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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF SEPSIS

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF SEPSIS

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This Guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with sepsis. It should be read in conjunction with Directive 2001/83/EC, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Acute Respiratory Distress Syndrome (CPMP/EWP/504/97)
- Points to Consider on Non-Inferiority Margin (CPMP/EWP/2158/99)
- Points to Consider on Adjustment for Baseline Covariates (CPMP/EWP/2863/99)
- Note for Guidance on Studies in Support of Special Populations: Geriatrics (CPMP/ICH/379/95)
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99)

This Guideline is intended to assist applicants during the development of products for the treatment of sepsis, where no current regulatory guidance exists. It is only guidance; any deviation from guidelines should be justified.

The scope of the present document is restricted to drug therapy preventing organ failure and death, which ultimately develop in sepsis as complications of the underlying infectious disease, and will not consider other drugs intended to be used in the treatment of underlying condition and supportive care. It also does not refer to non-infectious conditions presenting with a systemic inflammatory response syndrome, e.g. certain forms of acute respiratory distress syndrome (ARDS), which is addressed in a separate document.

1. INTRODUCTION

Sepsis is a severe and complex form of infection associated with a systemic inflammatory response syndrome (SIRS). However, in numerous patients who demonstrate all findings suggestive of sepsis, a source of infection cannot be confirmed. Although infection is the predominant etiology in the intensive care unit (ICU), SIRS may also develop after different types of injuries such as trauma, burns, acute pancreatitis, ischemia-reperfusion and major surgery including cardio-pulmonary bypass and abdominal surgery. The response involves a complex network of circulating mediators such as pro-inflammatory cytokines and changes of the coagulation/fibrinolysis systems. According to current understanding the critical pathophysiological trigger is a disturbance in equilibrium between pro-inflammatory response and concomitant anti-inflammatory mechanisms, which is closely linked to alterations in the

haemostasis system.

The generation of accurate statistics about sepsis is confounded by the imprecise and highly variable terminology used to describe sepsis by clinicians around the world. Recent European epidemiological studies indicate that up to about 20% of all ICU patients are admitted with or progress to sepsis during their stay in the ICU (with large differences between ICUs). The management of sepsis based on elimination of the causative infection by surgery, where possible, antibiotics, and supportive treatment (fluids, inotropes, vasopressors, replacement therapy of failing organ functions) has not sufficiently changed the mortality rate over the past decades. Sepsis remains an important and life-threatening problem and the most common cause of death in the ICU with mortality between 20 to 50% for severe sepsis and 45 to 80% for septic shock.

The remarkably diverse spectrum of illness encompassed under the term 'sepsis' - ranging in severity from mild systemic inflammation without significant clinical consequences to multi-system failure in septic shock with an exceedingly high mortality rate - and the many factors related to the pathogenesis of (severe) sepsis have made it difficult to effectively design clinical trials for the management of this disease. Planning, implementation and assessment of results of intervention studies on sepsis thus present enormous challenges. A number of large prospective randomized trials with various types of therapeutic intervention undertaken to modify the inflammatory response has been unsuccessful in improving the outcome. Given the high degree of complexity and the obvious difficulty to demonstrate that a certain medicinal product adds clinical benefit to the usually multimodal treatment of sepsis, a need for regulatory guidance on the design and analyses of medicinal products intended for the treatment of sepsis is identified.

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

2.1 Definitions and diagnostic criteria

Sepsis connotes a clinical syndrome that may occur in any age group, in markedly different patient populations, and in response to a multitude of microbial pathogens from multiple different anatomical sites within the human body. A concerted effort has been made to standardise definitions of sepsis by the use of international committees and consensus opinions from panels of experts in sepsis research. The following definitions of SIRS and sepsis were given in 1991 by the American College of Chest Physicians/Society of Critical Care Medicine in a Consensus Conference (Crit Care Med 1992; 20: 864-874) and were recently confirmed in an International Sepsis Definitions Conference as being generally still valid (Crit Care Med 2003; 31: 1250-1256).

