenia

In particular heparins and platelet aggregation inhibitors are known to cause (acute and delayed) thrombocytopenia which can be severe and the cause of serious bleedings or other complications (e.g. HIT 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.

5.3 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.

5.4 Rebound

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

5.5 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).

5.6 All cause mortality

All cause mortality is usually part of the efficacy evaluation. If - under circumstances which have to be reasoned by the sponsor - this is not the case, all cause mortality should be at least subject to the safety investigation.