الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

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

Adopted from European Medicines Agency

Version 1.0

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Saudi Food and Drug Authority

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Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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Executive summary

This guideline has been adopted from EMA to address first-in-human (FIH) and early phase clinical trials (CTs) with integrated protocols.

The adopted version is intended to further assist stakeholders in the transition from non-clinical to early clinical development and in identifying factors influencing risk for new investigational medicinal products (IMPs). The document includes considerations on quality aspects, non-clinical and clinical testing strategies, study design and on conduct of FIH/early CTs. 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 escalations, the criteria for maximum dose and the conduct of the trial inclusive of multiple parts.

1. INTRODUCTION

The purpose of FIH trials is to evaluate an investigational medicinal product (IMP) in humans for the first time, to study the human pharmacology, tolerability and safety of the IMP and to compare how effects seen in non-clinical studies translate into humans. Traditionally FIH CTs were most associated with a single ascending dose (SAD) design, which was subsequently followed by a multiple ascending dose (MAD) CT. 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 and early phase CTs with integrated protocols that combine a number of different study parts (e.g. SAD, MAD and food effects).

The safety and well-being of trial subjects patients or healthy volunteers) should always be the priority and special consideration should be given to characterising risk and putting in place appropriate strategies to minimise risk. The guideline aims to address as far as possible the important issues that may need consideration during the process of designing a set of studies in a clinical development programme. As IMPs are widely different in their pharmacological features and intended use

different parts of the guideline may be important for some and inapplicable to others. 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 medicine and the experimental approaches used to assemble information relevant to the safety of CTs should always be science-based and decisions should be based on a rigorous interpretation of the totality of the available data.

In the context of FIH/early CTs, data generated during a trial should also be used to inform the decision processes for the continuation of dosing. In those cases where an integrated protocol is used, the data generated during the trial should also be used to inform the decision to initiate a subsequent study part (e.g. MAD or food-effect component), or to inform the selection of the doses of IMP to be evaluated for components being conducted sequentially or in overlapping fashion, respectively.

Whenever dose is mentioned in this guideline, the expected exposure at that dose should always be taken into consideration (see sections 7.2, 7.3 and 7.4).

2. Scope

This guideline covers FIH/early CTs including those which generate initial knowledge in humans on tolerability, safety, PK and PD. These trials may also include collection of data on e.g. food or drug interactions, different age groups or gender, proof of concept and relative bioavailability of different formulations. These trials are often undertaken in healthy volunteers but can also include patients.

The guideline applies to all new chemical and biological IMPs. While advanced therapy medicinal products (ATMPs) are not within this scope, some principles of this guideline are relevant on a case-by-case basis.

3. Legal basis

The SFDA Law with the Royal Decree number (6/M) dated (25/01/1428 H; 13/02/2007) and its Executive implementing Regulation number (7-7-1428) dated

(25/07/1429 H; 28/07/2008).

The Law of Ethics of Research on Living Creatures and its Implementing Regulations.

SFDA Good Clinical Practice (GCP) Guideline.

The SFDA Regulations and Requirements for Conducting Clinical Trials on Drugs Guideline.

4. General considerations

The early clinical development of human medicinal products has an intrinsic element of uncertainty in relation to both the possible benefits and risks of a novel drug candidate. Uncertainty may arise from particular knowledge, or lack thereof, regarding the mode of action of the IMP, the presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies. In addition, risks may derive from the characteristics of the population to be studied, whether healthy volunteers or patients, including potential genetic and phenotypic polymorphisms influencing PD and PK (i.e. in the intended target or in enzymes and organ functions influencing PK).

The process of designing a set of studies in a development programme is governed by the attempt to reduce this uncertainty step-by-step by gathering relevant knowledge. Sponsors and investigators should identify, a priori for each clinical study, the potential risks that might arise and apply appropriate risk mitigation strategies.

