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**POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL  
PRODUCTS FOR THE TREATMENT OF ACUTE STROKE**

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**Note:**

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.

## POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF ACUTE STROKE

These Points to Consider are intended to provide preliminary guidance for the clinical investigation of drugs developed for the treatment of acute ischaemic and / or haemorrhagic stroke. They should be read in conjunction with Directives 75/318/EEC and 83/570/EEC as well as current and future EC and ICH guidelines, especially

- ICH Guideline on General Considerations on Clinical Trials
- ICH Guideline on Statistical Principles for Clinical Trials
- ICH Guideline on Dose Response Information to Support Drug Registration
- Studies in support of special populations: Geriatrics

### 1. INTRODUCTION

Acute stroke is one of the leading causes of death in the elderly population of the developed world. Moreover, individuals surviving the acute phase of a stroke often suffer from severe disabilities and handicaps thereafter. The number of years with a diminished quality of life caused by the sequelae of stroke is larger than that of any other disease in this age group except for dementia. Thus stroke is a heavy burden for the individual, their relatives, and society.

Cerebral ischaemia (with its various subtypes) is the most common cause of acute stroke (~ 80 %), followed by primary intracerebral haemorrhage and subarachnoid haemorrhage.

Cerebral ischaemia and haemorrhage represent two pathophysiologically distinct entities. Therefore, therapy oriented to the pathophysiology of these diseases usually varies.

To date no specific recommendation exist in Europe for the treatment of acute stroke. Earlier clinical investigations with medicinal products hypothetically efficacious in this indication were often performed by lumping all heterogeneous clinical varieties of stroke together before the appropriate high technology diagnostic measures currently used in order to differentiate the main pathological and pathophysiological types became available.

Currently, various specific clot-dissolving agents as well as a variety of compounds from different pharmacological classes, particularly the so-called neuroprotectives, are under investigation for the treatment of acute ischaemic stroke.

Together with technological advances concerning the development of modern brain imaging techniques, the whole field of stroke has developed in recent years from therapeutic nihilism – at least with respect to pharmacological interventions – to extensive clinical research.

Regulatory experience is still limited in this field. However, some experience from problems encountered in scientific advice procedures justifies the development of a Points to Consider paper which focuses on the treatment of acute ischaemic and / or haemorrhagic stroke. Treatment of subarachnoid haemorrhage as well as treatment for preventing recurrence following ischaemic stroke or transient ischaemic attacks are not a subject of this document.

## 2. STUDY OBJECTIVES

The therapeutic goals in the treatment of acute stroke may be diverse. Therapeutic agents in the field of acute stroke can be expected to

- improve functional / global outcome (e.g. disability and handicap), i.e. increase the patients' independence in basic and instrumental activities of daily living
- improve neurological deficits

The proof of efficacy strategy for investigational drugs should reflect these objectives.

As these patients are often frail or at high risk of complications, therapeutic agents in the field of stroke must be expected to be sufficiently safe. In ischaemic stroke, where antithrombotic agents may be used, special attention should be devoted to:

- the risk of increased mortality due to intracerebral and other major bleeding complications
- occurrence of symptomatic and asymptomatic intracranial haemorrhage

There is currently no ideal single stroke outcome scale available. Indeed, all the available outcome scales explore different domains of recovery and have their limitations. With respect to the heterogeneity of symptoms, severity, and pattern of recovery found in stroke, it is recommended to use a combination of different measurement tools (see section 3) to assess the aforementioned specific domains.

### 2.1 Primary efficacy endpoints

The primary efficacy variable should be specified a priori, depending on the effect expected from the study drug.

One option may be to measure the proportion of surviving patients who regain functional independence after stroke (survival free of disability or with only minor disability), as estimated by a functional outcome scale or a more global scale of disability or handicap.

The cut-off point for what is considered a favourable outcome (which may include minor disability) has to be defined and justified in the study protocol. This allows a dichotomic analysis, which is easy to perform and to interpret. In this case results from a neurological outcome scale should be supportive as a secondary efficacy variable.

Alternatively it may be shown that an agent effectively moves patients from the severe outcome to the moderate disability group and from moderate disability to the recovered group i.e. that the drug effect applies across all grades of severity of stroke, moving patients to a higher grade of independence in their activities of daily living. Again, for this kind of analysis, clinically relevant shifts need to be defined and justified in the study protocol. In this case a categorical analysis provides more information on the drug effect than a dichotomic analysis.

In that case a second primary efficacy variable should demonstrate an improvement in neurological deficit, as measured by one of the available neurological stroke scales in order to validate a specific effect of the study drug.

In addition to the demonstration of efficacy, a separate analysis of mortality is required as a safety parameter. A new agent is only acceptable for approval if there is no suspicion of a detrimental effect on mortality whatever the benefits on morbidity.

