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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 8613
E-mail: mail@emea.eu.int http://www.emea.eu.int

NOTE FOR GUIDANCE ON CLINICAL INVESTIGATIONS OF MEDICINAL PRODUCTS IN THE TREATMENT OF CHRONIC PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

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These notes are intended to provide guidance for the evaluation of medicinal products in the treatment of chronic peripheral arterial occlusive disease. They should be read in conjunction with the Directives 75/318/EEC as amended, as well as in conjunction with other EU and ICH "Notes for Guidance", especially those on:

- Pharmacokinetic Studies in Man
- Investigation of Drug Interactions (CPMP/EWP/560/95 – adopted Dec. 1997)
- Dose-Response Information to Support Drug Registration
- E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/99 – adopted Mar. 1998)
- E 10: Choice of Control Group and Related Issues in Clinical Trials (CPMP/ICH/364/95 adopted July 2000)
- E1A: The Extent of Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (CPMP/ICH/375/95 – adopted Nov. 1994).
- PTC on Application with 1.) Meta-analyses and 2.) One pivotal study (CPMP/EWP/2330/99 –
- adopted May 2001)

1. INTRODUCTION

Peripheral Arterial Occlusive Disease (PAOD) is caused by atherosclerosis affecting the arteries of the lower extremities and is characterised by clinical symptoms due to ischaemia. This guideline is concerned with chronic ischaemia in the lower limbs. Acute ischaemia and peripheral vascular disorders of inflammatory or immunologic origin such as Burger's disease and necrotic vasculitis are not considered because these diseases differ from arteriosclerosis obliterans in their clinical picture, in their evolution and in their prognosis.

Intermittent claudication (IC) is the most common debilitating symptom of PAOD. Initial treatment decisions for IC are based on cardiovascular risk factors, concurrent illness, health behaviours, and life expectancy. Recommendations are generally conservative and focus on symptomatic relief through risk factor modification (e. g. smoking cessation), exercise, and in some cases drug therapy. Although results with many other therapeutic modalities for IC have been published, their clinical usefulness remains uncertain among clinicians.

In patients with rest pain, ischaemic ulcers or gangrene it is recognised that at present invasive vascular interventions are the treatment of choice if such procedures are possible.

Chronic PAOD must be regarded as a marker of widespread atherosclerosis, and patients with chronic PAOD must be considered a high risk population for the development of cardiovascular ischaemic events.

Thus, therapy of chronic PAOD may focus on symptom relief or on the prevention of cardiovascular morbidity, amputation, and death.

2. GENERAL CONSIDERATIONS REGARDING PAOD TRIALS

2.1 PAOD Classification and Epidemiological Background

The degree of severity of chronic PAOD is most often classified using the system as developed by Fontaine, which rates the PAOD in four stages based on signs and symptoms: asymptomatic patients (stage I), intermittent claudication (stage II), rest pain (stage III), and trophic lesions (stage IV). Stages III and IV are equivalent to "critical limb ischaemia" (CLI),

a term which is widely used in Anglo-American countries. If another classification system is used, it should be properly justified.

The natural course of PAOD stage II shows a high variability, and after 5 to 10 years the claudication distance of 70 % to 80 % of patients remains stable or even improves, in 20 % to 30 % the course of the disease is progressive and 5 % to 10 % of claudicants will develop critical limb ischaemia. However, although the clinical course of intermittent claudication is relatively benign all PAOD patients (even if asymptomatic) are at high risk for cardiovascular events such as myocardial infarction, stroke or cardiovascular death.

2.2 Clinical Trial Features

There are several confounding factors which could influence the results of therapeutic clinical trials in PAOD:

Regular physical exercise improves symptoms of intermittent claudication. Thus, the frequent use of repeated exercise testing in clinical trials may lead to an improvement in exercise capacity independent of drug treatment. This should be considered in the design and analysis of such trials.

The cessation of smoking and regular physical exercise are of much importance in the treatment of intermittent claudication. Advice on smoking cessation and physical exercise should be given before patients are included in a clinical trial. Respective effects should be documented.

