

# CLINICAL TRIALS WITH HAEMATOPOIETIC GROWTH FACTORS FOR THE PROPHYLAXIS OF INFECTION FOLLOWING MYELOSUPPRESSIVE OR MYELOABLATIVE THERAPY

<b>Guideline Title</b>	<b>Clinical Trials with Haematopoietic Growth Factors for the Prophylaxis of Infection following Myelosuppressive or Myeloablative Therapy</b>
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<b>Additional Notes</b>	<b>This note for guidance should be read in the light of the Annex to Directive 75/318/EEC as amended which sets up the framework within which this note for guidance provides more details. One of its aims is to give guidance on the major efficacy end points that should be investigated for new Haematopoietic Growth Factors in confirmatory Phase III trials before the submission of a marketing authorisation application.</b>

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# CLINICAL TRIALS WITH HAEMATOPOIETIC GROWTH FACTORS FOR THE PROPHYLAXIS OF INFECTION FOLLOWING MYELOSUPPRESSIVE OR MYELOABLATIVE THERAPY

## 1. INTRODUCTION

This note for guidance should be read in the light of the annex to Directive 75/318/EEC as amended which sets up the framework within which this note for guidance provides more details.

Haematopoietic growth factors (HGFs) that act on the myeloid lineage have already been marketed in the EC. The medicinal products are used to reduce the risk of infection caused by neutropenia induced by cytotoxic chemotherapy or by myeloablative therapy preceding bone marrow transplantation.

There are a variety of potential efficacy end points that applicants might use to support marketing authorisation applications for new HGFs indicated for the treatment of iatrogenic neutropenia. One particularly important purpose of this note on clinical trials performed to support such applications is to give guidance on the major efficacy end points that should be investigated in confirmatory Phase III trials before the submission of a marketing authorisation application. The guidance given herein specifically addresses trials of HGFs for the already authorised therapeutic indications. Further guidelines may be required when novel uses of these agents are developed.

## 2. PHARMACODYNAMICS

The aim of Phase I studies is to acquire data on safety and dose response in the initial exposure of humans to the new HGF.

### Design of Phase I Trials

**Population:** healthy volunteers or, preferably, cancer patients who are not concomitantly receiving myelosuppressive or myeloablative therapy. The choice (either healthy volunteers or patients) should be justified by the applicant.

**Design:** parallel-group, dose response design with increasing dosage.

**Application:** single application.

The Phase I trials should preferably be conducted with the final medicinal product form. After completing Phase I, it should be possible to say that the new HGF can be safely used in a single application up to the defined (maximal tolerated or acceptable) dosage. Side effects to be expected, as well as effects on the blood cells should be described.

### 3. PHARMACOKINETICS

In addition to the determination of the basic pharmacokinetic data, the relationships between dose and responses should be investigated and an analysis of the relationships between pharmacokinetic measures (e.g. AUC) and with both pharmacodynamic measures (e.g. neutrophil count) and adverse effects should be performed.

#### Studies in Volunteers

In general, trials on healthy volunteers are suitable for determining basic pharmacokinetic data after single administration. If, however, severe side effects with the new growth factor are of serious concern, studies may have to be conducted exclusively in patients (see 3.2, below).

When trials in healthy volunteers are feasible, efforts should be directed at studying the effects of the new HGF on the "cytokine network". As more information becomes available about the secondary effects of HGFs on other cytokines, the effects of the new HGF on other cytokines, e.g. the various ILs and TNF $\alpha$ , should be investigated.

#### Studies in Patients

If the side effects encountered during the preliminary testing of a new HGF give rise to serious ethical concerns about tests in healthy volunteers, Phase I trial(s) should be conducted in patients who have a chance of benefiting from the new medicinal product. In such a situation the design of the Phase I trial(s) may be as follows: patients who are eligible for (first-line) palliative cytotoxic chemotherapy will be recruited for Phase I trials with a new HGF before the cytotoxic chemotherapy starts. Phase I investigations, including pharmacokinetics and the documentation of adverse events should be performed prior to chemotherapy.

In the Phase II trials a correlation between the blood concentration (e.g.  $C_{max}$ , AUC, trough levels) and the desired clinical effect should be determined.