Based on the degree of uncertainty, risk mitigation strategies include:

- Ensuring adequate quality of the IMP (section 5);
- Conducting additional non-clinical testing, to obtain data of relevance for the risk assessment which may include data to support assessment of relevance of animal models, e.g. by using human-derived material (section 6);

- Applying a scientific rationale in the selection of the starting dose, for dose escalation and when defining the maximum exposure to be achieved (section 7);
- Applying appropriate risk mitigating measures in the design and conduct of FIH/early CTs (section 8).

It is the sponsor's responsibility to define the degree of uncertainty of the IMP and to provide a description of how the risk(s) associated to this will be handled within the design and conduct of the FIH/early CTs.

Specific strategies to address identified and potential risks should also be appropriately detailed for all FIH/early CTs in the sponsor's Clinical Trial Application (CTA). Of note, risks during FIH/early CTs do not only come from the IMP but also from e.g. challenge agents, or invasive study procedures. These should be considered in any assessment of risk.

The quality of documents supporting the CTA should be adequate in format and scientific content to provide appropriate information to allow for a meaningful assessment of the adequacy of the risk minimisation efforts.

5. Quality aspects

Ensuring adequate formulation of the drug candidate is an important condition to reduce uncertainty when administering to humans. The requirements regarding physico-chemical characterisation are the same for all IMPs while more extensive characterisation may be required for complex or 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 for the intended mechanism of action, reliable and qualified. As major clinical decisions are based on knowledge

derived from the non-clinical data, it is important to reduce uncertainty by having a representative defined reference material early in the development programme to appropriately measure biological activity.

5.2. Qualification of the material used

As investigational material composition and process changes may occur during development, the material used in pivotal non-clinical studies should be representative of the material to be used for FIH/early CT administration. Differences in formulations used for non-clinical studies versus humans which could impact on exposure should be considered. It is important to have an adequate level of quality characterisation even at this early point of development. The sponsor should ensure that a characterisation of the product including its heterogeneity, degradation profile, product- and process-related impurities is performed. Special consideration should be given to the suitability and qualification of methods to sufficiently characterise the active substance and finished product.

5.3. Reliability of very small doses

Applicants should demonstrate that the intended formulation is suitable to provide the intended dose. There is a risk of reduced accuracy in cases where the medicinal product needs to be diluted to prepare very small doses, or it 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, e.g. adsorption losses, with primary packaging materials and administration systems should be addressed.

6. Non-clinical aspects

The development and evaluation of a new IMP is a stepwise process involving animal and human efficacy and safety information. The non-clinical data in PD, PK and toxicology and their translation to human are important basis for planning and conduct of a FIH/early CT.

The recommendations in the Guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (ICH M3(R2)) should be followed. A tabulated summary containing an overview of all relevant non-clinical data is considered helpful in the assessment process and should be included as an appendix to the Investigator's Brochure (IB).

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 influencing the design of CTs should be of high quality and reliability.

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-derived materials, is encouraged whenever scientifically relevant and sufficiently validated. The relevance and limitations of these in vitro models should be discussed in the supporting documents.

6.1. Demonstration of relevance of the animal model

The relevance of the selected animal model should be justified in the CT application. 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;
- on- and off-target binding affinities and receptor/ligand occupancy and kinetics.

For small molecule entities, in line with ICH M3(R2), at least one species used for toxicity testing (rodent or non-rodent) should be "pharmacologically" relevant, where both the presence of the target and the relative potency of the molecule against the target in the selected animal species and the intended patient population should be considered. The species should also be chosen based on their similarity to humans

with regard to in vitro metabolic profile.

For biotechnology-derived products, and in line with ICH S6(R1), 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.

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 rationale for the use of these animal models of disease to support safety should be provided.

Qualitative and quantitative differences may exist in biological responses to an IMP in animals compared to humans, e.g.

1. differences in affinity of the new candidate for molecular targets,
2. physiological differences in tissue distribution of the molecular target,
3. cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or compensatory responses to an initial physiological perturbation.

In this context, the use of in vitro human cell systems or human-derived material could provide relevant information about these translational differences and improve the understanding of the relevance of the animal models.