Even if claudication distances were considered clinically stable and stability was proven during the run-in phase of a clinical trial in PAOD stage II patients, a marked placebo effect cannot be avoided.

Experiences from previous trials indicate that observed variability of claudication distances between trials varies considerably. In addition, the distribution of these endpoints are often skewed. These factors should be considered when calculating the sample size and planning the analysis strategy (e.g. considering logarithmic transformation).

In patients hospitalised for critical limb ischaemia there is a high response rate as regards both rest pain and ulcer healing during placebo treatment. If this situation is not accounted for, the number of patients enrolled to a clinical trial may be inadequate for showing confident differences between active treatment and placebo.

2.3 Patient Selection

The criteria used for the diagnosis of PAOD in patients recruited for clinical trials must be clearly defined. The diagnosis, type of occlusive lesion (stenosis, complete block) and its location have to be confirmed by objective means. Treatment groups should be balanced in respect of patient demography, severity of disease, previous revascularisation procedures and duration of symptoms. This is usually ensured by adequate randomisation procedures. Influences of potential confounders such as cardiovascular risk factors (e.g. smoking, hypertension, hyperlipidaemia, diabetes mellitus) should be carefully taken into consideration in the analysis plan and respective therapeutic measures should not be changed during the course of the trial.

3. SPECIFIC RECOMMENDATIONS, PAOD FONTAINE STAGE II

3.1 Trial Design

A randomised parallel group, double-blind, placebo-controlled design is generally required. A placebo should be used for the control group since suitable reference substances have not yet been established in the symptomatic treatment of intermittent claudication. Active drug

controlled trials without a placebo arm may only be considered if the comparator drug has consistently shown superiority over placebo (assay sensitivity, see ICH E10)

A run-in phase of 2-6 weeks is recommended in order to verify the stability of the patient's conditions, e.g. comedication, stability of the claudication distances.

The active treatment phase in claudication trials should last for a minimum of 6 months for oral administration, and up to 8 weeks with parenterally administered compounds which are not recommended for long-term use.

Depending on the duration of active treatment, the length of ~~a~~ the follow-up period may vary. Generally, the cumulative duration of active treatment phase and follow-up period should not be less than 6 months. Double-blindness should be maintained during the whole period.

The allowed medication during the active treatment phase and follow-up period should be standardised as much as possible, and should be comparable for the treatment groups. The follow-up period should be specified à priori in the study protocol.

3.2 Patient Selection

The main inclusion criterion for stage II patients will be a history of typical intermittent claudication lasting for at least 6 months to ensure clinical stability. The clinical diagnosis of PAOD should be confirmed by objective evidence (e. g. reduced ankle systolic blood pressure). It is recommended that patients with high variability in the walking distance be excluded. For this purpose at least two treadmill tests should be performed with a time interval of ≥ 1 week. The maximum change in the claudication distance should not exceed a predefined threshold (e.g. 25 % for the absolute claudication distance (ACD)).

Walking training is considered the first treatment option in stage II patients. Therefore, it is expected that this therapeutic measure is tried for all patients before they are considered for entering the trial, unless otherwise justified. Furthermore, smoking habits should have been explored and advice on smoking cessation should have been given before patients are included in a clinical trial. The smoking habits should be stable for at least 3-6 months prior to inclusion into a clinical trial.

If walking training is applied during the study, some advantages may exist to use supervised, structured protocols

Claudication studies should not include patients suffering from illnesses limiting their exercise capacity (angina pectoris, heart failure, respiratory disease, orthopaedic disease, neurological disorders ...).

Stratification for diabetes mellitus is recommended.

3.3 Criteria of Efficacy

3.3.1 Primary Endpoints

(For prognostic endpoints including amputation reference is made to the section on prevention trials)

As the key symptom of stage II PAOD is intermittent claudication, walking distance should be the primary symptomatic endpoint.

