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Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

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Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

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Executive summary

This is the first revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'.

The revision is intended to further assist sponsors in the transition from non-clinical to early clinical development and identifies factors influencing risk for new investigational medicinal products (IMPs). The document includes considerations on quality aspects, non-clinical and clinical testing strategies and designs for first-in-human (FIH) clinical trials (CTs) and early phase CTs (see section 2). Strategies for mitigating and managing risks are given, including principles on the calculation of the starting dose to be used in humans, the subsequent dose escalation, the criteria for maximum dose and the conduct of the CT including the conduct of multiple parts.

1. Introduction (background)

Traditionally FIH CTs were most associated with a single ascending dose (SAD) design, which were subsequently followed by a multiple ascending dose (MAD) CT. Since then, integration of the non-clinical data available before FIH administration and the pharmacokinetic (PK), pharmacodynamic (PD) and human safety data emerging during a trial has evolved. Consequently, the increasing practice is to perform FIH trials and early phase CTs with integrated protocols that combine a number of different study parts (e.g. SAD, MAD and food effects).

In FIH/early CTs subjects are not expected to derive therapeutic benefit, except in certain patient populations. The aim should always be the safety and well-being of the trial subjects, whether patients or healthy individuals.

Quality aspects of the IMP should not, in themselves, be a source of risk for CTs. Nevertheless, special consideration should be given to certain factors which may add to the risk as described in this guideline.

The non-clinical testing and experimental approaches for FIH/early CTs are used to identify factors influencing the risks associated with an IMP.

Special attention should be given to the estimation of the initial dose to be used in humans and to the subsequent dose escalations to a predefined maximum dose. It should be noted that the expected exposure in humans at a dose to be given, in comparison to the exposure at which certain effects were observed in animals or earlier in the study in humans, is considered important. Therefore, whenever dose is mentioned in this guideline, the expected exposure at that dose should always be taken into consideration.

In defining an appropriate development programme for an IMP, information on safety needs to be integrated from many sources and reviewed in an iterative process. Strategies for development of a new medicine and the experimental approaches used to assemble information relevant to the safety of CTs should always be science-based, and decisions should be made and justified on a case-by-case basis. In those cases where an integrated protocol is used in a FIH CT, it is important to remember that data generated during the trial should also be used to inform the decision processes for the continuation of dosing.

2. Scope

This guideline covers non-clinical and quality issues for consideration prior to the first administration in humans and the design and conduct of CTs that generate first knowledge in humans during the early clinical development. The early phase CTs include, in this guideline, those which generate initial knowledge in humans on tolerability, safety, PK and PD after SAD or MAD. These trials may also include collection of data on food interaction, in different age groups as well as early proof of concept (PoC) or early proof of principle (PoP) parts and bioequivalence of different formulations. These trials are often undertaken in healthy volunteers but can, in certain situations, also include patients.

The current revision concerns the extension of the existing EU guidance to address FIH and early phase CTs with integrated protocols, and recommendations regarding the non-clinical and emerging clinical PK, PD and safety data to support them.

The guideline applies to all new chemical and biological IMPs. While many of the scientific principles included in this guideline apply to advanced therapy investigational medicinal products as well, these products are not included in the scope of this guideline.

3. Legal basis

This guideline applies to relevant Clinical Trial Applications (CTAs) submitted in accordance with Directive 2001/20/EC, which will be repealed by Regulation (EU) No 536/2014. The guideline 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, in particular:

- EudraLex - Volume 10 - Clinical trials guidelines.
- EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines. In particular, Annex 13: Manufacture of Investigational Medicinal Products.
- Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/2005-corr.).
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004).
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (CHMP//BWP/534898/2008).
- Clinical investigation of medicinal products in the paediatric population (ICH E11).
- Evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev.4).
- Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (ICH M3(R2)) and related Q&A document.
- Note for guidance on toxicokinetics: the assessment of systemic exposure in toxicity studies - questions and answers (ICH S3A).
- Pharmacokinetics: Guidance for repeated dose tissue distribution studies (ICH S3B).
- Preclinical safety evaluation of biotechnology-derived pharmaceuticals (ICH S6(R1)).
- Non-clinical evaluation for anticancer pharmaceuticals (ICH S9) and related Q&A document.

- Guideline for good clinical practice (ICH E6(R2)). November 2016.
- Questions and Answers by the CTFG on clinical trials. Head of Medicines Agencies' Clinical trial facilitation group. January 2012.
- Safety pharmacology studies for human pharmaceuticals (ICH S7A).
- Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (ICH S7B).
- Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes.

4. General considerations

When planning FIH/early CTs, sponsors and investigators should identify the potential factors of risk and apply appropriate risk mitigation strategies. These factors should be addressed appropriately for all FIH/early CTs in the sponsor's CTA.

Factors of risk may be derived from particular knowledge or lack thereof regarding the mode of action, the nature of the target, the relevance of animal models and/or findings in non-clinical safety studies.