High human-specificity of a medicinal product makes the non-clinical evaluation of the risk to humans more difficult in terms of degree of uncertainty. Although this does not imply that there is always an increased risk in a given FIH/early CT, an in-depth risk assessment is required. A cautious approach in the conduct and design of a CT with these products is needed.

6.2. Nature of the target

Beyond the mode of action, the nature of the target itself can impact on the potential risk inherent to the initial administrations to humans. Experimental and/or literature-data should be taken into account when defining the degree of uncertainty of the IMP. This may specifically include:

- The extent of the available knowledge of the biological function of the human target and potential "down-stream" effects. This should cover structure and regulation, tissue distribution and level of expression and disease specificity as well as species differences.
- A description of potential polymorphisms, homology and conservation of the target amongst animal species and humans, and the impact of these aspects on the intended effects of the IMP.
- Potential (off) targets closely related structurally and functionally to the intended one.

6.3. Pharmacodynamics

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

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

When defining the degree of uncertainty associated with the mode of action or effects, aspects to be considered may include:

- A mode of action that involves irreversible or long lasting binding to the primary target, due to pharmacological action or profile of the compound;
- Long lasting effects due to the PK profile of the compound;

- Previous exposure of humans to compounds that have the same, similar or related modes of action;
- PD data following repeated administration, especially when considering multiple ascending dose schedules;
- Evidence from animal models (e.g. knock-out, transgenic or humanised animals) indicative of potential serious pharmacologically-mediated toxicity.

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. 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, are of particular importance.

A PK/PD modelling approach is useful to inform clinical dose levels and schedules, taking into consideration repeated-dose applications as anticipated in the clinical setting. .

6.4. Pharmaco- and toxicokinetics

PK and toxicokinetic (TK) data, as per ICH S3, S6(R1), M3(R2) and related Q&A documents, should be available in all species used for the non-clinical safety studies conducted. These data should adequately support the interpretation of data from in vivo PD models and safety/toxicological studies 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. Possible polymorphisms e.g. in metabolic enzymes should be taken into account.

6.5. 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.

6.6. Toxicology

The toxicology programme should be designed taking the characteristics of the IMP and the relevant ICH guidelines S6(R1), S9 and M3(R2) into account.

Toxicity can be the result of exaggerated pharmacological actions. These types of effects should not be ignored when establishing a safe starting dose for humans and the exposures, at which these toxicities are observed, should be considered for the definition of the dose escalation range to be investigated in humans. Primary and secondary PD data 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 and applying risk mitigation strategies in the clinical setting. When serious toxicity or mortality is observed, these effects may require follow up studies to determine the cause of death or the mechanism of toxicity if this has not been possible to clarify within the studies undertaken, and if this information is relevant to the clinical trial design or safety monitoring plan. This is usually driven by the exposures where serious toxicity/mortality is observed. If these occur at exposures in far excess of the clinical range then cause of death or mechanism of action studies may not be necessary. Some serious toxicities are poorly translated to humans e.g. species-specific immune reactions with monoclonal antibodies. Such toxicities may be categorised as not

clinically relevant with the appropriate data and/or rationale.

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. Special attention should be given to the estimation of the exposure anticipated to be reached at the initial dose to be used in humans and to subsequent dose escalations to a predefined maximum expected exposure. 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 more relevant than the relative dose levels between animals and humans.

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 exposure. Furthermore, clinical data (e.g. PK, PD and reports of adverse events) emerging during the trial from previous dosed cohorts/individuals will also need to be taken into account (see section 8.2.7). Experience, both non-clinical and clinical, with molecules having a similar mode of action can also be useful.

The starting dose and a maximum exposure, as well as dose escalation steps during the CT, should be justified and outlined in the protocol. Decision-making criteria for adapting the planned dose escalation steps based on emerging clinical data should also be described in detail. Deviations from the prespecified dose escalation and decision-making criteria would warrant the submission of (a) substantial amendment(s). Substantial amendments will also be needed where the dose escalation has reached a pre-defined maximum exposure and an integrated analysis of available data leads to the Sponsor’s 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 protocol and may be summarised in the IB.