Claudication distances should be assessed using a standardised, reproducible test methodology. The preferred method to assess claudication distances is treadmill testing. There are two internationally accepted treadmill protocols, i.e. the constant workload protocol using a constant speed and grade (mostly 3.2 km/h and 12% grade), and the graded test where the speed is kept constant but the grade is varied, starting horizontally but then increasing in predefined steps (e.g. 2%) at predefined intervals (e.g. 2 min). The two tests differ, in that the

relationship between workload and walking time follows a linear function with the constant test but a curvilinear function with the graded test.

Both tests can be equally recommended for use in clinical trials but cannot be used in an interchangeable way; a decision on the treadmill protocol and the treadmill settings must be made beforehand and should not be altered by any study centre.

3.3.1.1 Initial claudication distance (ICD)

From a clinical point of view, ICD compared to absolute claudication distance (ACD) as symptomatic endpoint may be the more important variable, since patients seldomly force themselves to the extreme of ACD. On the other hand, ICD is more subjective.

If ICD is chosen as primary endpoint, ACD should be evaluated as a secondary endpoint.

3.3.1.2 Absolute claudication distance (ACD)

ACD can be used alternatively. However, if a graded treadmill protocol is used, ACD should be the primary efficacy variable. The reproducibility of ACD is superior to ICD with graded protocols.

If ACD is chosen as primary endpoint, ICD should be evaluated as a secondary endpoint.

3.3.2 Secondary Endpoints

Secondary endpoints should focus on clinically relevant data supporting the study aim.

3.3.2.1 Walking distance

ICD or ACD, respectively (depending on the chosen primary symptomatic endpoint).

3.3.2.2 Haemodynamic measurements

The measurement of peripheral arterial flow and pressure may be used as secondary endpoints. However, monitoring changes in peripheral haemodynamics alone, is an inadequate measure of treatment success in patients with claudication. Such measures poorly correlate with the patient's walking performance.

3.3.2.3 Interventional/surgical procedures

Other clinical parameters that should be taken into account are revascularisation procedures as well as frequency and height of amputations.

3.3.2.4 Quality of life

In trials with adequte sample size, an assessment of quality of life may be performed by using properly validated general and disease specific questionnaires.

3.3.2.5 Responder

Responders should be defined in order to further investigate the relevance of treatment effects.

4. SPECIFIC RECOMMENDATIONS, PAOD FONTAINE STAGE III

4.1 Trial Design

A randomised parallel group, double-blind, placebo-controlled design is generally required. A placebo should be used for the control group since suitable reference substances have not yet been established in the treatment of rest pain (PAOD stage III). Active drug controlled trials without a placebo arm may only be considered if the comparator drug has consistently shown superiority over placebo (assay sensitivity, see ICH E10).

A short run-in phase is recommended to provide some evidence of disease stability.

The duration of the active treatment phase depends on the aim of the study, the galenic formulation and the mode of action of the drug under investigation, and the endpoint(s) chosen. Also, the length of the follow-up period may vary but should be appropriate for the assessment of secondary efficacy endpoints or important safety variables, such as the frequency of reconstructive measures, morbidity and mortality, and the rate of major amputations. Generally, the cumulative duration of active treatment and follow-up period should not be less than 6 months. Double-blindness should be maintained during the whole period.

The allowed medication and basic local treatment during the active treatment phase and follow-up period should be standardised as much as possible, and should be comparable for the treatment groups. The follow-up period should be specified à priori in the study protocol.

4.2 Patient Selection

Only patients with rest pain due to chronic critical limb ischaemia, that is persistent recurrent pain at rest requiring analgesics for more than 2 weeks should be acceptable. Generally, patients eligible for surgical/interventional reconstruction should not be included. However, patients with a high perioperative/periinterventional risk for ischaemic complications may be included, provided that the study design guarantees that necessary invasive procedures are not delayed. The presence of critical limb ischaemia should be confirmed by objective evidence (e. g. systolic ankle pressures ≤ 50-70 mmHg or systolic toe pressures ≤ 30-50 mm Hg or transcutaneous partial oxygen pressures ($tcp0_2$) ≤ 10-20 mm Hg). If rest pain is used as the primary efficacy endpoint patients should not suffer from clinically relevant peripheral neuropathy.