SIRS: the general definition of SIRS comprises a profound, but non-specific activation of the inflammatory cascade with abnormalities in at least two or more of the following parameters: body temperature, heart rate, respiratory rate and white blood cell count.

Sepsis: is defined as SIRS where the systemic response is the result of an infection and is manifested by abnormal values in at least two or more of the above-mentioned criteria of SIRS.

Severe sepsis: is defined as sepsis associated with hypotension or hypoperfusion leading to distant organ dysfunction, such as reduced renal output, metabolic alterations like lactic acidosis, acute CNS dysfunction like restlessness, agitation or confusion

Septic shock: is defined as severe sepsis with hypotension unresponsive to adequate fluid resuscitation, along with the presence of hypoperfusion and organ dysfunction.

While consensus definitions of sepsis have proven to be of value, the lack of uniformity in interpretation of these definitions continues to be problematic. Further refinements in the definitions and predisposing factors of (severe) sepsis should improve the understanding and management of (severe) sepsis and septic shock.

Novel parameters that have been proposed at the International Sepsis Definitions Conference to its definition include additional *general variables* (edema or a positive fluid balance, and hyperglycemia in the absence of diabetes), additional *inflammatory parameters* (C-reactive protein, and procalcitonin), and additional *hemodynamic parameters* (central venous oxygen saturation, cardiac index).

2.2 Inclusion criteria

Sepsis is a heterogeneous syndrome in a heterogeneous population. The current scheme of classification does not enable distinction between SIRS, sepsis and severe sepsis on the basis of the underlying biochemical, immunological and abnormal coagulation features.

Identification of the target population is based primarily on clinical characteristics and the following parameters are particularly relevant for outcome:

- Severity of the disease (sepsis, severe sepsis, septic shock and related conditions, i.e. acute respiratory distress syndrome) which can be scored (*descriptive*: SOFA = Sequential Organ Failure Assessment; MODS = Multiple Organ Dysfunction Syndrome; GCS = Glasgow Coma Scale; LOD = Logistic Organ Dysfunction; ODIN = Organ Dysfunction and Infection) or translated into 'predicted mortality' (*prognostic*: APACHE = Acute Physiology and Chronic Health Evaluation; SAPS = Simplified Acute Physiology Score; MPM = Mortality Prediction Model).

  Validated scores should be used prospectively for definition of the inclusion criteria. In order to allow comparisons across studies it is advised to use APACHE or SAPS score apart from the scale preferred, both of which are validated for providing predicted mortality data in the targeted population.

- Duration (stage and potential reversibility) of the disease.

  As the pathophysiology of early phases of sepsis is different from that of late sepsis, a therapeutic intervention that may be effective at the early phase may not be effective in late sepsis and vice versa.

- Differentiation from non-infectious causes of SIRS by direct or indirect confirmation of an infectious cause of the disease including anatomical site of its focus (e.g. pulmonary, abdominal), type of organism (e.g. gram-negative or gram-positive bacteria, fungi), source of infection (e.g. nosocomial, community-acquired) and way of acquisition (e.g. medical, surgical, trauma). Missing of the etiological agent is not an exclusion criterion. The highest level of circumstantial evidence of infection should be sought in cases where direct proof of an infectious cause is not available.

  Biochemical markers for acute phase response and activation of coagulation/fibrinolysis (e.g. CRP, procalcitonin, interleukin-6, D-dimer, antithrombin-III, protein C) or other parameters including certain leukocyte phenotypes (e.g. HLA-DR of monocytes) are not diagnostic of severe sepsis. Therefore it is not a precondition to measure these parameters before starting specific treatment of (severe) sepsis and, consequently, they are not required as inclusion criteria in clinical trials except when directly investigated. However, it is strongly encouraged to measure such parameters as indicators of inflammation, coagulation and pathophysiological mechanisms, which should be targeted by the therapeutic intervention.