## **2.2 Secondary efficacy endpoints**

The choice of the secondary endpoints should be such that consistency of results across the several domains mentioned before is demonstrated.

New neuroimaging techniques are being developed in order to measure the volume of the infarcted area. Provided that their validity has been shown, they may be chosen as secondary endpoints. Further research is strongly encouraged in this field. However, MRI measures cannot be considered recognized efficacy surrogate endpoints and they only may supplement - but cannot replace - proper clinical outcome criteria, at least in phase III.

## **3. METHODS TO ASSESS EFFICACY**

Assessment scales for the measurement of stroke-related impairment, disability and handicap include neurological deficit scales, functional and global outcome scales as well as health-related quality of life scales (although the latter have not been developed specifically for stroke and have yet to be validated).

Rating scales and instruments to be used in acute stroke trials should be valid, reliable, sensitive to change and as easy and quick to administer as possible.

In the subsections below several examples of commonly used scales are mentioned. From a regulatory point of view, no specific recommendation is made. Other scales or tests – if validated for stroke – might also be acceptable. The applicant should justify his choice on the basis of test quality criteria, including responsiveness and cross-cultural applicability.

### **3.1 Functional outcome scales**

The Barthel Index of basic activities of daily living (ADL) has been the most widely used measure of functional outcome or disability in stroke studies. If a cut-off score for a positive response is used, its choice should be explained in the study protocol. Other ADL scales may be more appropriate in some special circumstances (e.g. for cognitively impaired or aphasic patients).

### **3.2 Global outcome scales**

Global outcome scales include the Modified Rankin Scale, a simple overall measure of disability and handicap, and the Glasgow Outcome Scale which is similar in structure.

As with functional outcome scales, the definition of what is considered a favourable outcome has to be stated and justified in the study protocol.

### **3.3 Neurological deficit scales**

Several neurological impairment scales have been used in clinical trials in acute stroke, particularly the following ones:

- Scandinavian Stroke Scale (SSS)
- Canadian Neurological Scale (CNS)
- National Institute of Health Stroke Scale (NIHSS)
- Unified Stroke Scale (USS)

Dichotomization of outcome (positive – negative) is not recommended for these neurological assessment scales as patients in the same category may be clinically distinct and important information might be missed.

### **3.4 Health-related quality of life (QoL) scales**

At present, QoL-scales are not among the primarily focussed endpoints in stroke. If these scales are used, they should be validated for stroke. Development of validated scales is encouraged for future trials.

In case QoL-scales are used as additional evidence, special attention should be paid to possible confounding factors such as post-stroke depression or change in the environment that might interfere with the specific treatment effects.

## **4. SELECTION OF PATIENTS**

The target population according to the claimed indication has to be specified and reflected in the patient selection criteria. Inclusion / exclusion criteria should relate to the hypothetical mechanism of action of the particular drug under study.

All efforts should be made to assure that the trial population is as close as possible to the target population the treatment is intended for, still allowing a certain heterogeneity with respect to severity, localisation and etiology.

Young ischaemic/haemorrhage stroke patients have a higher probability of a favourable outcome than elderly patients, and therefore slight imbalances in number of young patients may give biased results. This should be taken into account by stratification and/or in the analysis.

### **4.1 Differential diagnosis**

Depending on the mode of action of the agent under development, it may be absolutely essential, for safety reasons, to differentiate between infarction and haemorrhage by adequate imaging techniques before enrolment in the study.

E.g. in case of thrombolytics it is necessary to definitively exclude patients with haemorrhagic stroke, haemorrhagic infarction, or subdural and extradural haematomas from participation in the clinical trial. Without CT imaging before randomisation there may be up to 15% of intracerebral haemorrhages in the clinically defined trial population.

Diagnostic tests should include cranial computed tomography (and examination of the cerebrospinal fluid only if subarachnoid haemorrhage is suspected but not found on CT imaging).

As an intention-to-treat analysis should be the primary analysis (see 6), post hoc exclusion of patients with other than the claimed indication from the efficacy evaluation (or other specific subgroups, respectively) would impose a major methodological problem.

Therefore, it is important that the accuracy of the diagnosis “ischaemic and / or haemorrhagic stroke” (including further specification and differentiation, if necessary) be ensured as much as possible by appropriate neurological examination and adequate diagnostic procedures before inclusion in the trial.

In case of compounds with less safety concerns (e.g. neuroprotectives) it may be allowed to include patients with different aetiologies (including ischaemic and haemorrhagic stroke) from the safety point of view, even if for instance a therapeutic benefit is only expected in patients with ischaemic brain infarction. This means that such an “emergency treatment” could be given in any suspected acute stroke without the additional delay of performing and interpreting brain imaging. In that case a modified intention-to-treat analysis may be acceptable provided that the exclusion of patients is justified by independent, non-interested parties. However, a non-modified intention-to-treat analysis, including all patients enrolled in the trial, is still required as the main benefit-risk-

assessment for the population receiving such an agent, that is patients with ischaemic and haemorrhagic stroke.