It is strongly recommended to study diabetic patients and none-diabetic patients in separate trials or to use appropriate stratification.

4.3 Criteria of Efficacy

4.3.1 Primary Endpoints

(For prognostic endpoints including amputation reference is made to the section on prevention trials)

4.3.1.1 Pain at rest

The main symptomatic efficacy endpoint in stage III is the relief of pain at rest.

The intensity of the pain should be assessed by means of standardised methods (e. g. visual analogue scale). Pain relief should be defined as „complete relief of pain while off analgesics“. In addition, complete pain relief should be coupled with the absence of the development of ischaemic lesions. Furthermore, it has to be shown that the drug under investigation has no analgesic properties. Since pain at rest is a soft endpoint influenced by variables such as mood, motivation, and other factors, the standardisation of the trial methodology is of utmost importance. This does not only refer to the methodology used to quantify pain but does include factors such as the time of pain assessment (same time of the day, preferably at drug trough levels), the personnel taking the measurement (which should not change), and the assessment of analgesic consumption.

4.3.2 Secondary Endpoints

Secondary endpoints should focus on clinically relevant data supporting the study objective.

4.3.2.1 Consumption of analgesics

The consumption and the type of analgesics should be measured and documented, although the comparison of patients on different analgesics schemes may be difficult.

4.3.2.2 Haemodynamic measurements

The measurement of peripheral arterial flow and pressure at ankle level is a further clinical parameter. However, such measurements poorly correlate with the patient's clinical outcome.

4.3.2.3 Interventional/surgical procedures

Other clinical parameters that should be taken into account include the rate of revascularisation procedures, minor amputations as well as frequency and height of major amputations.

4.3.2.4 Quality of life

In trials with adequate sample size an assessment of quality of life may be performed by using properly validated general and disease specific questionnaires.

4.3.3 Response Based Endpoints

In case a patient sample has been successfully treated by conservative, interventional, or surgical means or a combination thereof and it is intended to study the overall medium-term/long-term outcome, a response based concept can be applied. Response would be defined as the patient being alive, having both legs, having no wound or pain, and being off analgesics. This endpoint concept would consider the time period for which the response can be maintained.

5. SPECIFIC RECOMMENDATIONS, PAOD FONTAINE STAGE IV

5.1 Trial Design

A randomised parallel group, double-blind, placebo-controlled design is generally required. A placebo should be used for the control group since suitable reference substances have not yet been established in the treatment of ischaemic lesions (PAOD stage IV). Active drug controlled trials without a placebo arm may only be considered if the comparator drug has consistently shown superiority over placebo (assay sensitivity, see ICH E10).

A short run-in phase is recommended to provide some evidence of disease stability.

The duration of the active treatment phase depends on the aim of the study, the galenic formulation and the mode of action of the drug under investigation, and the endpoint(s) chosen. Also, the length of the follow-up period may vary but should be appropriate for the assessment of secondary efficacy endpoints or important safety variables, such as the frequency of reconstructive measures, morbidity and mortality, and the rate of major amputations. Generally, the cumulative duration of active treatment and follow-up period should not be less than 6 months. Double-blindness should be maintained during the whole period.

The allowed medication and basic local treatment during the active treatment phase and follow-up period should be standardised as much as possible, and should be comparable for the treatment groups. The follow-up period should be specified à priori in the study protocol.