4.1. Mode of action

While a novel mode of action might not necessarily add to the risk per se, consideration should be given to the novelty and extent of knowledge of the supposed mode of action, as well as the characteristics of the target. This includes the nature and intensity of the effect (e.g. extent, amplification, duration, (ir)reversibility) and other mechanistic effects of the IMP on the intended target(s) and potential off-targets. The type and steepness of the dose response relationship as measured in experimental systems, which may be linear within the dose range of interest, or non-linear (e.g. plateau with a maximum effect, over-proportional increase, U-shaped, bell-shaped, time dependent), are of particular importance.

For example, the following aspects might require special attention:

- A mode of action that involves a target that is associated to multiple signalling pathways (target with pleiotropic effects), e.g. leading to various physiological effects, or targets that are ubiquitously expressed, as often seen in the immune or nervous system.
- A biological cascade or cytokine release including those leading to an amplification of an effect that might not be sufficiently controlled by a physiologic feedback mechanism (e.g. in the immune system or blood coagulation system).
- A mode of action that involves irreversible or long lasting binding to the primary target, either due to pharmacological action or the PK profile of the compound. For instance, if the duration of the pharmacological activity is linked to regeneration of the receptor, rather than being related to the PK profile of the molecule.

When analysing risk factors associated with the mode of action, aspects to be considered may include:

- Previous exposure of humans to compounds that have similar or related modes of action.

- The usefulness of PD data following repeated dosing testing. While single dose PD data can be used for an initial interpretation of the potential outcome of multiple dosing, consideration should be given to conducting repeated dose pharmacology studies or to include PD endpoints in repeated dose toxicity studies.
- Evidence from animal models (e.g. knock-out, transgenic or humanised animals) for the potential risk of serious pharmacologically-mediated toxicity.
- Novelty of the molecular structure of the active substance(s), for example a new type of engineered structural format, such as those with enhanced receptor interaction as compared to previously characterised compound(s).

4.2. Nature of the target

Beyond the mode of action, the nature of the target itself might impact on the potential risk inherent to the initial administrations to humans. Sponsors should carefully review and discuss any potential risks associated with the intended target in humans, which should include the following aspects, based on the available data:

- The extent of the available knowledge on the structure, tissue distribution (including expression in/on cells of the human immune system), cell specificity, disease specificity, regulation, level of expression, and biological function of the human target including “down- stream” effects, and how it might vary between individuals in different populations of healthy subjects and patients. If such data are limited, this should be highlighted.
- If possible, a description of polymorphisms of the target in relevant animal species and humans, and the impact of any such polymorphisms on the pharmacological effects of the medicinal product.
- Potential off-target effects, with particular focus on, but not limited to, targets closely related/similar to the intended one.

4.3. Relevance of animal species and models

The sponsor should discuss the relevance of the non-clinical models to humans taking into account the target, its structural homology, distribution, signal transduction pathways and the nature of pharmacological effects (See section 6.1).

4.4. Findings in non-clinical safety studies

The findings in non-clinical safety studies that are considered to be relevant to humans should carefully be considered when designing FIH/early CTs (See section 6.5).

5. Quality aspects

The requirements regarding physico-chemical characterisation are the same for all IMPs with additional biological characterisation of biological products.

Specific areas to be addressed include determination of strength and potency, qualification of the material used and reliability of very small doses.

5.1. Determination of strength and potency

To determine a safe starting dose, the methods used for determination of the strength and/or the potency of the product need to be relevant, reliable and qualified. As major clinical decisions are based on the non-clinical data, it is important to have a representative defined reference material early in the development programme to appropriately measure biological activity.

5.2. Qualification of the material used

The material used in non-clinical studies should be representative of the material to be used for FIH/early CT administration. It is important to have an adequate level of quality characterisation even at this early point of development. A characterisation of the product including its heterogeneity, degradation profile and process-related impurities should be performed. Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and drug product.

5.3. Reliability of very small doses

Applicants should demonstrate that the intended formulation of the doses is suitable. There is a risk of reduced accuracy in cases where the medicinal product needs to be diluted, to prepare very small doses, or the product is provided at very low concentrations as the product could be adsorbed to the wall of the container or infusion system. The compatibility of the product with primary packaging materials and administration systems should be discussed.

6. Non-clinical aspects

The quality of documents supporting the CT application should be state-of-the-art in format (e.g. as per Good Clinical Practice (GCP)) and scientific content thus providing adequate information on the performed non-clinical studies to allow for a meaningful assessment. The inclusion of a tabulated summary containing an overview of all relevant non-clinical data is encouraged.

The sponsor should confirm that all pivotal non-clinical safety studies in support of the CT application are conducted in compliance with Good Laboratory Practice (GLP). All other studies (e.g. PK and PD) should be of high quality and consistent with the principles of GLP.

In accordance with the 3Rs principles on animal use (Directive 2010/63/EU), a scientifically satisfactory method or testing strategy, not entailing the use of live animals should be used wherever possible. The use of in vitro studies, including studies using human material, is encouraged whenever possible.

6.1. Demonstration of relevance of the animal model

The search for a relevant animal model should be documented and the model selected should be justified in the Investigator's Brochure (IB).

The demonstration of relevance of the animal model(s) may include comparison with humans of:

- target expression, distribution and primary structure. However, a high degree of homology does not necessarily imply comparable effects;
- pharmacodynamics;

- metabolism and other PK aspects;
- tissue cross-reactivity studies using human and animal tissues (e.g. monoclonal antibodies).

