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POSITION PAPER ON NON-CLINICAL SAFETY STUDIES TO SUPPORT CLINICAL TRIALS WITH A SINGLE MICRODOSE

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1. INTRODUCTION

Non-clinical safety studies to support the conduct of human clinical trials for pharmaceuticals has been internationally harmonised by the International Conference on Harmonisation as outlined in International Conference on Harmonisation (ICH) Topic M3: Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, Topic S7A: Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals and Topic S7B: Note for Guidance on Safety Pharmacology Studies for assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. However, different regional requirements still exist with regard to non-clinical studies to support the first dose to humans.

2. SCOPE

This Position Paper defines common standards of the non-clinical safety studies needed to support human clinical trials of a single dose of a pharmacologically active compound using microdose techniques.

In the current context, the term "microdose" is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained in vitro and in vivo (typically doses in, or below, the low microgram range) and at a maximum dose of ≤ 100 microgram. An example of such a clinical trial is the early characterisation of a substance's pharmacokinetic- / distribution properties or receptor selectivity profile using positron emission tomography (PET) imaging[1], accelerator mass spectrometry (AMS) or other very sensitive analytical techniques.

The clinical trials covered by this Position Paper will be exploratory in nature (pre - phase I) and may be conducted with a single test substance or with a number of closely related pharmaceutical candidates to choose the preferred candidate or formulation for further development. In any case the total amount of test compound(s) administered should not exceed 100 micrograms.

The non-clinical safety testing should be sufficient to assess the safety of clinical trial participants and patients in line with the requirements outlined in the Helsinki Declaration. However, the extent of required studies should be proportionate to the nature and scope of the clinical trial. Therefore the CPMP proposes that certain deviations from the existing CPMP/ICH notes for guidance to support pre-phase I clinical trials may be scientifically justified.

3. OVERVIEW OF EXISTING GUIDANCE FOR NON-CLINICAL SAFETY STUDIES TO SUPPORT SAFETY IN FIRST HUMAN CLINICAL TRIALS OF NEW PHARMACEUTICAL CANDIDATES

Non-clinical studies to support human clinical trials have been harmonised (see Introduction); regional differences still exist regarding non-clinical testing to support the first dose to humans. In the European Union, repeated dose toxicity studies in two species (one non-rodent) for a minimum duration of 2 weeks are required to support a single, first human dose. However, in the United States of America, single dose acute toxicity studies are in some cases considered sufficient to support a single dose human clinical trial.

[1] In the context of Positron emission tomography (PET) using an isotope labelled ligand, if the study requires the measurement of both total and displaceable binding, the "single dose" may be divided into two separate infusions given within the estimated (chemical) half-life of the labelled ligand.

In 1996, the FDA published a notice on single dose acute toxicity studies for pharmaceuticals that would allow for the use of single-dose toxicity studies to support single dose studies in humans.

ICH M3 includes a requirement for safety pharmacology studies, which is detailed further in the ICH S7A guideline and guidance on the assessment of QT interval prolongation by non-cardiovascular medicinal products is given in the ICH S7B guideline.

For biotechnology-derived medicinal products, the safety assessment should be considered on a case-by-case basis, which would also apply to single microdose human clinical trials. Guidance is given in ICH Topic S6.

For anticancer medicinal products, guidance for non-clinical evaluation before first human dose is given in the CPMP Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products.

4. RECOMMENDATIONS

4.1 Extended Single-Dose Toxicity Study and Other Effects on Vital Organ Function

The ICH M3 recommendation is for safety pharmacology, single dose toxicity studies and repeated dose toxicity studies. This set of studies may be replaced by an extended single-dose toxicity study in only one mammalian species if the choice of species could be justified based on comparative in vitro metabolism data and by comparative data on in vitro primary pharmacodynamics / biological activity.

The extended single-dose toxicity study should include a control group, and a sufficient number of treatment groups to allow the establishment of the dose inducing a minimal toxic effect. For compounds with low toxicity a limit dose approach could be used. Allometric scaling from animal species to man[2] and using a safety factor of 1000 should be used to set the limit dose. If a toxic effect is observed at the limit dose, the non-toxic dose level should be established.

The number of animals should be sufficient to ensure reliable interpretation of the study results. The use of both genders should be considered. The extended single-dose toxicity study should be designed to obtain the maximum amount of information from the smallest number of animals. Two routes of administration should generally be used, the intravenous as well as the intended clinical route, which would also allow assessment of local tolerance. When intravenous dosing is the route of administration in humans, this route alone in animal testing would generally be sufficient.

The study period should be 14 days and include an interim sacrifice on Day 2 (day of dosing defined as Day 1). All mortalities should be recorded. Time of onset, duration, and reversibility of toxicity and clinical observations should be recorded. Gross necropsy should be performed on all animals, including those sacrificed moribund, found dead, or terminated at Days 2 and 14. .

The extended single-dose toxicity study should be designed to obtain information on haematology and clinical chemistry at a minimum of two time points (Days 2 and 14) and histopathology.

Information should also be obtained on any other organ system where the test substance localises and e.g., those organ systems intended to be visualised by imaging agents.

In addition, all available background information on the test substance and/or close pharmaceuticals as well as on the therapeutic class with respect to vital organ function and

[2] See CPMP/ICH/283/95 for factors in allometric scaling

other safety parameters obtained in drug screening should be provided. Examples of such data are receptor screening profiles, activity at HERG and other ion channels, effect on action potentials, behavioural screens etc.

4.2 Genotoxicity Studies

In vitro genotoxicity studies should be performed as recommended in relevant ICH guidance.

However, if a test substance belongs to a well-known chemical class for which genotoxicity data are available on other class representatives, performance of abridged/reduced versions of mutation test in bacteria (Ames test) and chromosome aberration, mouse lymphoma or in vitro micronucleus tests may be sufficient. If abridged/reduced versions of genotoxicity tests are used, data demonstrating that the modification is scientifically justified and provides valid data should be provided. If an equivocal or positive finding is obtained, additional testing should be performed.

4.3 Local Tolerance Studies

Local tolerance studies may not be needed when the clinical route of administration is used in the extended single-dose toxicity study.

5. FINAL REMARKS

With respect to radiopharmaceuticals, the corresponding stable isotope test substance should be used for both the extended single-dose toxicity study and the genotoxicity studies.

Before entry into man, adequate information should be available on the primary pharmacodynamics of each test substance in the screening programme, e.g., when a number of structural analogues are included in the screening programme.

A sponsor should always ensure that an appropriate safety assessment is performed before entry into humans. If toxicity is observed, this may need to be clarified by additional investigations before entry into humans. Margins of safety and type of toxicity observed should be assessed.

All non-clinical safety studies should be conducted in accordance with the principles of Good Laboratory Practice (GLP).

The reduced/abbreviated testing (as compared to the ICH guidance M3, S7Aand S7B) outlined above is not sufficient to support clinical trial situations with escalating dose regimes or higher doses / exposures than indicated above. Guidance for such trials is found in the ICH M3, S7A and S7B.

The non-clinical safety assessment of biotechnology-derived products should be considered on a case-by-case basis as outlined in ICH Topic S6. Guidance for non-clinical testing of anti-cancer medicinal products is given in the CPMP Note for Guidance on the Pre-clinical Evaluation of Anti-cancer Medicinal Products. The extended single-dose toxicity study approach and the recommendation for genotoxicity studies given in this Position Paper may not be relevant for these product categories.