For starting and maximum doses (exposures) for Exploratory Clinical Trials, reference is made to the ICH M3(R2) guideline. 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 the present FIH/early CT guideline.

7.2. Starting dose for healthy volunteers

In general, the no observed adverse effect level (NOAEL) should be determined in the non-clinical safety studies performed. The NOAEL is a generally accepted benchmark for safety when derived from appropriate animal studies and can serve as the starting point for determining a reasonably safe starting dose. The exposures achieved at the NOAEL in the most relevant animal species used (which might not necessarily be the most sensitive species) should 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.

The starting dose for healthy volunteers should be a dose expected to result in an exposure lower than the PAD, unless a robust scientific rationale can be provided for a higher dose. Depending on the level of uncertainty regarding the human relevance of findings observed in nonclinical studies (see sections 4.1 to 4.4) and the knowledge of the intended target (see sections 6.1 and 6.2), the starting dose should either be related to the MABEL, PAD or NOAEL. A scientific rationale for the starting dose should be included in the protocol and may be included in the IB.
In order to further limit the potential for adverse reactions in humans, safety factors are 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;
- the characteristics of the safety findings;
- uncertainties related to the estimation of the MABEL, PAD 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. The reasoning behind the safety factors used should be detailed in the IB and protocol.

7.3. Starting Dose for patients

Similar considerations as outlined in section 7.2 apply for the identification of a safe starting dose in patients. 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 safe to use. The starting dose should also take into account the nature of disease under investigation and its severity in the patient population included in the CT. In some

instances, a starting dose that is substantially lower than the human expected pharmacological dose may not be appropriate. In all cases, a rationale should be provided and the subjects included in the CT should be informed.

If potential differences in target distribution, pharmacokinetics or safety profile of the IMP between healthy volunteers and patients can be foreseen, consideration should be given to reverting to a SAD design (with dose escalation as appropriate) in the first patient cohort.

Other approaches may also be considered in specific situations, e.g. for studies in oncology patients (see ICH S9) or other severe or life-limiting diseases. 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 or life-limiting diseases if appropriately justified.

Special populations, such as paediatrics (see ICH E11), deserve additional specific considerations.

7.4. Dose escalation

In addition to defining a starting dose and a maximum exposure (see sections 7.5 and 8.2.10), criteria for dose increases during a CT should be outlined in the protocol (see section 8.2.9). The maximum fold increase in dose/exposure from one cohort to the next, as well as a maximum number of cohorts to be evaluated, should be stated. The choice of the dose levels should include an estimate of exposure levels to be achieved, potential adverse effects (if any), and if relevant and feasible, an estimate of potential PD effects. 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 the non-clinical studies and adapted following review of emerging clinical data from previous cohorts (see sections 8.2.7 and 8.2.9). The size of the dose increments should take into account the steepness of the dose/exposure-toxicity or dose/exposure-effect curves and uncertainties in the estimation of these relationships. Another factor for consideration is the reliability with which potential

adverse effects can be monitored in humans before potential serious/irreversible effects develop. Furthermore, if there is evidence of non-linear PK potentially resulting in a supra-proportional increases in exposure, smaller dose increments, particularly in the later parts of SAD/MAD, should be considered. If emerging clinical data reveal substantial differences from non-clinical or modelling and simulation data, adjustment of the planned dose levels may be warranted. A change of the planned dose levels should take aspects such as steepness of dose-response curve or saturation of target into account. If available data indicate a plateauing of exposure, this should be taken into account when deciding on dose escalation steps (and frequency of dosing in MAD parts). Changes in dose levels may require a substantial amendment unless such changes are covered by predefined decision criteria in the protocol.

7.5. Maximum exposure and dose

An expected maximum exposure level, which should not be exceeded in the study without approval of a substantial amendment, should be pre-defined in the protocol for each study part. The maximum exposure should be justified based on all available non-clinical and clinical data, including PD, PK, findings in toxicity studies and exposure at the expected therapeutic dose range. Target saturation should be taken into account when appropriate, then the maximum exposure should consider when complete inhibition or activation of the target is achieved and no further therapeutic effect is to be expected by increasing the dose.

