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**POINTS TO CONSIDER ON THE CLINICAL DEVELOPMENT OF
FIBRINOLYTIC MEDICINAL PRODUCTS IN THE TREATMENT OF
PATIENTS WITH ST SEGMENT ELEVATION ACUTE MYOCARDIAL
INFARCTION (STEMI)**

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POINTS TO CONSIDER ON THE CLINICAL DEVELOPMENT OF FIBRINOLYTIC MEDICINAL PRODUCTS IN THE TREATMENT OF PATIENTS WITH ST SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION (STEMI)

PREAMBLE

This document intends to address the EU regulatory position on the main topics of the clinical development of new fibrinolytics in the treatment of patients with ST segment elevation acute myocardial infarction (STEMI). The scope of the present document is restricted to fibrinolytic therapy and will not consider other drugs intended to be used in the acute or chronic treatment of patients with STEMI. However, it must be understood that, under the term fibrinolytic therapy, this document refers to the whole fibrinolytic, anticoagulant and antiplatelet strategy under which each specific fibrinolytic agent has demonstrated an optimised benefit/risk ratio. On the other hand, the recanalisation strategy in patients with acute coronary syndrome (both STEMI and NSTEMI) is considered a rapidly evolving field where new combination strategies (revascularisation procedures, fibrinolytics, GPIIb/IIIa antagonists, LMWH, etc) are currently being assessed. In this regard, there is still little regulatory experience for giving specific recommendations on all possible strategies and study designs. Consequently, requesting scientific advice on case-by-case basis is recommended.

This Note for Guidance document should be read in conjunction with the Directives 75/18/EEC, as amended, as well as in conjunction with other pertinent regulatory European and ICH documents, with special emphasis on:

- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96)
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Points to Consider on the Clinical Investigation of New Medicinal Products for the Treatment of Unstable Angina Pectoris or Non-Q-Wave Myocardial Infarction (CPMP/EWP/570/98).

There is no current regulatory guidance on this field.

1. BACKGROUND

Myocardial infarction (MI) is (rapid development of) myocardial necrosis due to a critical imbalance between the oxygen supply and demand of the myocardium. The most common cause of MI is acute coronary occlusion, at the site of previous narrowing of the epicardial blood vessels due to atherosclerotic plaques, plaque rupture with subsequent exposure of the basement membrane and platelet aggregation, fibrin accumulation, thrombus formation, haemorrhage into the plaque. Varying degrees of vasospasm may also occur. This can result

in partial or complete occlusion of the vessel and subsequent myocardial ischaemia and necrosis.

MI is one of the leading causes of death in most developed countries. Its incidence varies greatly within the EU, ranging in males from 200 cases per 100.000 inhabitants per year in the Mediterranean area up to more than 800 cases per 100.000 inhabitants per year in northern countries as Finland or the United Kingdom. The event rate in females is considerably lower ranging from 20 to 250 cases per 100.000 women depending on the geographic region. This male predilection tends to dilute over 70 years. The overall mortality from MI at 30 days remains high (around 25%) and has not substantially changed over the last 15 years, mainly at the expense of pre-hospital deaths. Ninety percent of deaths occur within the first 24 hours of symptoms onset and most of them within the first 60 minutes. Nevertheless, recanalisation therapies (pharmacological or interventional) and supportive pharmacological approaches (antiplatelets, heparins, ACE inhibitors, beta-blockers) have yielded a substantial decrease of in-hospital mortality of patients with MI. In this sense, fibrinolytic treatment leads to a relative reduction of in-hospital mortality by around 20% as compared to placebo for those patients who are candidates for reperfusion therapy (50% of the patients who arrive alive to the hospital).

All fibrinolytic agents act directly, or indirectly, as plasminogen activators. Two main groups can be considered: fibrin-specific agents (e.g. Alteplase -tPA-, Reteplase -rPA-, Tenecteplase -TNK-tPA-) and non-fibrin specific agents (streptokinase -SK-, urokinase -UK-).

In the last decades the benefit of the use of fibrinolytics in patients suffering from STEMI has been consistently established, indicating that early therapy with drugs targeting coronary recanalisation decreases infarct size and improves patient's survival. A meta-analysis of initial clinical trials comparing streptokinase, alteplase and anistreplase with placebo definitely showed that fibrinolytic therapy is efficacious within 12 hours of symptom onset. Since then, extensive clinical experience has been gained with these and other fibrinolytics drugs like reteplase, tenecteplase, etc.