Animal models of disease that are thought to be similar to the human disease may provide further insight into pharmacological action and PK (e.g. disease-related expression of the target) as well as dosing in patients and safety (e.g. evaluation of undesirable promotion of disease progression). Therefore, in certain cases, studies performed in animal models of disease may be used as an acceptable alternative to toxicity studies in normal animals. The scientific justification for the use of these animal models of disease to support safety should be provided.

Non-clinical studies in non-relevant species may give rise to misinterpretation and are discouraged. Where no relevant species exists, the use of homologous proteins or the use of relevant transgenic or humanised animals expressing the human target should be considered. The data gained from these models might be more informative when the interaction of the IMP with the target has similar physiological consequences to those expected in humans. The use of in vitro human cell systems could provide relevant additional information, especially for the translation of the mode of action from animal to human.

Qualitative and quantitative differences may exist in biological responses to a new IMP in animals compared to humans. For example, there might be differences in affinity of the new candidate for molecular targets, but also physiological differences in tissue distribution of the molecular target, cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or compensatory responses to an initial physiological perturbation.

Where there is evidence of species-specificity of action from in vitro studies with human cells compared with cells from a test species, the value of the in vivo response of the test species may be significantly reduced in terms of predicting the in vivo human response. It should be noted that a similar response in human and animal cells in vitro is not necessarily a guarantee that the in vivo response will be similar.

In practice this means that non-clinical studies with highly human-specific medicinal products may:

- not reproduce the intended human pharmacological effect in animals;
- give rise to misinterpretation of PK and PD results;
- not identify relevant toxic effects.

A weight-of-evidence approach should involve integration of information from in vivo, ex vivo and in vitro studies into the decision-making process.

High human-specificity of a medicinal product makes the non-clinical evaluation of the risk to humans more difficult, but does not imply that there is always an increased risk in FIH/early CTs. However, in these cases, a proper discussion of the potential risks should be given to justify the conduct of a CT.

6.2. Pharmacodynamics

Primary PD studies should address the mode of action related to therapeutic use and provide knowledge on the interaction of the IMP with the intended target as well as with related targets.

The selectivity and specificity of the IMP as well as secondary pharmacodynamics, defined as effects of the IMP on other than the desired therapeutic targets, should be critically evaluated and documented. This might also include effects on other downstream or physiologically integrated endpoints.

The primary and secondary PD should be conducted in vitro, using animal and human-derived material and in vivo using animal models, as relevant. These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes, duration and (ir)reversibility of effect, dose-response relationships and physiological turn-over of the target.

Data on the functionality of additional functional domains in animals, e.g. Fc receptor system for monoclonal antibodies, should be present.

A dose/concentration-response curve of the pharmacological effect(s) should be established with sufficient titration steps to detect significant pharmacological effects.

A state-of-the-art PK/PD modelling approach is recommended, taking into consideration repeated dose applications as to be expected in the clinical situation.

6.3. Pharmacokinetics

PK and toxicokinetic (TK) data, as per ICH S3, S6(R1), S9, M3(R2) and respective Q&A documents (if present), should be available in all species used for the non-clinical safety studies conducted and should adequately support the interpretation of data from in vivo PD models before starting FIH/early CTs. Sponsors should supply a brief summary of the analytical assays used to characterise the non-clinical PK and TK, including their accuracy, precision and limits of quantification.

Systemic exposures at pharmacodynamically active doses in the relevant animal models should be determined and considered especially when PD effects are suspected to contribute to potential safety concerns.

6.4. Safety pharmacology

Standard core battery data should be available before the first administration in humans as outlined in ICH guidelines S7A, S7B, S6(R1), S9, M3(R2) and related Q&As.

Additional studies to investigate effects in these and other organ systems should be conducted on a case-by-case basis where there is a cause for concern, e.g. in case of low selectivity of the IMP for its primary target.

6.5. Toxicology

The toxicology programme should be performed in relevant animal species (see section 6.1) and include TK as discussed in section 6.3.

When factors influencing risk are identified (see sections 4 and 6.2.), the inclusion of additional endpoints to the toxicology studies should be considered.

Toxicity can be the result of exaggerated pharmacological actions. However, these types of effects should not be ignored when establishing a safe starting dose for humans and the corresponding exposure will contribute to the determination of the dose escalation range to be investigated in humans. Primary and secondary PD can support the generation of mechanistic hypotheses regarding the toxicities seen in vivo and help in the interpretation of the human relevance of these findings.

An evaluation as to whether the target organs identified in the non-clinical studies warrant particular monitoring in the CT should be undertaken. Serious toxicity should lead to a more cautious approach

when setting doses in the FIH/early CTs. If mortalities and/or serious toxicity are observed in non-clinical studies, an evaluation of putative mechanism of toxicity and/or cause of death is expected to be addressed (e.g. consideration of histopathological examination of deceased animals, which is certainly necessary in pivotal studies and should also be considered for dose range finding studies).

7. Dosing selection for FIH and early clinical trials

7.1. General aspects

Careful dosing selection of an IMP is a vital element to safeguard the subjects participating in FIH and early CTs. Dose selection should also take into account a reasonably rapid attainment of the trial objectives (e.g. assessment of tolerability, PD or PK profile) without exposing large numbers of subjects.