  Age of the patient affects outcome with elderly patients (>65 years) being at increased risk of mortality, implying that treatment benefit may be seen preferentially in this age group, yet there should be no reason for excluding patients according to their demographic characteristics (see also section 4.3.1. Studies in elderly).

2.3 Baseline characteristics

In view of the considerable heterogeneity of the patient population generally included in sepsis trials it is important to accurately define baseline characteristics. Thus, the broad patient population at entry should be categorised according to various parameters including age, source of infection (e.g. post-surgery, medical, community acquired), type of infection/organism, underlying disease, co-morbidity, pre-medication, severity score and time-point of treatment intervention, for subsequent analysis of prospectively defined subgroups or a priori stratification. For scientific purposes, it may also be valuable to monitor genetic predisposing factors and immunological markers.

A new conceptual framework for understanding sepsis has been developed, called the PIRO concept (predisposition, infection, response and organ dysfunction). Although not sufficiently established at the moment, the components of the PIRO concept could become useful in the future as collection of

parameters for determining all relevant aspects of the disease including outcome of therapeutic intervention.

2.4 Concomitant therapy

In sepsis, extensive concomitant therapy with antibiotics, supportive care (e.g. fluids, inotropes, vasopressors, replacement therapy of failing organ functions) and surgical treatment are usually employed. These measures should be comparable among treatment groups to be investigated, with careful recording and documentation, and should be standardised as far as possible (see also section 4.2. Main therapeutic studies).

It is anticipated that concomitant treatment will be performed according to best standard of care relevant to the European Union. It is recommended to select only centres which are able to include sufficient numbers of patients to allow for a meaningful stratification of results by centre. Especially in multi-centre studies appropriate antibiotic treatment and hemodynamic support in the prevention of hypoperfusion as examples of critical treatment aspects should be implemented and documented. Definition of antibiotic therapy to some extent will be dependent on the identification of etiological agents (microorganisms causing the infection) and the results of antimicrobial susceptibility tests.

3. METHODS TO ASSESS EFFICACY

3.1 Efficacy criteria in exploratory studies

The objectives of exploratory trials include proof-of-concept, dose and schedule finding and the identification of appropriate patients for inclusion in confirmatory trials.

Non-clinical studies and the assumed pharmacology of the experimental compound should be used to guide the selection of pharmacodynamic measures of activity. Ideally, any pharmacodynamic endpoints chosen have already undergone some type of validation in terms of association with morbidity and/or mortality and are quantifiable in that the beneficial effect of intervention can be estimated. The pharmacodynamic endpoint should also fit well to the proposed mechanism of action of intervention (biological plausibility). In addition, it is advisable to include general markers of inflammatory response and activation of coagulation/fibrinolysis. Population PK/PD modelling is encouraged.

Organ function, e.g. using an organ dysfunction score (see also 2.2. Inclusion criteria, descriptive scores) should normally be assessed. Serial organ dysfunction scores provide a dynamic representation of disease progression, and changes in the mean scores can be used to reflect patient response to therapy. Any scores to be employed should be justified and/or validated.

In addition to calculations of frequency of complications/organ failure, alternative morbidity measures may calculate complication-free survival (i.e., the number of days during which the patient does not have the complication during a given [usually beyond 27 days] time period: for example, ventilator-free survival, vasoactive drug-free survival, dialysis-free survival, or ICU-free survival). The choice of outcome is dependent on the clinical illness being tested and the likely effect of the intervention.

Mortality should always be reported and the data collected should enable a comparison with the findings from phase III confirmatory trials.

In order to identify patients for inclusion in confirmatory studies, the interaction between treatment and disease severity, pathophysiological phase and the timing of intervention should be investigated.

3.2 Efficacy criteria in main therapeutic studies

Sepsis and severe sepsis/septic shock may be differentiated on the basis of disease severity and will therefore affect the choice of endpoints. Mortality as an endpoint is most relevant in severe sepsis and septic shock, whereas in other cases morbidity could be acceptable.