The use of a maximum dose can in some instances be warranted, e.g. in studies where exposure cannot be adequately measured.

In general, the maximum exposure of healthy volunteers should be within the estimated human pharmacodynamic dose range. However, exposure levels exceeding the pharmacodynamic dose range can, if scientifically justified and considered acceptable from a safety perspective, be carefully explored, taking into consideration the uncertainty as outlined in section 4.

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 inappropriate for healthy volunteers.

7.6. 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 all 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.

A maximum duration of dosing should be stated in the protocol for every cohort. The expected exposure after multiple dosing (Cmax and AUC0-tau) 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, higher exposures in a MAD part can be considered, provided this option is pre-specified and below the set maximum exposure. Multiple dosing parts can also explore different dosing regimens and schedules, such as a move from once daily dosing to twice daily dosing.

7.7. Route of administration

The choice of route of administration for dosing in humans should be based on the non-clinical data, the characteristics of the IMP, and the intended therapeutic use.

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

8. Planning and conduct of FIH and early clinical trials

8.1. General aspects

Trials should be designed in a way that optimises the knowledge to be gained from the study without exposing excessive numbers of subjects while ensuring the safety of participants. The overall study design should justify 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 degree of uncertainty and the potential risks identified. Key aspects of the design include:

- choice of study population (see section 8.2.3);
- first/starting dose, maximum dose and exposure and maximal duration of treatment (see section 7);
- route and rate/frequency of administrations;
- half-life (PK/PD), and therefore washout times, of the IMP if the same subjects are participating in multiple cohorts; or accumulation for multiple dosing parts;
- number of subjects per cohort;
- sequence and interval between dosing of subjects within the same cohort;
- dose escalation increments;
- transition to next dose increment cohort or next study part;
- stopping rules;
- safety (and/or effect) parameters to monitor and intensity of monitoring;
- trial sites (see section 8.4);
- inclusion of a placebo.

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 clinical trial protocol is a core document of a trial which is drafted as one of the first steps in any research project. The protocol should precisely describe what is being done in the trial and the rationale behind key decisions so that the trial can be subject to scrutiny in regulatory assessment.

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 and highlighting any overlap between study cohorts and parts is encouraged.

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

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 prior to making a decision on proceeding to the next part (see section 8.3).

All parts, and the criteria to move from one part to another, should be predefined within an integrated protocol, as should possible modifications, based on the totality of available information and the related uncertainty. When definite doses cannot be predefined in all study parts, (dose selection) criteria should be established in the protocol. These criteria should integrate data from previous study parts. Feasibility to review and adapt the planned study design based on emerging clinical data should also be considered.

Any changes outside these predefined criteria should be implemented via a substantial amendment.

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

- Overlap of SAD and MAD parts may be acceptable. However, any overlap should be scientifically justified and supported by decision points and a review of available data before starting the MAD part (see also section 7.6).
- Other single dose parts (e.g. food interaction) 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. drug-drug interaction) should generally not overlap with earlier SAD or MAD cohorts. All relevant SAD and MAD data should be reviewed before starting these parts. Deviation from this should be justified in the protocol.

8.2.3. Choice of subjects

Particular clinical factors to consider in the decision to conduct a study in healthy volunteers or patients include:

- whether the toxicities foreseen/risks associated can support the inclusion of healthy volunteers;
- the relative presence of the target in healthy subjects or in patients;
- the possible higher PK, PD or safety profile variability in patients;
- the potential differences between the targeted patient group and healthy subjects;
- possible interactions with subject's lifestyle, e.g. smoking, use of alcohol or drugs;
- the use of other medications with the possibility for adverse reactions and/or difficulties in the interpretation of results;
- a patient's ability to benefit from other products or interventions;
- the predicted therapeutic window of the IMP;
- factors relating to special populations, including age, gender, ethnicity and genotype(s).

The key inclusion and exclusion criteria for trials involving healthy participants should consider an adequate set of vital signs (including ECG), laboratory values and clinical assessments that should be within normal ranges. Deviations outside these ranges may be possible if justified.