5.2 Patient Selection

Only patients with ischaemic skin lesions (that is persistent, non-healing ulceration or gangrene) due to chronic critical limb ischaemia, with or without rest pain should be acceptable. Generally, patients eligible for surgical/interventional reconstruction should not

be included. However, patients with a high perioperative/periinterventional risk for ischaemic complications may be included, provided that the study design guarantees that necessary invasive procedures are not delayed. The presence of critical limb ischaemia should be confirmed by objective evidence (e. g. systolic ankle pressures ≤ 50-70 mmHg or systolic toe pressures ≤ 30-50 mm Hg or transcutaneous partial oxygen pressures ($tcp0_2$) ≤ 10-20 mm Hg)

In diabetic patients macroangiopathy (rather than microangiopathy or neuropathy) should be the leading cause for the lesion(s). Patients with skin lesions of mixed arterio-venous origin or patients suffering from a vasculitis should not be included.

It is strongly recommended to study diabetic patients and non-diabetic patients in separate trials or to use appropriate stratification.

5.3 Criteria of Efficacy

5.3.1 Primary Endpoints

(For prognostic endpoints including amputation reference is made to the section on prevention trials)

5.3.1.1 Ulcer healing

In PAOD stage IV, the main symptomatic efficacy end-point is complete healing of all necroses and ulcerations. Ulcer healing must be defined as healing of all ischaemic ulcers in both legs (all ulcers epithelialised as assessed by an independent physician and documented by photography). Since quantification of partial healing may be difficult to assess objectively and since the clinical relevance of partial healing remains unclear, only total healing of lesions should be reported as main efficacy criterion.

5.3.2 Secondary Endpoints

Secondary endpoints should focus on clinically relevant data supporting the study objective.

5.3.2.1 Pain

Pain (if existing) should be quantified. The healing of ischaemic lesions should be accompanied by relief of pain.

5.3.2.2 Consumption of analgesics

The consumption and the type of analgesics should be measured and documented, although the comparison of patients on different analgesics schemes may be difficult.

5.3.2.3 Haemodynamic measurements

The measurement of peripheral arterial flow and pressure at ankle level is a further clinical parameter. However, such measurements poorly correlate with the patient's clinical outcome.

5.3.2.4 Interventional/surgical procedures

Other clinical parameters that should be taken into account include the rate of revascularisation procedures, minor amputations as well as frequency and height of major amputations.

5.3.2.5 Quality of life

In trials with adequate sample size an assessment of quality of life may be performed by using properly validated general and disease specific questionnaires.

5.3.3 Response Based Endpoints

In case a patient sample has been successfully treated by conservative, interventional, or surgical means or a combination thereof and it is intended to study the overall medium-

term/long-term outcome, a response based concept can be applied. Response would be defined as the patient being alive, having both legs, having no wound or pain, and being off analgesics. This endpoint concept would consider the time period for which the response can be maintained.

6. SPECIFIC RECOMMENDATIONS FOR TRIALS ON THE PREVENTION OF ISCHAEMIC EVENTS (PREVENTION TRIALS)

6.1 General Comments and Background

Patients suffering from any stage of PAOD (Fontaine stages I-IV) are at high risk for cardiovascular ischaemic events particularly myocardial infarction and stroke. The prognosis of patients suffering from PAOD and coronary heart disease (CHD) is worse than the prognosis of age matched patients with CHD alone. Thus, the cardiovascular prognosis of PAOD sharply contrasts with the relatively benign course of the disease in the legs, particularly in Fontaine stages I and II.

For intermittent claudication the 5-, 10-, and 15 year mortality rates are approximately 30 %, 50 %, and 70 %, respectively with cardiovascular mortality accounting for approximately 65 % of the mortality from all causes.

Given the fact that the treatment of cardiovascular complications is a major socio-economic factor, prevention trials might even be more important than trials merely focussing on improvement of symptoms.

If critical limb ischaemia (CLI) is present the (predominantly cardiovascular) mortality rate increases substantially with approximately 20% of patients dying during the first 6 to 12 months after CLI onset, and 2-, 5-, and 10 year mortality rates of approximately 35%, 70%, and 100%, respectively.