All available non-clinical information (PD, PK, TK and toxicological profiles, dose or exposure/effect relationships, etc.) should be taken into consideration for the calculation of the starting dose, dose escalation steps and maximum dose. Furthermore, clinical data (e.g. PK, PD and reports of adverse events) emerging during the trial from previous dosed cohorts/individuals needs to be taken into account, in line with pre-specified decision criteria. Experience, both non-clinical and clinical, with molecules having a similar mode of action can also be useful.

The starting dose and estimated exposure levels chosen for all cohorts and study parts should be pre-specified and a justification for these steps should be outlined in the study protocol. Submission of a substantial amendment(s) can be used, if required, to adjust the predefined dosing selection, depending on data emerging during the CT. Substantial amendments will also be needed where dose escalation has reached a pre-defined maximum exposure and the absence of clinical effects leads to a conclusion that further careful escalation is warranted.

The methods used and calculations on how doses and estimated exposure levels were determined, including methods for modelling (e.g. PK/PD and physiologically-based pharmacokinetic (PBPK)) should be included in the IB and summarised in the protocol.

For starting and maximum doses for Exploratory Clinical Trials, reference is made to ICH M3(R2). If an IMP has been administered to humans under the paradigm of microdose trials, as outlined in ICH M3(R2), any subsequent study using a non-microdose should be considered within the scope of this guideline.

7.2. Starting dose

In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed. The exposures achieved at the NOAEL in the most relevant and sensitive animal species used should then be used for estimation of an equivalent exposure for humans. Estimation should be based on state-of-the-art modelling (e.g. PK/PD and PBPK) and/or using allometric factors.

Exposure showing PD effects in the non-clinical pharmacology studies, including ex vivo and in vitro studies in human tissues if feasible, should also be determined and these data should be used to determine the minimal anticipated biological effect level (MABEL) in humans and an estimation of the pharmacologically active dose (PAD) and/or anticipated therapeutic dose range (ATD) in humans. When using these approaches, potential differences in sensitivity for the mode of action of the IMP between humans and animals need to be taken into consideration. In addition, the calculation of the

MABEL, PAD and/or ATD should consider target binding and receptor occupancy studies in vitro in target cells from human and the relevant animal species and exposures at pharmacological doses in the relevant animal species. Whenever possible, all relevant data should be integrated in a suitable modelling approach for the determination of the MABEL, PAD and/or ATD.

In order to further limit the potential for adverse reactions in humans, a safety factor(s) is generally applied in the calculation of the starting dose in humans.

Safety factors should take into account potential risks related to the novelty of the active substance, its pharmacodynamic characteristics, including irreversible or long lasting findings and the shape of the dose-response curve, the relevance of the animal models used for safety testing, uncertainties related to the estimation of the MABEL, and the expected exposure in humans. Furthermore, findings in the non-clinical studies and how well potential target organ effects can be monitored in the CT should also be addressed and may influence the safety factors used.

Any safety factors used should be justified and detailed in the IB and protocol.

When the methods of calculation (e.g. NOAEL and MABEL) give different estimations of the starting dose for humans, the lowest value should be used, unless justified. Such a justification should be included in the IB and CT protocol.

In healthy volunteers, the starting dose should ideally result in an exposure to a subject that is below that which would be expected to produce a PD response.

7.3. Dose escalation

Dose increases at any time during a CT should always be justified and outlined in the protocol (see section 8.2.9). The choice of the subsequent dose levels should include some estimate of the potential PD effects and exposure levels to be achieved as well as adverse effects seen (if any). The calculated PAD/ATD should also be taken into account. The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in non-clinical studies and by emerging clinical data. The steeper the increase in the dose/toxicity or dose/effect curves, or if there are uncertainties in the estimations of these relationships, the lower the dose increment should be selected. Another factor for consideration is the reliability with which potential adverse effects can be monitored in humans before they escalate into something serious/irreversible. Furthermore, if there is evidence of non-linear PK, smaller dose increments, particularly in the later parts of SAD/MAD, should be considered. If emerging clinical data reveal significant differences from non-clinical or modelling and simulation data, a substantial amendment may be required to adjust planned dose levels unless this possibility was discussed including predefined decision criteria and approved in the protocol.

Any dose skipping should take aspects such as steepness of dose-response curve or saturation of target into account and requires a substantial amendment.

7.4. Maximum dose and dose range

The design of FIH or early CTs often aims to determine a dose or exposure-response curve for the most relevant pharmacological effect(s), and includes a maximum predefined dose or exposure margin. Deviations from this principle should be justified and may lead to more cautious approaches.

A maximum dose or exposure, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined and justified in the protocol for the full CT and/or each

study part. This justification should be based on all available non-clinical and clinical data, including PD, PK, findings in toxicity studies and exposure at the expected therapeutic dose range. In addition, if non-clinical data or modelling data indicate a plateauing of exposure, this should be taken into account for the defined maximum dose, regardless as to whether increasing of doses is viewed as a safety concern.