3.2.1. Primary efficacy endpoint

All cause mortality is the most relevant endpoint in clinical trials of severe sepsis/septic shock. Short-term (28-day) all cause mortality should be the primary efficacy endpoint in studies assessing the efficacy of drugs in patients with life-threatening acute illnesses. Shorter time spans may be insufficient to demonstrate the true benefit of a drug, whereas with longer time spans, the effects of the drug itself become increasingly difficult to differentiate from other causes of mortality, particularly those related to

co-morbidities.

The majority of patients with sepsis who die do so within the first month after diagnosis, however, several studies have suggested longer-term mortality due to sepsis, even after adjustment for differences with respect to co-morbidities at baseline. The use of a single-point mortality rate as a marker of drug efficacy in sepsis may thus be insensitive to possible longer-term survival benefits of a drug under investigation. Therefore, the 28-days primary mortality endpoint should be supported by 3-months mortality data and preferably also by long-term mortality data at a minimum of 6 months.

In cases, where treatment aims at prevention of organ failure or progression from sepsis to severe sepsis in a patient population with a low mortality risk, other parameters than mortality might substitute for the primary mortality endpoint. However, in these cases it is recommended to seek regulatory advice.

3.2.2. Secondary efficacy endpoints

In-hospital mortality, ICU length of stay, and hospital length of stay are secondary efficacy endpoints as well as other parameters of sepsis morbidity (see above, 3.1. Efficacy criteria in exploratory studies).

To corroborate findings in exploratory studies, it is advisable to include key dynamic markers of activity. Population PK/PD modelling may provide additional insight as regards, e.g. the temporal dynamics of the underlying condition and the activity of the experimental compound.

A treatment that reduces mortality may reduce morbidity, but equally, it may have no effect or even increase morbidity. Therefore information on both mortality and morbidity is required to evaluate the net effect of a therapy.

The choice of time-points for assessment of morbidity is critical as some of the morbidity parameters may present in a transient manner. The observation period therefore must be sufficiently long.

Many patients who survive sepsis will continue to have increased morbidity that lead to reduced quality of life. Examples of chronic debilitating diseases include critical illness neuropathy and terminal renal failure. In long-term trials quality of life could be assessed by use of validated scores, e.g. the SF-36 questionnaire. In this case, evaluation should be performed for at least 3 and up to 12 months. It is also recommended to provide data with regard to neurological function 6 months after randomisation.

4. STRATEGY AND DESIGN OF CLINICAL TRIALS

4.1 Exploratory studies

Exploratory studies should normally be performed in a broad patient population with well-defined subpopulations. Although the sample size is usually too small to draw formal conclusions these studies may help to identify target populations that could benefit more. It is accepted, however, that convincing non-clinical data and the assumed pharmacology of the experimental compound may provide a relevant rationale to restrict the study population in these studies to, e.g. patients with a hyper-inflammatory response.

The standard therapeutic approach in sepsis generally comprises several treatments aimed at control of infection and organ support. Thus, interactions with various drugs likely to be used in sepsis should be appropriately investigated following the existing guidance (Note for Guidance on the Investigation of Drug Interactions, CPMP/EWP/560/95).

In critical care patients, pharmacokinetics are often altered not only due to changes to drug metabolism and excretion by impaired organ function, but also due to extracorporeal circulation of blood with in many cases unpredictable effects on drug elimination. Therefore, drug/metabolite levels or indirect indication of some parameter of the drug's pharmacodynamics should be obtained. This should also be taken into account in initial dose-response studies, conducted following the existing guidance (Note for Guidance on Dose Response Information to support Drug Registration, CPMP/ICH/378/95).

In most cases and due to the unpredictable dynamics of the underlying disease, randomised, placebo and/or dose/schedule comparative trials provide the only means to generate interpretable data.