2. SELECTION OF PATIENTS

2.1. Inclusion criteria

Patients should normally present with symptoms suggesting myocardial necrosis (chest pain lasting at least 20-30 minutes) and ECG changes suggesting coronary arterial occlusion (ST segment elevation of ≥ 0.1 mV in two or more limb leads or ≥ 0.2 mV in two or more contiguous precordial leads). Although not included in some clinical trials, patients with symptoms and left bundle branch block -LBBB- not known to be previously present are also candidates for recanalisation therapy.

Biochemical markers for myocardial necrosis (i.e. CK, CK-MB and troponins) are not required to start fibrinolytic treatment and, consequently, as inclusion criterion in clinical trials. However, they should be recorded as an indicator of myocardial damage.

A clear relationship exists between the time window (from symptom onset to fibrinolysis) and the therapeutic benefit. The greatest benefit occurs within the first 3 h. Treatment benefit beyond 12 hours is considered marginal. The GUSTO I study showed that front-loaded regimen of alteplase has survival benefit (1%) over SK in STEMI with symptom onset ≤ 6 hours, although it is associated with a slight increase of intracranial haemorrhage (0.2-0.4% absolute higher risk than SK). Most clinical trials performed in recent years only included patients within a 6-hour symptom window. Nevertheless, there is no regulatory reason for not considering the inclusion of patients beyond this time-period (i.e. >6-12 hours from symptom

onset), thus reflecting the recommendations issued in currently available STEMI management guidelines. In any case, the consequences of the decision finally adopted on this issue regarding the study design, the selection of the comparator and the planned claim should be considered thoroughly. (See section 4).

There is no reason for excluding patients according to their demographic characteristics or infarction location. Treatment benefit is observed and clinically relevant regardless of gender, age, body weight and regional practices, although the proportionate reduction in mortality may differ.

2.2. Exclusion criteria

The benefit of fibrinolytic therapy in patients with NSTEMI or with isolated ST-segment depression has not been established, and there is some data suggesting potential harm from fibrinolytic therapy in these patients. Therefore, unless the purpose of the trial is targeting this specific population for new efficacy and safety data, these patients should be excluded.

Patients with absolute contraindications to fibrinolytic therapy should also be excluded from clinical trials.

3. EFFICACY CRITERIA

3.1. Efficacy criteria in initial therapeutic studies

Angiographic endpoints (TIMI flow grades)

Dose finding studies are usually based on angiographic measurements, using the TIMI (Thrombolysis in Myocardial Infarction) perfusion grades as the major evaluation criteria. In principle, the rate of TIMI 3 flow (complete recanalisation) of the infarct related artery at 90 minutes is normally 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. However, an earlier evaluation of the patency pattern (i.e. 30 and 60 minutes) may provide important information on the speed of recanalisation. Whatever is the timepoint selected as primary outcome, it must be properly justified and pre-specified in the clinical trial protocol.

Angiograms should preferably undergo central blinded reading, particularly when open designs become unavoidable.

It must be emphasised that some drugs providing higher complete recanalisation rates than alteplase have failed to demonstrate any additional survival benefit. Therefore, for the time being, angiographic evaluations are not considered as surrogate for survival when assessing fibrinolytic drugs.

Electrocardiographic endpoints (ST segment elevation resolution)

There is limited regulatory experience on the use of the resolution of ST elevation as a marker of recanalisation in phase II clinical trials with fibrinolytics. According to published data, it might be a good indicator of cardiac reperfusion subsequent to fibrinolytic therapy. Moreover, this endpoint can be measured also in centres without angiographic facilities. Therefore, the use of ST resolution might be acceptable as an indicator of myocardial reperfusion as a part of the dose finding package for new fibrinolytic agent. However, its use as the sole basis for the selection of the dose to be assayed in phase III clinical trials is discouraged until more information on the reliability of this variable as a predictor of recanalisation becomes available.