Approximately 10% of CLI patients will undergo primary amputation with healing rates varying between 30% and 90%, and re-amputation rates between 4% and 30%. Overall, approximately 40% and 50% of CLI patients will lose their leg within 6-12 months and approximately 15% will also require contralateral amputation within 2 years. Thus, in order to evaluate the fate of CLI patients comprehensively, cardiovascular morbidity and mortality, all-cause mortality and (bilateral) amputation rates have to be taken into account.

6.2 Study Design

A randomised, parallel group, double-blind, controlled study design is generally required. Depending on the class of drug tested and its mechanism of action, placebo and/or active drug controlled trials may be adequate.

Treatment should last for a minimum of 12 months, but longer periods are recommended.

In exceptional cases (e.g. large scale, multicentre, multinational trial) one single confirmatory trial could be sufficient for the proof of efficacy of the tested drug if the results are clinically relevant and statistically persuasive (see PTC on Application with 1.) Meta-analyses and 2.) One pivotal study (CPMP/EWP/2330/99).

6.3 Patient Selection

Generally all patients with a proven diagnosis of PAOD (Fontaine stages I-IV) are eligible for clinical trials on the prevention of ischaemic events. Thus, patients may present with a history of intermittent claudication, previous peripheral (lower extremity) vascular intervention such as surgical endarterectomy, bypass grafting or abdominal aortic aneurysm repair, transcutaneous endoluminal procedures (PTA, stenting), minor or major amputations because

of PAOD, or may be asymptomatic if PAOD has been proven by objective means (e.g. haemodynamics and non-invasive imaging studies or angiography).

Regarding the cardiovascular prognosis it is recommended that the patient sample to be included in a clinical trial should be homogeneous. Whereas a combined sample of patients in Fontaines' stages I and II would fulfil this requirement, patients with intermittent claudication and CLI should be studied separately or appropriate stratification techniques should be applied.

Diabetics and non-diabetics should be studied separately or stratified.

6.4 Background Therapy

Recent trials have provided evidence that the use of antiplatelet drugs is effective in reducing the frequency of ischaemic cardiovascular events in PAOD patients. Thus, there is justification to use antiplatelet drugs for both treatment arms to be compared in cases in which drugs to be investigated have no antiplatelet properties.

6.5 Criteria of Efficacy

Since the goal of prevention trials is the prevention of PAOD associated morbidity and mortality, cardiovascular morbidity (e.g. myocardial infarction, stroke), amputation and death are considered to be the clinically most meaningful endpoints. They may be used in isolation or in form of a composite, combined endpoint. The components of a composite endpoint will depend on the clinical stage of PAOD. Whereas cardiovascular morbidity/mortality and all cause mortality will be the most appropriate components for trials in mild to moderately severe diseased patients (Fontaine stages I and II), the rate of major amputations should also be considered in trials including CLI patients (Fontaine stages III and IV).

The question on whether to use all-cause mortality or cardiovascular mortality as a component of a composite endpoint will depend on the estimated frequency and the possibility to identify cardiovascular death. Also the trial hypothesis, whether this is superiority on non-inferiority, may play a role, particularly if the incidence of cardiovascular- and non-cardiovascular death does differ substantially. However, as a general rule, all-cause mortality should be given preference as long as there are no persuading arguments for the use of cardiovascular mortality. If a composite endpoint is used and significantly influenced by the drug under investigation, evidence should be provided that the drug’s beneficial effect positively influences all endpoint components.

6.5.1 Primary Endpoints

6.5.1.1 Mortality

All-cause mortality or cardiovascular mortality alone has rarely been used as a primary efficacy endpoint in prevention trials. However, either all-cause or cardiovascular has always to be considered as an important component of a composite efficacy endpoint.

6.5.1.2 Cardiovascular morbidity

Prevention studies have provided evidence that antiplatelet drugs given to patients with PAOD reduce the frequency of myocardial infarction, stroke, and vascular death. However, cardiovascular morbidity alone should not serve as a single primary endpoint, but should be incorporated into a composite primary endpoint which also includes mortality.