#### Assay Methodology

Usually, a bioassay will be available for the concentration assays when a new HGF reaches Phase I of the clinical trials. However, a more specific test system (e.g. RIA, EIA, ELISA) should be developed and employed for the pharmacokinetic investigations.

### 4. PHASE II CLINICAL TRIALS

#### Objectives

The object of the Phase II studies is to evaluate dose dependent effects of the HGF in patient groups after receiving myelotoxic therapy.

The Phase II trials should answer questions about how

- the degree and
- duration

of the neutropenia can be modified by

- the dosage.

If more than one route of administration has been investigated, recommendations as to the preferred route or routes should be justified. Data on the equivalence (or in-equivalence) of the pharmacodynamic effects on neutropenic end points for the different routes will be required.

### **Design of Phase II Trials**

Population:	Representative of the indications requested.
Design:	Double-blind, randomised, parallel group dose response design.
Dosage/administration:	The variables that would usually be investigated are: <ul style="list-style-type: none"> <li>• magnitude of daily dose;</li> <li>• route of administration;</li> <li>• time of first dose in relation to myelosuppressive therapy.</li> </ul>

### **Endpoints to be Studied on a Regular Basis**

The following measures of the differential white blood cell count should be determined in the Phase II trials:

- depth of the nadir of neutrophilic granulocyte count;
- duration from the beginning of the myelosuppressive or myeloablative therapy to the occurrence of the nadir;
- frequency of a nadir of less than 500 and less than 100 neutrophilic granulocytes per  $\mu\text{l}$
- duration of the neutropenia (= number of days with less than 500 and less than 100 neutrophilic granulocytes per  $\mu\text{l}$ ).

Studies should be carried out in a well defined group of patients using only one chemotherapy regimen in each trial. Groups should be stratified with regard to chemotherapy regimen at randomisation provided that different chemotherapy regimens are to be studied. The myelosuppressive intensity of the chemotherapeutic regimen should be specified (see 4.5 below).

### **Secondary Endpoints**

- Adverse events including frequency of (culture-confirmed) infections and neutropenic fever.
- Laboratory safety monitoring including haemoglobin, lymphocyte and platelet count.
- The percentage of the scheduled dose that was delivered.

### **Intensity of Chemotherapy Regimens**

Cytotoxic regimens can be categorised according to their myelosuppressive intensities; i.e. the degree (nadir) and duration of white cell reduction. It is possible that the dose of an HGF required to counteract the white cell effect of different cytotoxic regimens will differ according to the myelosuppressive intensity of the regimens. Accordingly, in the Phase II studies with a new HGF, the relationship between HGF dose and response should be

investigated in relation to the different intensities of white cell suppression associated with different cytotoxic regimens. The applicant should justify the categories used to define the intensity of myelosuppression. The trial reports should state explicitly whether or not patients were stratified by intensity of myelosuppressive cytotoxicity before they were randomised into treatment groups.

Phase II of the clinical investigation should be concluded with the recommendation of a dosage regimen for Phase III trials. The Phase III protocols should include justifications, based on the data from Phase II, as to the timing of the initiation of treatment and as to its duration. The dosage regimens used in the Phase III trials should take account of any evidence of differences in dose response relative to the intensity of the myelosuppressive regimen from the data acquired in the Phase II trials (see 4.5, 1st para. above).

## 5. PHASE III TRIALS

### Objectives

The goal of Phase III investigations is the confirmation of the clinical efficacy of the proposed regimen(s) for the new HGF. The studies should allow the posology to be defined in terms of dose, route of administration, timing of the initiation of treatment and the duration of treatment. Any recommendations as to differences in dosage regimen relative to differences in the severity of the myelosuppressive therapy must have been confirmed in these Phase III trials.

The efficacy of the HGF will be determined by the demonstration that its administration as recommended in the product particulars:

- significantly reduces the frequency of infection  
and/or
- is equivalent to a validated standard therapeutic procedure with respect to frequency of infections.

Furthermore, the Phase III trial must provide sufficient data to assure that the administration of the HGF is safe in the above mentioned therapeutic situation. (The effect on other organs and receptors should also be identified.)