8.2.4. Subject assessments and interventions

The subject safety assessments that will be routinely conducted, their timing and any additional monitoring actions or interventions (such as radiological or PD assessments) should be pre-specified in line with the known pharmacological and non-clinical safety profile and balanced against the degree of uncertainty. There should also be routine general monitoring (e.g. vital signs, ECG, respiratory signs and symptoms, clinical laboratory values or general neurological assessment, physical examination and interview) to detect potential unexpected adverse effects that are not related to known properties of the IMP. Repeated assessments, integrating available knowledge with rapid processing of emerging information, are crucial for the recognition of developing toxicity at an early stage.

The exact nature of the assessments and their timing should be provided in the study protocol. Any proposal to routinely omit an assessment should be scientifically based. Emerging clinical data may also be used to support altering the frequency or timing of assessments, either within pre-specified limits in the protocol or via a substantial amendment.

The length of follow-up of subjects should be specified within the protocol (e.g. for possible delayed adverse reactions). The sponsor should describe how safety monitoring should be extended until parameters return to within the normal range or to baseline, as appropriate for the population. Extended monitoring should also be considered, e.g. when the mechanism entails enzyme inhibition or activation (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 cohort depends on the variability of both PK and PD parameters and the trial objectives.

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 repeat a dose level where any of the dose escalation stopping rules (see section 8.2.10) has been met. 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.

Inclusion of the same subjects across multiple cohorts, for example as part of an alternate cohort dosing scheme, is possible but should be scientifically justified in the protocol. Re-enrolment into higher dose cohorts is only possible after an appropriately defined washout period and provided the subject has not met any discontinuation criteria.

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 (often known as sentinel dosing). Flexibility in this approach is allowed but should be on a risk-proportionate basis with a clear scientific rationale for any proposals not to use this strategy.

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. This approach is expected for all single and multiple dosing cohorts, in order to reduce the risks associated with exposing all subjects in a cohort simultaneously. This sentinel approach may continue or also start to 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 the maximum

clinical exposure levels defined in the protocol (see sections 7.5 and 8.2.9), in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not meet stopping criteria.

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 will depend on the PK and PD characteristics and the level of uncertainty associated with the product (see section 4). At the end of the observation period, there should be a clearly defined review of all available data for the sentinel subjects before dosing of further subjects in the cohort, with dose stopping rules in place to prevent further dosing if any rule is met (see also section 8.2.10).

8.2.7. **Precautions to apply between cohorts and study parts**

Administration to the next cohort should not occur before participants in the immediately preceding cohort have been treated and PK, PD and clinical safety data as appropriate from those participants are reviewed in accordance with the protocol. Review of all previous cohorts' data in a cumulative manner should also be taken into account. 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.

While there can be no delay for safety data, a lack of PD information or a reduced PK data set could be acceptable in some cases.

The 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, 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.

Timing between cohorts 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.

Prior to any further part following (or overlapping with) the SAD part or any other 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.

8.2.8. Data review for decision

The data supporting dose escalation or beginning of a new study part in alignment with the predefined criteria in the protocol are key and should be described in the protocol.

The timing and data specified in the protocol for the decision should reflect the uncertainty associated with the IMP, but also the population and intervention. Despite this pre-defined information, consideration should be given to a review of all data generated until the time of the decision.

The following are regarded as minimum criteria for data review:

- 'Evaluable' subjects should be defined, i.e. subjects who have completed all planned study visits at least until the time of the decision as detailed in the protocol. 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 if at least one administration (of IMP/placebo) has occurred.
- Data collection as planned in the protocol in a given dosing cohort should be complete to proceed to the next dose cohort

8.2.9. 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 the stop is a final end of dosing or a temporary halt. Restart is possible without a substantial amendment if review leads to a conclusion which is fully within predefined conditions for the relevant stopping criterion.

Any submitted substantial amendment should include a rationale for the proposed dosing and 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 subjects in a cohort are dosed staggered; − during multiple dosing;
- progression to the next part of the trial;
- any dose escalation parts of the trial.