6.5.1.3 Amputation

The rate of major amputations can be considered as a primary endpoint or as a component of a composite primary endpoint.

Only major amputations, above the ankle, should be counted. Both legs must be considered for the assessment of amputation rates.

The criteria for major amputations are to be specified à priori in the study protocol to avoid relevant centre-related effects (e.g. a more conservative or a more progressive attitude towards the indication for amputation).

6.5.1.4 Composite Endpoints

The most adequate endpoint in prevention studies is a composite endpoint, if specified à priori, and if consisting of clinically relevant components. Such an endpoint may include cardiovascular morbidity (e.g. stroke, myocardial infarction) and all-cause mortality. Major amputation as a component of a composite endpoint should be considered in more severe stages of PAOD (stages III/IV).

6.5.2 Secondary Endpoints

6.5.2.1 Components of the composite end-point

If the primary end-point is a composite end-point, the components of this composite endpoint should be evaluated as secondary endpoints.

6.5.2.2 Mortality

If survival is not a part of the primary endpoint of the study, all-cause mortality and cardiovascular mortality should be evaluated.

6.5.2.3 Cardiovascular morbidity

If cardiovascular morbidity is not a part of the primary endpoint of the study, it is strongly recommended to evaluate cardiovascular morbidity.

6.5.2.4 Amputation

If major amputation is not a part of the primary endpoint, the frequency of major amputation should be evaluated in CLI patients.

7. CONCOMITANT THERAPY

Vasoactive substances other than the test drug, haemodilution or rheological therapy are not allowed during the study. Other pharmacotherapy which is considered relevant for the treatment of PAOD of relevant for the prevention of cardiovascular events in general must be documented. It should be maintained during the course of the study. If this is not possible, e.g. during follow-up or deterioration, the study design must consider this appropriately. All other medicinal products can be given, as long as they have no established effect on the investigated parameters. However, their administration must be fully documented.

In PAOD stage IV basic local treatment (e. g. local wound treatment, removal of necrotic tissue, antibiotics) must be documented and should be standardised as much as possible.

Due to the fact that PAOD patients have a high risk for cardiovascular events it is recommended to use antiplatelet agents as background therapy during the study if antiplatelets are not the study medication.. It is desirable to avoid any change in medication.

8. DEVELOPMENT STRATEGY

8.1 Human Pharmacology Studies

The objectives of studies related to human pharmacology are the investigation of the pharmacodynamic and pharmacokinetic properties of the new drug in volunteers and/or uncritically ill patients of both sexes and risk groups.

Studies involving the first administration of medicinal products for PAOD to man do not essentially differ from those dealing with other cardiovascular medicinal products.

8.1.1 Pharmacodynamics

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

A parallel group (placebo)-controlled design is recommended, although in some cases a cross-over design could be considered.

Depending on the nature of perceived mechanism of action, these studies may include data on arterial peripheral blood flow, haemorheological parameters etc.. The pharmacodynamic activity of the new drug should be defined as much as possible.

Dose response curves should be produced since information on the relationship between dose, plasma-concentration and pharmacological activity is usually helpful for the subsequent clinical development.

Effects on the peripheral arterial circulation can be assessed in different ways, e. g. by changes in peripheral heamodynamics and blood flow (e.g. ultrasound Doppler and duplex techniques, venous occlusion plethysmography), and changes in microcirculation (e. g. laser Doppler flow measurement, transcutaneous pO2). The methods of assessment should be fully described and their accuracy and reliability given.

If medicinal products under development are assumed to affect platelet aggregation, fibrinolytic activity, flexibility and aggregation of erythrocytes, leukocyte function, or plasma viscosity, these properties should be studied in order to elucidate underlying mechanisms and contributory factors.

The usefulness of some of these methods has been questioned due to high variability, or dubious predictive value, but they may serve screening purposes and can provide supportive evidence in dose-finding trials.