## **4.2 Severity**

It may be reasonable to exclude patients with milder types of stroke (with a high probability of spontaneous recovery) or very severe strokes (with large cerebral damages already beyond repair) from participation in clinical trials. If such patients are to be excluded, appropriate cut-off scores in neurological rating scales should be defined in the study protocol and justified with reference to existing epidemiological knowledge concerning the natural course and final outcome after acute of stroke.

## **4.3 Co-morbidity**

It is important that the study population be carefully characterised with respect to possibly confounding co-morbidity factors. The study protocol should therefore ensure that existing pre-stroke disorders are assessed and efforts are made to differentiate stroke-related disability from other overlapping disabilities caused by e.g. dementia, claudication or osteoarthritis. Patients who were not independent in their activities of daily life before the occurrence of stroke should be excluded from pivotal trials. Concomitant disorders which may affect stroke outcome (e.g. fever, hyperglycaemia, low blood pressure atrial fibrillation) should be documented.

# **5. DESIGN OF CLINICAL TRIALS**

## **5.1 Therapeutic exploratory trials**

For therapeutic exploratory trials, in addition to the primary safety objective, an assessment of efficacy (in the hypothesis generating sense) may be made on the neurological outcome and/or a surrogate brain imaging measure only.

## **5.2 Therapeutic confirmatory trials**

As no specific treatment for acute stroke is approved until now in Europe, randomised double-blind placebo-controlled study designs are necessary for confirmatory phase III trials.

A study duration of three months is considered appropriate for such pivotal studies.

Special attention should be paid to therapeutic setting variables. It should be kept in mind that a potential marketing authorisation will have to reflect the conditions of use in the clinical trials. Questions of generalisability of the results to settings where different medical practice exist will be of particular concern to regulatory authorities.

These include local characteristics such as times to hospital admission / time to drug administration, availability of intensive-care settings, trained staff, neuroradiological technology and diagnostic expertise in a medical emergency situation. Large international multicentre trials will help answer these questions through analysis of center/country effects.

It is important to ensure that early (non-pharmacological) standards of care and rehabilitation measures are standardized and comparable for all patients in both treatment groups in order to avoid bias.

In the clinical studies, all specific medications, which may have an impact on the therapeutic outcome, should be recorded up to day 90 (or the latest assessment point, respectively).

Interaction studies with medicinal products routinely used in this population

(e. g. drugs against hypertension, ASA, heparin, coumarin) should be performed.

Treatment with medicinal products is only one part of therapy of stroke. Trials must be performed only when appropriate infrastructure is present. As described in ICH

E 9 (Statistical Principles for clinical trials), every large trial should have a scientifically qualified steering committee and an independent data-monitoring committee.

## **6. STATISTICAL CONSIDERATIONS**

Intention-to-treat analysis will be the primary statistical analysis if superiority over placebo is to be demonstrated. However, per-protocol analysis should be presented as well. Data from both analyses are expected to be consistent in order to allow approval.

For the confirmatory trials the statistical analyses should follow the plan described in the study protocol as it is stated in ICH E 9.

There are regulatory concerns pertaining to any post hoc modifications of the pre-specified analysis plan.

Any modification of the original analysis plan must be duly justified by references to existing scientific evidence and implemented before any information about assignment of the patients to treatment groups (blinded or unblinded) is available.

Pitfalls with respect to modifications of the pre-specified analysis plan encountered so far include

- post hoc change of cut-off scores for dichotomization
- post hoc change of the definition of treatment success / failure
- post hoc exploratory subgroup stratification concerning time-window for initiation of therapy, initial severity, age groups, etc

A marketing authorisation cannot be expected on the basis of secondary subgroup analyses (even if pre-specified in the study protocol) in cases where the primary analysis has failed to demonstrate efficacy.

## **7. SAFETY ASSESSMENT**

A regulatory licensing decision requires careful weighing of the expected benefits against the new medicinal product's potential risks.

Therapeutic agents in the field of stroke must be expected to be sufficiently safe with respect to the risk of intracranial haemorrhage and other serious or life threatening complications.

Special attention should be paid to the occurrence of

- death (mortality data should be specified with regard to the underlying causes)
- intracranial haemorrhage/haemorrhagic transformation (definition to be given in the study protocol) resulting in new symptoms or in worsening of the existing symptoms, in the case of antithrombotic/thrombolytic drugs
- brain oedema resulting in herniation and death

Further potential adverse events that are to be documented carefully include

- epileptic seizures
- cardiac conduction disturbances, arrhythmias
- effects on coagulation and fibrinolysis
- hypotension / hypertension
- hyperthermia
- hyperglycaemia
- severe infections
- deep vein thrombosis, pulmonary embolism, and venous thromboembolism
- vomiting
- anxiety, hallucinations, agitation