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**GUIDELINE ON CLINICAL TRIALS WITH HAEMOPOIETIC GROWTH FACTORS FOR
THE PROPHYLAXIS OF INFECTION FOLLOWING MYELOSUPPRESSIVE OR
MYELOABLATIVE THERAPY**

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GUIDELINE ON CLINICAL TRIALS WITH HAEMOPOIETIC GROWTH FACTORS FOR THE PROPHYLAXIS OF INFECTION FOLLOWING MYELOSUPPRESSIVE OR MYELOABLATIVE THERAPY

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1. INTRODUCTION

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

This Guideline should be read in the light of the Council Directive and other relevant guidelines listed below.

- Council Directive 91/507/EEC
- Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance – Nonclinical and Clinical Issues (CPMP/3097/02/REV)
- Guidance on biosimilar biological medicinal products containing recombinant human granulocyte-colony stimulating factor, (EMA/CHMP/BMWP/31329/2005)

For a Marketing Authorisation (MA) application dossier of an HGF claimed to be biosimilar to a reference product already authorised, comparability of the test product to an authorised reference product in the EU, should be demonstrated.

One particularly important purpose of this note for guidance concerning clinical trials performed to support such applications is to give guidance on the major efficacy end points that should be investigated in confirmatory trials before the submission of a marketing authorization application. The guidance given herein specifically addresses trials of HGFs for the already authorized therapeutic indications. Further guidelines may be required when new therapeutic indications for these agents are developed.

The following guidance is applicable to new biological products. However, developments in the modification of these haemopoietic growth factor proteins through pegylation, can modify not only the HGF's formulation properties but also both its pharmacokinetic (PK) and pharmacodynamic (PD) performance. This translates into the development of a long-acting HGF requiring less frequent dosing than its parent drug through a longer half life and slower elimination rate, with the consequent impact on improved quality of life, compliance and cost effectiveness. Accordingly, PK/PD methodology as currently specified, may not be the most appropriate under such circumstances. However, such modifications to study design for a line extension to the original product may not generally be necessary. In addition, PK/PD methodology would need to be modified for those products which are considered to be biosimilar. For these reasons alternative designs of clinical studies are needed and these issues are covered in sections 8 of this guideline.

2. PHARMACODYNAMICS

The aim of human pharmacology trials is to acquire data on safety and dose response in the initial exposure of humans to the new HGF.

2.1 Design of Human Pharmacology 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: dose tolerance, dose-response dose escalation design.

Application: single and/or repeated escalating dosing in successive groups.

The trials should preferably be conducted with the final drug form. After completing human pharmacology trials, it should be possible to conclude that the new HGF can be safely used in a range of single doses and /or used for the duration of the specified period at a selected dose level. Side effects to be expected, as well as effects on the blood cells should be described.

The trials should allow for recommendation of some doses for repeated administration, or some single dose levels for a single administration in the case of a prolonged release form (e.g. a pegylated HGF)

of a HGF, to be further investigated in exploratory trials, i.e. in patients after start of cytotoxic chemotherapy or myeloablative therapy.

The absolute neutrophil count is an acceptable surrogate marker in pharmacodynamic (PD) studies.

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 α , should be investigated.

3. PHARMACOKINETICS

In addition to the determination of the basic pharmacokinetic data, the relationships between pharmacokinetics and pharmacodynamics 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.

3.1 Studies in Volunteers

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

In addition, as repeated dosing with an HGF in healthy volunteers may lead to excessive hyper-leukocytosis without reaching maximum tolerable dose for another AE other than hyper-leukocytosis, trials in patients may be required to investigate repeated dosing at higher dose levels.

3.2 Studies in Patients

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

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

3.3 Assay Methodology

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

4. EXPLORATORY CLINICAL TRIAL

4.1 Objectives

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

The 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 non-equivalence) of the pharmacodynamic effects on neutropenic endpoints for the different routes will be required.

4.2 Design of Exploratory Trials

Population: Representative of the indications requested.

Design: Double-blind, randomized, parallel group dose-response design.

Dosage/administration: The variables that would usually be investigated are:

- magnitude of daily dose and cumulative dose during the chemotherapy cycle
- route of administration
- optimum time of first dose in relation to chemo therapy

4.3 Endpoints to be Studied on a Regular Basis

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

- Incidence of grade 4 neutropenia and duration
- Median time to absolute neutrophil count recovery as defined
- Incidence of febrile neutropenia (defined as a rise in axillary temperature to above 38.5 centigrade for a duration of more than 1 hour while having an absolute neutrophil count $<0.5 \times 10^9/L$)
- Adverse events including frequency of (culture-confirmed) infections and neutropenic fever.
- Laboratory safety monitoring including haemoglobin, lymphocyte and platelet count.
- The percentage of the actually delivered vs. scheduled cumulative chemotherapy dose.
- Mobilisation of CD34+ cells (AUC and maximum concentration)
- Cumulative HGF dose
- Number of transfusions
- 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 μl
- duration of the neutropenia (=number of days with less than 500 and less than 100 neutrophilic granulocytes per μl)

Studies should be carried out in a well defined group of patients (e.g. one type of cancer, same stage of disease) 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 must always be specified (see 5.2 below).