8.1.2 Pharmacokinetics and interactions

General guidance is provided in the guidelines on “Pharmacokinetic Studies in Man” and “Investigation of Drug Interactions” (CPMP/EWP/560/95). As for studies conducted to elucidate possible kinetic interactions, a mechanistically based approach to dynamic interaction studies is recommended, e.g. with vasoactive medicinal products, or products affecting the thrombocyte function, as appropriate.

8.2 Initial Therapeutic Studies

The purpose of this development phase is to identify those patients with chronic PAOD who may benefit from the drug under investigation and to establish suitable therapeutic dose ranges.

The dose and therapeutic schedule should be selected according to the results of previous studies, and usually three dose levels (low, medium, and high) are assessed. These studies should be carried out in selected patients with strict inclusion and exclusion criteria.

A randomised, double-blind, parallel group, placebo-controlled design is recommended. Primary assessment criteria depend on the aim of the study (e.g. walking distance in claudication trials, relief of rest pain and ulcer healing as symptomatic endpoints in critical limb ischaemia).

In general the treatment period should be in the range of 2 to 3 months. However, the overall duration of dose response studies may vary and should be properly justified considering the mechanism of action and the main end-point of the study. A run-in period is recommended for dose-response.

For more general aspects of dose-response studies see Dose-Response Information to Support Drug Registration.

8.3 Main Therapeutic Studies

Studies aiming at the proof of efficacy must have a confirmatory statistic approach – e.g. a demonstration of superiority, equivalence or non-inferiority has to be pre-specified in the protocol.

The biostatistical design and analysis should be performed in accordance with the Note for Guidance on Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products.

Generally, studies which investigate the possibility to reduce the risk of several serious events (prevention studies) and which therefore may use a combined endpoint as a primary variable should be designed to either show a significant difference between the treatment groups or be designed as non-inferiority studies with suitable comparators.

However, a significant benefit in the composite endpoint should be coupled with evidence that none of the components is negatively influenced.

Walking distance is a weak symptomatic endpoint. Hence it is of particular importance to balance the effect in walking distance (if this constitutes the primary variable) against the safety profile. In order to avoid discussion during registration process it is therefore recommended to plan the study in such a way that the results regarding walking distance indicate a clinically relevant effect in addition to its statistical significance.

The duration of the trial depends on the aim of the study and the endpoint(s) chosen

However, the length of exposure to the drug should be sufficient to ensure that tolerance (if expected) will not develop.

Confounding factors, such as the initiation or the change of lipid-lowering or anti-platelet therapy and changes in smoking habits, should be carefully documented during the trial and considered in the efficacy evaluation.

9. SAFETY ASPECTS

All adverse effects occurring during the course of clinical trails should be fully documented. Any groups specially at-risk should be identified. Special efforts should be made to assess potential adverse effects that are characteristic of the class of drug being investigated.

Adverse drug events occurring during the course of the treatment should be carefully recorded throughout all study phases, including data about their nature, frequency, intensity, and relevance.

Particular attention should be paid to the following specific side effects:

9.1 Blood pressure and heart rate

This may be either symptomatic or asymptomatic. Special attention should be paid to orthostasis and first-dose phenomenon.

9.2 Neurohumoral activation and pro-arrhythmic and/or pro-anginal effects

Depending on the particular pharmacodynamic properties of the new agent, measurement of effects on neurohumoral compensatory mechanisms, heart rate, ECG and Holter monitoring should be performed at frequent intervals throughout the study.

Effects on cardiac conduction (PR, QRS, QT and QTc) should be documented.

9.3 Rebound, withdrawal phenomena

Withdrawal phenomena, especially rebound phenomena should be studied specifically.

9.4 Mortality, cardiovascular morbidity

If not investigated as efficacy endpoint, a separate analysis on all-cause mortality, cardiovascular morbidity / and vascular death should be made on basis of the major clinical trials. A new agent in PAOD is only acceptable for registration if there is no suspicion of a detrimental effect on mortality and cardiovascular morbidity.

Otherwise, additional studies to clarify the drug effect on these parameters are mandatory.