### Design of Phase III Trials.

As a rule, confirmatory trials should be conducted as placebo controlled clinical trials (see annex to Directive 75/318/EEC as amended) and should demonstrate superiority of the test treatment. In so far as effective alternative treatments are already authorised it may be unethical to treat patients with a placebo. In such cases equivalence trials with the best available standard therapy as control should be carried out. As a general rule, Phase III controlled clinical trials should employ a blind technique.

The sample size for each trial should be large enough to provide a reliable and useful answer to each question posed.

More than one regimen of the growth factor may need to be tested if Phase II data are not clear cut.

The intensity of the chemotherapy regimens investigated should be classified as outlined under 4.5 above.

Where multicentre studies are carried out all efforts should be directed at standardising concomitant therapies (e.g. antibiotic policies) between centres. The criteria for discharge from hospital should be specified and should be the same for all study centres. Similarly, the criteria for the initiation and discontinuation of treatment with intravenous anti-bacterial agents should be specified and should be the same for all centres.

No more than 2 or 3 chemotherapeutic regimens should be included in pivotal studies and groups should be stratified for regimen at randomisation.

### **Primary Endpoints**

Frequency of infections.

The criteria for infections due to the neutropenic state should be clearly specified; two criteria are recommended as follows:

- positive culture of pathogenic organisms during the neutropenic state;
- fever (defined as a temperature above 38.5°C) during the neutropenic state.

In all trials the sample size estimation should be based on the expected frequency of culture-confirmed infections.

It is strongly recommended that the effect of treatment with the new HGF on mortality due to infections and overall mortality should be investigated.

#### **Combining Different Types of Infection**

Since a variety of infections occur in neutropenic patients, it is preferable to analyse treatment differences in terms of type of infection. Where different types of infection are combined for the purpose of the analysis of treatment differences, some method of weighting which takes account of the clinical relevance of the infections that are to be combined should be employed. For example, it would not be appropriate to give the same weight to cellulitis as to septicaemia.

### **Secondary Endpoints**

The following are endpoints that will not be regarded as confirmatory, but which should usually be investigated:

- full haematology including haemoglobin and recovery of platelet and granulocyte count;
- the numbers of transfusions used to treat thrombocytopenia and anaemia;
- time in hospital;
- time in Intensive Treatment Unit;
- use of iv antibiotics;
- percentage of scheduled dose that was delivered.

### **Safety Evaluation**

In addition to the usual safety evaluation, the following points should be analysed and reported for every Phase III trial for safety considerations:

- Overall survival.

- Efficacy of the chemotherapy regimen(s) in terms of time to progression and frequency of (complete) objective tumour remissions.
- If applicable and depending on the therapeutic situation (non-infectious), complications of myelosuppressive or myeloablative therapy such as frequency of acute and chronic GVHD, frequency of transplant failure, reactivation of latent viral infection and mucous membrane ulceration should be analysed and reported.

## 7. POINTS TO CONSIDER FOR THE INDICATION

The indication should reflect the group of patients studied, the dose intensity of the myelosuppressive or myeloablative chemotherapy studied and the data generated in the clinical trials.

If a number of studies are to be performed, they should be planned to cover different diseases.

If in any phase of the clinical trial particular diseases (e.g. myeloid malignancies) were excluded from the protocol due to a particular concern of the investigators, these diseases and the reasons for their exclusion should be listed under the heading “Contra-indications”; the reason for the contraindication should be given, namely: lack of evidence of safety and efficacy in these groups of patients.

## 8. COMBINATIONS OF HGFS

Two different situations can be considered:

### **A New HGF (A) has an Additional Effect to an Authorised Growth Factor (B) and is Effective as a Monotherapy**

In this situation the new growth factor should be investigated in Phase I and II trials as described above. In addition to monotherapeutic pharmacodynamics and safety the combination of A and B should be studied as described under item 7.2. It should be demonstrated in trials with 3 arms consisting of A alone, B alone and the combination of A and B, that the combination of A and B provides a benefit greater than either A or B used alone.

### **A New HGF (A) has an Additive Effect to an Authorised HGF (B), but is Not Effective as Monotherapy**

After the new medicinal product has been tested in Phase I trials, the combination should be studied as if it were one medicinal product.

In Phase II trials particular efforts should be made to determine the optimum dose ratio of medicinal product A and B.

In phase III trials it should be confirmed that the optimum dose ratio of the combination is superior to B alone.