5. CONFIRMATORY TRIALS

5.1 Objectives

The objective of confirmatory trials 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 confirmatory trials.

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

a) significantly reduces duration and/or severity of febrile neutropenia and is supported by improved outcomes such as reduction of frequency of documented infections, days of hospitalisation, intravenous antibiotic usage, quality of life or survival.

and/or

b) is equivalent to a validated standard therapeutic procedure such as antibiotics and supportive care with respect to frequency of outcomes as mentioned above in (a)

Furthermore, the confirmatory 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.)

5.2 Intensity of Chemotherapy Regimens

For all new products, superiority to a placebo add-on a (standard) chemotherapy regimen with established frequency of febrile neutropenia should be demonstrated whenever possible. However, a non-inferiority design could be an acceptable option.

If the duration and frequency of febrile neutropenia is well documented (there are more than 20% of patients with febrile neutropenia on a given chemotherapy regimen): placebo is considered unethical and a 2-arm trial versus active comparator is recommended.

If the incidence of febrile neutropenia is less than 20%, then the use of a placebo arm only is acceptable, since there is currently no justification for the use of prophylactic G-CSF if <20% of patients experience febrile neutropenia, as there is no evidence of a clinical benefit. However, treatment of the placebo arm with G-CSF should be discouraged but should be dealt with by a dose reduction in subsequent cycles. Nevertheless, prophylactic G-CSF may be used for subsequent cycles of chemotherapy where applicable.

If however, the duration of febrile neutropenia is not well documented for a given chemotherapy treatment regimen, then a placebo arm should be used in addition to an active comparator. A statistically significant superiority of the test product should be demonstrated over placebo, following which non-inferiority with the reference product should be shown for the primary endpoint.

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 exploratory 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.

In the case of haematological malignancies trial reports should document whether, for example, standard chemotherapy or high dose intensive chemotherapy regimens have been utilised. Additionally, the use of HGFs to sensitise patients to chemotherapy should be recorded. Full details of these chemotherapy regimens should be documented.

Exploratory trials should be concluded with the recommendation of a dosage regimen for confirmatory trials. The confirmatory protocols should include justifications, based on the data from exploratory trials, as to the timing of the initiation of treatment and as to its duration. The dosage regimens used in the confirmatory 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 exploratory trials

5.3 Design of Confirmatory Trials.

As a rule, confirmatory trials should be conducted as placebo controlled clinical trials (see Council Directive 91/507/EEC) 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, confirmatory controlled clinical trials should employ a double-blind technique. Equivalence margins should be pre-defined and justified, based on a review of clinical trials with the reference product and delta should be defined by taking into account the duration of severe neutropenia with a reference drug and a given chemotherapy regimen.

A single superiority trial with active comparator, may be adequate if it demonstrates substantial evidence, which has not arisen by chance as shown by the robustness of the primary endpoint data and the strength of the evidence, together with consistency of the secondary efficacy endpoints. Alternatively, two non-inferiority (equivalence) trials may be performed.

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

The selection criteria should include information regarding prior therapy with HGFs, previous prophylactic treatment (antibacterial/ antifungal /other) comorbidity, histological type of tumour (where applicable), definition of infection and/or fever and definition of the leucocyte/neutrophil count.

Sample size estimation should be based on the primary endpoint. It is acceptable to include in the analysis afebrile patients receiving antibiotics, who do not fulfil the criteria for febrile neutropenia.. However, such patients should be analysed separately for duration and incidence of severe neutropenia. Both analyses should show similar results, for test and comparator otherwise the SPC should accurately reflect findings from observed data.

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

The intensity of the chemotherapy regimens investigated should be classified as outlined under 5.2 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 antibiotics agents should be specified and should be the same for all centres.

It is recommended to use the same chemotherapeutic regimens in the same population of patients in pivotal studies, otherwise groups should be stratified for regimen at randomisation.

5.4 Surrogate endpoints for the reduction of infection.

The primary endpoint for confirmatory clinical trials should adequately demonstrate efficacy of the HGF which should be clinically meaningful so that, for example, it significantly reduces the frequency of documented infections. However, this may not always be appropriate or possible since it is dependent, for example, on the disease population being studied (e.g. solid tumours or haematological malignancies), as well as the intensity of chemotherapy and or radiotherapy being utilised (myeloablative or non-myeloablative), which may affect important considerations such as sample size, thus making clinical trials infeasible. Accordingly, appropriate surrogate endpoints need to be considered which would indirectly imply a reduction in infections. Incidence and duration of febrile and/or severe (grade 4) neutropenia in relation to the first chemotherapy cycle would be acceptable surrogate endpoints.