For integrated protocols, where it may not be possible to predefine definite doses in all study parts, a clear statement should be included that the doses will be chosen based on predefined (dose selection) criteria. These criteria should integrate data from previous study parts once these are completed and should not exceed the maximum exposure unless justified by the sponsor when requesting a substantial amendment (see also stopping criteria in section 8.2.10).

If an absolute maximum dose cannot be provided, then this should be justified and the maximum fold-increase in dose from one cohort to the next should be clearly stated as well as a maximum number of cohorts to be evaluated. A maximum exposure limit would be expected in this situation.

In general, the exposure at the expected human therapeutic dose range should not be exceeded in studies in healthy volunteers, unless scientifically justified.

Target saturation should be taken into account, e.g. if the intended therapeutic effect is linked to enzyme inhibition, then the maximum dose should consider when complete inhibition is achieved and no further therapeutic effect is to be expected by increasing the dose.

For trials or trial parts that include patients, the maximum tolerated dose (MTD) (if applicable) should be clearly defined and not be exceeded once it has been determined. The potential therapeutic/clinically relevant dose (exposure) and the expected benefit/risk balance should always be considered when defining the dose range. A trial design using a MTD approach is considered to be unethical for healthy volunteers.

7.5. Moving from single to multiple dosing

The selection of an appropriate dosing interval and duration of dosing for all multiple dosing cohorts and study parts should take into account the specific PK and PD characteristics of the IMP, the available non-clinical safety data, and human PK, PD and safety data from subjects in previous single dose cohorts. Particular attention should be paid to linear versus non-linear PK in the expected concentration range, the PK half-life versus duration of action and the potential for accumulation.

Cohorts administered multiple doses can explore different dosing regimens and allow for flexibility in the dosing schedule, such as a move from once daily dosing to twice daily dosing. However, previous MTD doses (and corresponding exposure and/or effects) should not be exceeded and a maximum duration of dosing should be stated in the protocol for every cohort. The chosen dose, as well as expected exposure after multiple dosing (C_{max} and AUC_{0-t}), should have been covered during preceding SAD parts/trials. If, however, emerging clinical data following multiple dosing suggests tolerance to adverse effects seen in a SAD part of a study, a substantial amendment to the protocol to cover higher doses in a MAD part can be considered.

7.6. Route of administration

The choice of route of administration for dosing in humans should be justified based on the non-clinical data.

In the case of an intravenous administration, a slow infusion may be more appropriate than a slow bolus. This would allow for a timely discontinuation of the infusion to mitigate an adverse outcome.

7.7. Patients

Similar considerations for the starting dose as outlined in section 7.2 apply. The goal of selecting the starting dose for FIH/early CTs in patients, i.e. where there are no previous data in healthy volunteers, is to identify a dose that is expected to have a minimal pharmacological effect and is reasonably safe to use. The starting dose should also take into account the nature of disease under investigation and the severity of the disease in the patient population included in the CT. In some instances, a starting dose that is substantially lower than the human expected therapeutic dose may not be appropriate. If a higher dose is proposed, a rationale should be provided and the subjects included in the CT should be informed.

When moving from healthy volunteers to patients, consideration should be given to reverting to a single dose design (with dose escalation as appropriate) in the first patient cohort.

Other approaches may also be considered in specific situations, e.g. for studies with conventional cytotoxic IMPs in oncology patients (see ICH S9). In general, the highest dose or exposure tested in the non-clinical studies may not limit the dose-escalation or highest dose investigated in a CT in patients with advanced cancer and also in other life limiting diseases if appropriately justified.

Furthermore, some special populations, such as the paediatric population, may deserve additional specific considerations (as per ICH E11).

8. Planning and conduct of FIH and early clinical trials

8.1. General aspects

The overall study design should be scientifically justified and careful consideration should be given to the inclusion of each study part considering the data each will provide and the time available for integrated assessment. Safety should not be compromised in the interests of speed of acquiring data or for logistical reasons.

Risk mitigation activities should be proportionate to the potential risks identified. Key aspects of the trials should be designed to mitigate identified risk factors, including but not limited to:

- study population (see section 8.2.3);
- first/starting dose, maximum dose and maximal duration of the treatment;
- route and rate/frequency of administration;
- the half-life (PK/PD) of the IMP if the same subjects are participating in multiple cohorts;
- number of subjects per dose increment (cohort);
- sequence and interval between dosing of subjects within the same cohort;
- dose escalation increments;
- transition to next dose cohort or next study (part);
- stopping rules;

- trial sites (see section 8.4).

It is recognised that placebo is often included as part of the design of FIH/early CTs.

It is recommended that a PD measure is included, when appropriate and feasible, in order to facilitate the link with the non-clinical experience and support dose escalation decisions.

8.2. Protocol

8.2.1. Overall design

The protocol should describe the strategy for managing risk including a specific plan to monitor for and manage likely AEs or adverse reactions as well as the procedures and responsibilities for modifying or stopping the trial if necessary. If there is an integrated protocol there should be a decision at a predefined time point on proceeding to the next part.

Graphical representation of the overall scheme of the proposed trial in real-time showing intervals to allow rolling review, timing of all reviews and decision points, as well as any overlap between phases or parts is encouraged.

Details on the size of the cohorts, including how many subjects are on active and how many are on placebo treatment should be included and justified.