4.2 Main therapeutic studies

Efficacy of a new treatment in sepsis should be established in randomised, double-blind, controlled studies. The population enrolled in these trials should be in accordance with the claimed indication

including prognostically important parameters of disease stage and severity, age, underlying cause and co-morbid condition.

In general, efficacy should be demonstrated in comparison with placebo. Currently, no active comparator is available for which the treatment effect size has been firmly established. Therefore, a non-inferiority margin cannot be defined (Points to Consider on Non-Inferiority Margin, CPMP/EWP/2158/99). Also in those cases where the patient population to be included closely matches the one for which an active comparator has proven effective superiority has to be shown in the present situation.

Typically both, the new as well as the control treatment are used as add-on to standard therapy. Because standard therapy often is poorly defined with marked geographical differences in the employment of recent recommendations from professional societies for pharmacological and other interventions including mechanical ventilation, standard therapy in main therapeutic studies needs to be clearly defined (see also section 2.4. Concomitant therapy). It is recommended that the results are stratified according to the participating centres.

Dose and duration of drug administration are critical determinants of efficacy and safety. The relevance of pharmacokinetic considerations in critically ill patients should be reflected in flexible rather than fixed dosing determined by patient parameters based on pharmacologically plausible results from phase II dose-finding studies.

Pre-defined analysis of subgroups is recommended according to prognostically relevant factors as well as other parameters that play a role in the clinical management of the disease including demographics, disease severity, concomitant treatment and biochemical markers.

4.3 Studies in special populations

4.3.1. Studies in elderly

As survival rates in the critically ill elderly may be lower than those in the younger critically ill, studies must focus on customising treatment to optimise physiologic recovery, quality of life, and functional status.

Increased susceptibility to infections is partly due to old age and co-morbid conditions such as uraemia. Major surgery in the elderly is of particular infectious risk especially if performed in emergency.

While it is not necessary to conduct separate trials in this age group, a reasonable number of elderly patients as outlined in ICH E7 (Note for Guidance on Studies in Support of Special Populations: Geriatrics, CPMP/ICH/379/95) should be included in clinical studies.

4.3.2. Studies in children

Despite new understandings in pathophysiology, sepsis mortality remains high in children. As opposed to adults, paediatric considerations include a more likely need for intubation due to low functional residual capacity; more difficult intravenous access; fluid resuscitation based on weight; decreased cardiac output and increased systemic vascular resistance as the most common hemodynamic profile; and greater risk of hypoglycemia with aggressive glucose control.

Major differences can be detected in a number of variables, such as predisposing factors, type of pathogenic organism, underlying disease characteristics, diagnostic criteria, usefulness of a scoring system for assessment of organ dysfunction, etc. between the different paediatric age groups. Therefore, a new drug intended for the treatment of sepsis in the paediatric population should be investigated in separate clinical studies in those age groups as defined in ICH E11 (Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population, CPMP/ICH/2711/99), especially also in the neonates. Due to the complexity of all aspects to be considered a detailed recommendation for the design of these trials would be beyond the scope of the present guideline. Companies are therefore encouraged at this stage to seek regulatory advice for the paediatric development plan.

5. CLINICAL SAFETY EVALUATION

5.1 Specific adverse events to be monitored

All adverse events (AE) should be collected and analysed using a pre-planned methodology. Special emphasis should be put on AE predicted by the pharmacodynamic properties of the investigational product As for other medicinal products, AE need to be fully documented by system organ class.

Any groups at increased risk of AE should be identified. Appropriate ways of observing safety for trials in such vulnerable patient populations are warranted. Safety of all patients should generally be surveyed by a Data Monitoring Committee.

Depending on the product, an assessment of antibody formation might be necessary. Consideration should also be given to the potential interference/contribution of concomitant therapy.

5.2 Interaction studies

Depending on the mechanism of action and based on the results of non-clinical data, phase I and phase II trials possible safety concerns arising from PK or PD interactions with commonly co-prescribed medications should be investigated in phase III studies.