5.5 Primary Endpoints

Incidence and duration of febrile and/or severe (grade 4) neutropenia in relation to the first chemotherapy cycle.

Febrile neutropenia is defined as a rise in axillary temperature to above 38.5 °C for a duration of more than 1 hour while having an absolute neutrophil count (ANC) $<0.5 \times 10^9/l$.

In all trials the sample size estimation should be based on the primary endpoint.

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

5.6 Secondary Endpoints

The following are endpoints that will not be regarded as confirmatory, but which would be consistent with and support the primary endpoint and 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.
- 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 or clinically diagnosed infections
- fever (defined as a temperature above 38.5°C) during the neutropenic state

Types of Infection

Since a variety of infections occur in neutropenic patients, it is recommended that a distinction be made between bacterial and non-bacterial infections, between primary infection and superinfection and between culture confirmed and unconfirmed infections .

Data should also be documented with respect to the site of infection, pathogen distribution (gram positive, gram negative and the most frequently identified pathogen), resistance patterns and response.

- percentage of scheduled chemotherapy dose that was delivered
- Proportion with chemotherapy doses reduced, omitted, or delayed
- Number of days of delay of chemotherapy
- Occurrence and/or resolution of chemotherapy-induced mucositis
- Overall quality of life

5.7 Safety Evaluation

In addition to the collection and reporting of adverse events safety evaluation, the following points should be analysed and

reported for every confirmatory 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 the HGF is a protein, anti-HGF antibodies should be monitored for at least 12 months .

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 other opportunistic infections should be analysed and reported.

Although actual numbers are not specified, there should be an adequate safety database, which should be justified.

Immunogenicity

The safety database is dependent on the experience of the innovator and reference products as well as on the general considerations for recombinant growth factors.

Even if no clear immune-mediated adverse effects of the original product have been recorded, such reactions are by no means excluded for new/changed products. The CHMP guideline for comparability, non-clinical and clinical issues, gives detailed guidance for the investigation of immunogenicity (EMA/CPMP/3097/02/Final). While no absolute numbers are specified, the safety

database should include between 300-600 patients including healthy volunteers followed up for at least a year or the size of the database should be justified if this is not possible.

6. 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 "Warning"; the reason for the warning should be given, namely: lack of evidence of safety and efficacy in these groups of patients.

7. COMBINATIONS OF HGFS

Two different situations can be considered:

7.1 A New HGF (A) has an Additional Effect to a Licensed Growth Factor (B) and is Effective as a Monotherapy

In this situation the new growth factor should be investigated in human pharmacology and exploratory 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.

7.2 A New HGF (A) has an Additive Effect to a Licensed HGF (B), but is Not Effective as Monotherapy.

After the new drug has been tested in human pharmacology trials, the combination should be studied as if it were one drug.

In exploratory trials particular efforts should be made to determine the optimum dose ratio of drug A and B.

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

8. PEGYLATED PRODUCTS

The guidelines described above are applicable to all products, however, the following exceptions with respect to pegylated products are outlined below.

Pharmacodynamics

Design of human pharmacology trials

The design of the study should include ascending dose tolerance, dose response design with increasing dosage following a single dose in healthy volunteers and/or patients.

Pharmacokinetics

The pharmacokinetic parameters including AUC, C_{max}, T_{max}, T_{1/2} and CL, should be determined after a single dose

Studies in Patients

A randomised open label dose escalation study should be used to evaluate the pharmacokinetics, efficacy and safety using the PK parameters defined above (i.e. AUC, C_{max}, T_{max}, T_{1/2} and CL). The PK linearity and dose dependence should be determined from such studies

Design of exploratory trials

A dose finding study should be used to determine the optimum dose of the pegylated product to provide both neutrophil support and tolerability profile. The design should include at least 3 dose levels of the pegylated product and should be compared with the standard dose of the non-pegylated product. PK linearity and dose dependence should be determined and serum levels should be compared with neutrophil recovery.

A randomised exploratory study should be used to compare an optimal single dose of the pegylated product with the standard dose of the non-pegylated product.

Confirmatory trials

Pegylated products should be evaluated using, double blind, randomised controlled trials in the patient population and compare weight based and/or fixed doses of pegylated versus non-pegylated products. These should demonstrate non-inferiority with the comparator. Trial design should also take into account the incidence of febrile neutropenia with the cytostatic regimen and choice of comparator as outlined in section 5.2. An appropriate primary endpoint for these trials would include duration of severe neutropenia. However, secondary endpoints as outlined in section 5.6 need not be defined in the case of pegylated products.