8.2.2. Integrated protocols

The practice of conducting FIH/early CTs with integrated protocols means that the information generated in previous parts needs to be analysed and integrated into an assessment in a limited timeframe as defined in the protocol prior to making a decision on proceeding to the next part.

Within an integrated protocol all parts need to be predefined, including possible modifications, with specification on the basis of existing data and information, e.g. all non-clinical and, if available, clinical data. Any changes outside the predefined criteria should be communicated to the competent authority(ies) and ethics committee(s), as applicable. For decision making see section 8.3.

Regarding the time sequence for the conduct of different parts, the following recommendations apply:

- A certain overlap of SAD and MAD parts may be considered acceptable. However, any overlap should be scientifically justified and supported by a decision-tree and a review of the available data before deciding on starting the MAD part.
- Other single dose parts (e.g. food interaction (FI)) could be conducted in parallel to the SAD part provided the dose chosen and the expected exposure are equal to or lower than that which was reached in a concluded preceding SAD cohort where all relevant data has been reviewed and no dose escalation stopping criteria were met.
- Other study parts that involve multiple dosing (e.g. FI and drug-drug interaction) should not overlap with any earlier SAD or MAD cohorts. All relevant SAD and MAD data should be reviewed before starting these parts. Deviation from this should always be justified in the protocol.

8.2.3. Choice of subjects

The decision to conduct a study in healthy volunteers or patients should be scientifically justified. Factors to consider include:

- the known risks inherent in the type of IMP;
- the molecular target;
- any long lasting or irreversible pharmacological effect;
- any immediate and potential long term toxicity;
- the relevance of the non-clinical safety testing;
- the relative presence of the target in healthy subjects or in patients; e.g. cancer patients;
- the possible higher variability in patients;
- the potential pharmacogenomic differences between the targeted patient group and healthy subjects;
- possible interactions with subject's lifestyle, e.g. smoking, use of alcohol or drugs, excessive exercise;
- the use of other medications with the possibility for adverse reactions and/or difficulties in the interpretation of results;
- the patients' ability to benefit from other products or interventions;
- the predicted therapeutic window of the IMP;
- concomitant exposure of subjects to IMPs across trials. To alert to this, consideration may be given to trial sites participation in e.g. national initiatives to prevent over-volunteering, where available.

The key inclusion and exclusion criteria for trials involving healthy participants should also be in line with normal ranges of vital signs (including ECG) and safety laboratory values.

8.2.4. Subject assessments and interventions

The subject safety assessments that will be routinely conducted and any additional monitoring actions should be pre-specified and justified in line with the known non-clinical and pharmacological profile. There should also be routine general monitoring to detect potential unexpected adverse effects that are not related to known properties of the IMP (e.g. vital signs, ECG, respiratory signs and symptoms, clinical lab values or general neurological assessment, physical examination and interview). Repeated assessments, integrating all available pharmacological, PK, PD and toxicological knowledge, and rapid processing of this information are crucial for the recognition and interpretation of developing toxicity at an early or potentially reversible stage.

All planned assessments and interventions, for example clinical chemistry or radiological assessments, should be clearly pre-specified. The exact nature of the assessments, and their timing should be provided. Any subsequent proposal to omit an assessment should be justified, such as if a finding in non-clinical data is shown to be animal specific.

Follow-up of subjects should be specified within the protocol (e.g. for possible delayed adverse reactions). The sponsor should justify how safety monitoring should be extended for healthy volunteers until parameters return to within the normal range or to baseline. Other examples of when extended monitoring should be considered include when the mechanism entails enzyme inhibition (monitoring should continue until enzyme activity has returned back to baseline or to an acceptable percentage of

baseline) or when prolonged PD effects are observed regardless of duration of target inhibition or PK profile of the IMP.

8.2.5. General considerations for all cohorts

The number of subjects per dose increment (the cohort size) depends on the variability of both PK and PD parameters and the trial objectives such as justifying progression to the next cohort.

A maximum number of cohorts that will be dosed and the corresponding doses with the expected exposure for each cohort should be stated in the protocol.

Flexibility can be allowed for the number of cohorts to be investigated but any plan to include optional additional cohorts should be clearly pre-defined and the underlying rationale provided.

It is not acceptable to allow repetition of a dose level or cohort where that dose has met any of the dose escalation stopping rules (see section 8.2.10.). If repetition of cohorts is allowed in the protocol then only a lower or intermediate dose level would be acceptable and this should be clearly indicated.

8.2.6. Precautions to apply between treating subjects within a cohort

It is considered appropriate to design the administration of the first dose in any cohort so that a single subject receives a single dose of the active IMP. When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort.

There should be an adequate period of time between the administration of treatment to these first subjects in a cohort and the remaining subjects in the cohort to observe for any reactions and adverse events. The duration of the interval of observation should be justified and will depend on the properties of the IMP and the interpretation of the available data, including non-clinical PK and PD. Experience and identified risk factors from CTs with comparable IMPs/medicinal products should also be considered. At the end of the observation period there should be a clearly defined review of all data before allowing dosing of further subjects in the cohort, in the same manner as the precautions applied between cohorts (see section 8.2.7) and there should be dose stopping rules in place to prevent further dosing if any rule is met (see also section 8.2.10). In the event of any serious adverse reaction, further administration of the IMP to subjects should be immediately stopped, so that further subjects in the cohort are not exposed.