3.2. Efficacy criteria in main therapeutic studies

3.2.1 Primary efficacy endpoint

All cause mortality is the most relevant endpoint in clinical trials. Short-term (30/35-day) all cause mortality is the primary efficacy endpoint in studies assessing the efficacy of fibrinolytic drugs in patients with STEMI. Medium-term mortality (6-month/1-year) should also be recorded in order to assess the maintenance of the short-term effect.

3.2.2. Secondary efficacy endpoints

In-hospital mortality, myocardial reinfarction, heart failure, left ventricular function, ventricular tachyarrhythmias, and the data related to the need for rescue (emergent or planned) recanalisation procedures (PTCA, stent and or CABG) should also be collected. As regional differences in revascularisation policies are likely to occur in multicentre multinational clinical trials, it is advisable to state in the study protocol the a priori criteria for revascularisation. A blind adjudicating committee is strongly recommended thus assuring homogeneous criteria for endpoint assessment.

4. SAFETY CRITERIA

4.1. Stroke

Intracranial haemorrhage is the main safety issue related to fibrinolytic treatment. Strokes should be carefully recorded and a CT-scan or other suitable neuroimaging technique performed in order to assess their aetiology (ischaemic or haemorrhagic). The safety database should be large enough to determine any relevant increased risk of haemorrhagic stroke associated with the use of the new agent as compared to the reference drug. In addition, an adequate benefit/risk assessment according to age and gender, paying special attention to the elderly should be performed. Pivotal trials should allow to characterise adequately overall, haemorrhagic and disabling stroke rates in order to rule out any clinically relevant excess risk of intracranial haemorrhage with the new drug. A margin for such an excess risk that is considered as clinically relevant should be clearly stated in advance in the clinical trial protocol.

4.2 Other safety criteria

The rates of bleeding events, either serious or no serious, the site of bleeding and the need of blood transfusions and the number of transfused units should also be recorded. Bleeding events should be categorised according to an acknowledged classification system (e.g. TIMI classification). It is strongly advisable to use the same classification throughout the whole clinical development program.

Other cardiovascular adverse events like clinically relevant arrhythmia (idio-ventricular rhythm and ventricular fibrillation may occur at the time of reperfusion), cardiogenic shock, severe heart failure (Killip III), sustained hypotension, acute mitral regurgitation, acute ventricular septal defect, pericarditis, pulmonary embolism, and tamponade, among others, should be carefully recorded.

Efforts should be made to identify clinical circumstances with an excess risk for bleeding or presenting certain cardiovascular adverse event (e.g. gender, age, bodyweight, invasive procedures, Killip class, time after the onset of symptoms, etc).

Anaphylaxis and hypersensitivity reactions should carefully be recorded and analysed. Furthermore, the potential antibody response against the drug should be characterised, including determination of neutralising activity.

5. CRITICAL ISSUES WHEN DESIGNING CLINICAL TRIALS

5.1. Initial therapeutic studies

The objective of this development phase is to find the optimal dosage regimen of the new agent and comparing its angiographic performance with a reference treatment. The dose finding strategy is normally expected to include at least 2 clinical trials (as described below). However, if properly justified by the applicant, alternative approaches might be considered acceptable.

Thus initially, and starting from the lowest effective dose, increasing doses should be evaluated until a plateau effect on patency is reached or unacceptable safety problems occur. This process might be well performed in a sequential, open clinical trial. Appropriate rescue strategies should be planned for those patients treated with the lowest dose-levels of the new fibrinolytic regimen.

Based on the results from this initial study, a comparative study is requested. Dose-ranging study should be conducted in parallel groups comparing at least three doses of the tested drug to an active control group. This study would preferably be double blind, although it is recognised that masking completely different treatment schedules might be difficult. In any case, a blind central reading of angiographic measures is considered unavoidable. Whenever other endpoints different from angiographic readings (i.e. ST resolution) the blinding of the study is considered of paramount importance. The identified doses with a predicted positive benefit/risk relationship should be preferably compared with the most active treatment actually available. At present, front-loaded alteplase, which has demonstrated higher coronary artery patency rates at 90 minutes compared with SK, is considered to be the reference comparator. This type of study is usually of medium size (several hundred of patients) to gather safety data related to morbidity and mortality.