Separate rules can be in place for each of the bullet points 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 and criteria for the situation where stopping rules are met.

Stopping rules for healthy volunteer trials should include, but not be limited to:

- a ‘serious’ adverse reaction* (i.e. a serious adverse event considered at least possibly related to the IMP administration) in one subject;
- ‘severe’ non-serious adverse reactions (i.e. severe non-serious adverse events considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system-organ-class.

Consideration should be given to stopping criteria based on a rolling review of the data that takes account of 'moderate' non-serious adverse reactions (i.e. moderate adverse events at least possibly related to the IMP administration) in blinded or unblinded fashion 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 (mechanistic and/or chemical). Changes from baseline measurements should also be considered, and not just absolute cut-offs based on upper or lower limits of normal that might apply for healthy volunteers.

A dose stopping criterion comprising a maximum clinical exposure (Cmax or AUC) should generally be included (see section 7.5). When reviewing emerging data in relation to this criterion, the maximum exposure observed in individual subjects within a cohort rather than the mean exposure should be taken into account.

8.2.10. Monitoring and communication of adverse events/reactions

The trial design should provide a specific plan for monitoring for adverse events or adverse reactions. The mode of action of the investigational medicinal product, findings in the non-clinical toxicity studies and any anticipated responses should be used to identify likely adverse 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.

Treatment strategies for potential risks/adverse reactions should be described in the protocol, as appropriate. This should include the availability of specific antidotes where they exist and a clear plan of availability of supportive treatment emergency facilities and experienced and trained medical staff.

A rationale for the length of the monitoring period and the nature of monitoring within, and if deemed appropriate outside, the research site should be provided in

the protocol.

Of high importance in the protocol is a plan for prompt communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) or serious safety-related protocol deviations between the sponsor, all study sites, investigators, trial subjects, and SFDA. 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, investigators, trial subjects, and SFDA.

Sponsors should ensure that processes are in place, before the trial starts, for expedited reporting of any SUSARs to the investigator(s), ethics committee(s), and SFDA.

In the case of emerging safety issues, for example severe or serious adverse reactions, the Sponsor should inform investigators and participants (at any site) as soon as possible, and at least prior to any planned next dosing.

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 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, where knowledge of the treatment received is needed for the immediate management of a subject, can be done at the investigators discretion without involvement of the monitor or sponsor and arrangements for this should be documented.

The composition of any decision making group or safety review committee should be documented in the protocol. Other details to include are the exact remit of the group and the roles of all members in the committee and their relation to the sponsor. Consideration should be given to the inclusion of independent experts who are (at least) external to the study. Written statements and conclusions by any decision-making or safety review group must be in place before allowing trial progression at the noted times as per protocol. This includes documentation of appropriate quality

control checks on the data reviewed.

8.4. **Investigator site facilities and personnel**

FIH/early CTs should take place in appropriate clinical facilities and be conducted by trained investigators and medical staff with appropriate levels of training and experience of early phase trials. The training should include 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. inpatient care), 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 and other hospital 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). If multiple sites must be involved, e.g. in patient studies where multiple sites are often required for enrolment, the protocol should include appropriate measures to reduce any extra risks that might arise from the use of multiple sites.

Abbreviations

ATD - Anticipated therapeutic dose

ATMP – Advanced therapy medicinal product

AUC - Area under the curve

CHMP - Committee for Medicinal Products for Human Use

Cmax - Maximum concentration

CT - Clinical trial

CTA - Clinical trial application

CTR - Clinical Trial Regulation

ECG - Electrocardiogram

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

MTD - Maximum tolerated dose

NOAEL - No observed adverse effect level

PAD - Pharmacologically active dose

PBPK - Physiologically-based pharmacokinetic

PD - Pharmacodynamic

PK - Pharmacokinetic

SAD - Single ascending dose

SFDA – Saudi Food and Drug Authority

SUSAR - Suspected unexpected serious adverse reaction

TK - Toxicokinetic