This approach may also be appropriate at later stages of study design, e.g. on the steep part of the dose response curve, when approaching target saturation levels or exposure margins to non-clinical NOAELs, in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not meet stopping criteria.

8.2.7. Precautions to apply between cohorts

Administration in the next cohort should not occur before participants in the previous cohort have been treated and PK data, where available, or possible AEs from those participants are reviewed in accordance with the protocol. Thus all relevant data from cohort “n” should be reviewed prior to allowing dosing of cohort “n+1”. Review of all previous cohorts’ data in a cumulative manner is preferred. Late emerging safety issues that may have occurred after the time-point for the dose escalation decision (e.g. 48h safety data for each subject set as the minimum data required but significant event(s) happening at 7 days post dose) can then be considered.

All emerging PD, PK and safety data should be critically reviewed against the pre-defined stopping criteria (see section 8.2.10), including exposure limits that are not to be exceeded. Account should be taken of any signs related to potential PD or toxicity targets identified in non-clinical studies. While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be justifiable in some cases, such as a short duration of the PD effect.

The review should include comparison of PK, PD or PK/PD data from any previous cohorts with known non-clinical data and safety information to inform the decision, as well as comparison to any initial or updated PK and/or PD modelling and simulation. The model and planned dose(s) should be adapted accordingly, if needed. In addition, the review should consider whether adaptation of the protocol in other areas is required to ensure continuing safety of trial participants, such as safety monitoring parameters and timings or length of the follow-up period. In specific situations where PK, PK/PD models are of limited value (e.g. signs of dissociation between PK and PD profiles and potential toxicities due to off-target effects at the administered human doses) dose escalation schemes and progression to further study parts need to be more cautious (e.g. consider a slower progression of the dose escalation scheme).

Unanticipated responses may require a revised dose escalation. Conversely, since the initial doses may be very low, it is anticipated that early cohorts may not show any pharmacological effects.

Time intervals between cohorts should be guided by non-clinical and clinical PK and PD data and, if appropriate, by data from comparable (investigational) medicinal products. The time interval should be stated in the protocol. Flexibility to allow for a defined longer review time in the event of emerging data could be accepted, but shortening of the review time for any dose escalation should always require a substantial amendment.

The same principles apply when detailing the review between different parts of the study.

8.2.8. Precautions to apply between study parts

In general, the same approach as between cohorts applies (see previous section 8.2.7.), including review of all previous finished study parts and cohorts data in a cumulative manner (PK, PD, safety) and including late emerging information. The actual data need to be compared to the initial simulated expectations and refined in line with available clinical information. The planned dose(s) should be adapted accordingly, if needed.

Prior to any further part following (or overlapping with) the SAD part, sufficient information should be available from completed preceding parts or/and cohorts to ensure safety of selected dose/exposure prior decision to start the part.

For studies with multiple parts, consideration may be given to submitting an interim report to the competent authorities for review as a substantial amendment prior to the start of further dosing phases.

8.2.9. Dose escalation scheme

The amount of data required in the review prior to allowing dose escalation or beginning of a new study part – in alignment with the predefined criteria in the protocol – is key and the following are regarded as minimum criteria to include in the protocol:

- 'Evaluable' subjects should be defined and it is expected that these are subjects who have completed all planned study visits.

- Data collection from all subjects in a given dosing cohort should be complete to proceed to the next dose cohort. When it is considered that not all subjects in a cohort may meet the definition of “evaluable”, the protocol should clearly define the minimum number of evaluable subjects required for review. This number should be adequate for data review and reliable decision-making.
- Subjects who have discontinued for any reason should also be considered in the relevant component of data review.

All data (e.g. safety, PK and any other available information, such as PD) for the evaluable subjects should be considered for review.

8.2.10. Stopping rules

The protocol should define unambiguous stopping rules which result in an immediate stop to dosing. It should further be specified in the rule if it implies a final end of dosing or a possible temporary halt with dosing re-starting after a full evaluation of available data and the approval of a substantial amendment. The submitted substantial amendment should include a justification of the proposed dosing for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable.

Stopping rules should be defined for each of the following:

- final stop to dosing and termination of the trial;
- stopping for an individual subject, at any time in the trial;
- stopping within a cohort
  - when allowing remaining subjects in a cohort to be dosed after the preceding subjects have completed the first dosing period;
  - during multiple dosing;
- progression to the next part of the trial;
- any dose escalation parts of the trial.

Separate criteria can be in place for each of the above, or it may be appropriate to use the same criteria for several areas of the protocol. For example, stopping rules for dose escalation could be the same as those for within a cohort or those for individual subjects. Integrated protocols should clearly outline decision points for situation where stopping rules are met.

Stopping rules for healthy volunteer trials should include:

- a ‘serious’ adverse reaction (AR) (i.e. a serious adverse event (AE) considered at least possibly related to the IMP administration) in one subject;
- ‘severe’ non-serious ARs (i.e. severe non-serious AEs considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort.