5.2. Main therapeutic studies

5.2.1. Selection of the comparator and study hypothesis

The use of fibrinolytics in STEMI results in reduced mortality, therefore, placebo-controlled trials are considered ethically unacceptable, except in subpopulations where the clinical benefit of these compounds is not well established. Thus, main therapeutic studies should be parallel, double blind and active controlled.

Most of the clinical and research experience in this field has been gained with either SK or alteplase. Initial clinical trials comparing streptokinase with placebo definitely showed that fibrinolytic therapy is efficacious in STEMI within the first 12 hours after symptom onset. Subsequently, a front-loaded regimen of alteplase showed a significant survival benefit in patients with STEMI symptom onset ≤ 6 hours over SK.

Ideally, a new fibrinolytic agent would be expected to show superiority over the control arm. In this case, both SK and alteplase (or even any of the available fibrinolytic drugs) are considered as acceptable comparators. Under this hypothesis, the inclusion of patients with 0-12 hours of symptoms is acceptable and strongly recommended.

Taking into account the above-mentioned consideration, it is expected that standard non-inferiority trials with new fibrinolytic agents should be performed using front loaded alteplase as the active comparator. In order to preserve the fairness of the comparison and assure assay sensitivity, the target population should be the one for which the therapeutic benefit with the control drug is expected to be optimal (i.e. onset of symptoms ≤ 6 hours). For other target

populations (i.e. for patients with symptoms onset 0-12 hours) superiority trials are highly desirable. Considering that the body of evidence on the benefit/risk ratio for fibrinolytic therapy in STEMI beyond 6 hours is considerably weaker than between 0-6 hours, a case-by-case approach is recommended and nearly unavoidable.

5.2.2. Considerations when establishing a clinically relevant difference and a non-inferiority margin

In principle any superiority in terms of mortality over of an active comparator could be regarded as clinically relevant, provided that the safety profile is also acceptable.

When defining an acceptable non-inferiority margin, the variability in the observed mortality proportions must be taken into consideration and, therefore a conservative approach to defining the non-inferiority margin is advisable. Both relative and absolute margins should be specified in the protocol, and the most conservative of these for the observed event rates adopted for the final analysis. In the recent past differences of 14% relative or 1% absolute (whichever proves smallest) have been accepted. These margins were based on 'all cause mortality' rates at day 30 close to 6.5%-7%. In this situation, both the relative and the absolute criterion produce fairly identical requirements for estimating the sample size needed for a new study. Should in the future, medical progress further reduce mortality the aforementioned recommendations need to be revised.

5.2.3. Concomitant treatments

With clot-specific fibrinolytic agents such as tPA, rPA and TNK-PA, immediate administration of heparin after administration of the fibrinolytic agent clearly diminishes reocclusion after successful recanalisation. With the non-specific plasminogen activators, however, such as SK, it is unclear if heparin is beneficial.

Patients allocated to the control arm should be administered background antithrombotic therapy according to the standards recommended for the selected comparator. The administration of antithrombotic drugs should not interfere with the blindness of the study and double dummy techniques should be applied when necessary.

All patients should receive appropriate background therapy, including antiplatelets and, when not contraindicated, betablockers and ACE inhibitors. Statins, when indicated, should also be considered.

Treatment strategy in acute coronary syndrome is a fast evolving field. A number of major therapeutic options will need to be factored when designing clinical trials in this therapeutic area:

- Policy about PCI (primary rescue, early/late systematic, late conservative) and, in conjunction with PCI, the need for additional antithrombotic treatments (i.e. thienopyridines, GP IIb IIIa receptor antagonists, LMWH).
- Policy about other anti-thrombotic agents
- Pre-hospital and or hospital setting

5.2.4. Necessity and relevance of predefined subgroup analysis

Analysis of both mortality and stroke rates in specific predefined subgroups according (among others) to age, time to onset of treatment, infarct location, body weight, gender, and region (if applicable) will be required. It is anticipated that the effect of a new fibrinolytic will be shown to be consistent across all strata, and the purpose of these analyses is to confirm that fact. Claims of efficacy on specific subgroup of patients are not acceptable for drugs unable to

demonstrate to be effective and safe in the entire population studied. On the other hand, even if efficacy is satisfactorily shown for the whole population of the study, specific subgroups of patients could be excluded from the indication if the benefit-risk ratio is observed to be unfavourable for them or if not adequately represented.