Consideration should be given to stopping criteria based on a rolling review of the data that takes account of ‘moderate’ non-serious ARs (i.e. moderate AEs at least possibly related to the IMP administration) and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other

IMPs in the same class. In patients, changes from baseline measurements should also be considered, and not just absolute criteria based on upper limits of normal that might apply for healthy volunteers.

A dose stopping criterion of the clinical exposure (C_{max} or AUC) equivalent to the exposure achieved at the NOAEL determined in the most sensitive non-clinical species, adjusted by safety factors if appropriate and based on available PK data, should be included.

Comparisons of the non-clinical and clinical exposure should be based on the maximum clinical exposure in an individual subject within a cohort and not mean (average) clinical exposure in a cohort.

Consideration should also be given to the addition of stopping rules based on toxicity seen in animals, particularly if monitoring of toxicities is feasible in the clinic, e.g. if the toxicity is reversible, or linked to the mode of action or a putative target.

Additional stopping rules should also be based on what is known about the PD of the drug (e.g. mode of action, chemical structure and others compounds in class or other classes).

8.2.11. Monitoring and communication of adverse events/reactions

All clinical staff should be trained to identify those reactions and how to respond to those or any other adverse events or reactions. Rapid access to the treatment allocation codes should be constantly available, where relevant. It is therefore imperative that in any double-blind study design there are clear instructions in the protocol for unblinding in the case of an emergency.

In cases where there is a risk of a certain type of adverse reaction occurring in humans, a treatment strategy should be described in the protocol. This should include the availability of specific antidotes where they exist and a clear plan of availability of supportive treatment emergency facilities and medical staff.

The length of the monitoring period and the nature of monitoring within, and if deemed appropriate outside, the research site should be justified.

Of high importance in the protocol is a prompt communication plan for SAEs and suspected unexpected serious adverse reactions (SUSARs) or serious safety-related protocol deviations between the sponsor, all study sites and investigators and trial subjects. It is particularly important in the case of multicentre trials to clearly define the processes for communication of safety data or rapid implementation of corrective or preventive actions between the sponsor and all study sites and investigators and trial subjects.

Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to the Member States concerned (MSC) (competent authority(ies)/ethics committee(s)), to the investigator(s) and to the EudraVigilance Clinical Trial Module.

In the case of emerging safety issues, investigators and participants (at any site) are to be informed as soon as possible, and at least prior to any planned next dosing in multiple part or sentinel design. Any SUSAR in a healthy volunteer should be also reported to the MSC without undue delay.

8.3. Documentation of sponsor and investigators responsibilities

The responsibilities of the sponsor and investigator(s) (as well as any other experts or study staff) in decision making and the timing of any decisions should be clearly defined in the protocol. Responsibility with regard to breaking the treatment code in emergency situations should also be

documented. It is also the case that unblinding in an emergency may be needed without involvement of the monitor or sponsor.

The composition of any decision making group or committee should be documented in the protocol so that their appropriateness to participate in the monitoring and decision-making can be established. Other details to include are the exact remit of the group and the roles of all members in the committee or in relation to the sponsor. The members of the group should also be sufficiently independent from IMP administration and monitoring.

8.4. Investigator site facilities and personnel

FIH/early CTs should take place in appropriate clinical facilities and be conducted by trained investigators who have acquired the necessary expertise and experience in conducting early phase trials and medical staff with appropriate level of training and previous experience of early phase trials. The training should include, as an example, relevant medical expertise and GCP training. They should also understand specific characteristics of the IMP, and of its target and mode of action.

FIH/early CTs should take place under controlled conditions (e.g. hospitalisation), with the possibility of close supervision of study subjects during and after dosing as required by the protocol. Units should have immediate access to equipment and appropriately qualified staff for resuscitating and stabilising individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of intensive care unit facilities. Procedures should be established between the clinical research unit and its nearby intensive care unit regarding the responsibilities and undertakings of each in the transfer and care of patients. All FIH/early CTs for an IMP should preferably be conducted at a single site (to gather collective experience). When different sites are involved, this should be justified.

Abbreviations

AE - Adverse event

AR - Adverse reaction

ATD - Anticipated therapeutic dose

AUC - Area under the curve

CHMP - Committee for Medicinal Products for Human Use

C_{max} - Maximum concentration

CT - Clinical trial

CTA - Clinical trial application

CTFG - Clinical Trial Facilitation Group

CTR - Clinical Trial Regulation

ECG - Electrocardiogram

FI - Food interaction

FIH - First-in-human

GCP - Good Clinical Practice

GLP - Good Laboratory Practice

IB - Investigator's Brochure

ICH - International Conference on Harmonisation

IMP - Investigational medicinal product

MABEL - Minimal anticipated biological effect level

MAD - Multiple ascending dose

MSC - Member State concerned

MTD - Maximum tolerated dose

NOAEL - No observed adverse effect level

PAD - Pharmacologically active dose

PBPK - Physiologically-based pharmacokinetic

PD - Pharmacodynamic

PK - Pharmacokinetic

PoC - Proof of concept

PoP - Proof of principle

SAD - Single ascending dose

SAE - Serious adverse event

SUSAR - Suspected unexpected serious adverse reaction

TK - Toxicokinetic