General aspects to consider for FIH/early phase I clinical trials with medicinal products

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1. Introduction

During FIHs/early phase I clinical trials an investigational medicinal product is applied in humans for the first time and initial data on tolerability, safety, pharmacokinetics (PK) and pharmacodynamics (PD) are generated. Furthermore, these trials aim to translate effects observed in a non-clinical setting into humans. Related to the intrinsic element of uncertainty of possible benefits and risks of a novel drug candidate, the trial participants (healthy volunteers or patients) are estimated to be at unforeseen risk of serious adverse events including potential emergency situations such as uncontrolled immune cascades, anaphylactic shock or even cardiac arrest. Therefore, both the, EMA[1], FDA[2]and ICH[3] have provided helpful guidance documents on how to approach FIH/early phase I clinical trials to promote safety and mitigate these risks.

With this position paper, Swissmedic and swissethics aim at highlighting several important points to consider in the management and practical conduct of FIH/early phase I trials.

[1] EMEA/CHMP/SWP/28367/07 Rev. 1 Committee for Medicinal Products for Human Use (CHMP) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, 20 July 2017

[2] FDA, Center for Drug Evaluation and Research. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers.

[3] ICH Guidelines

2. Sponsor requirements

The sponsor has to identify the risks in a clinical trial and to mitigate these risks in the design and conduct of the trial accordingly (ICH GCP E6 (R2): 5.0.2-5.0.4). The risk assessment should take into account the safety profile of the investigational medicinal product, the set-up of the trial, the population studied, the specific pharmacological dose regime and maybe further additional factors. This risk assessment should be documented.

Due to the limited safety data available, the following aspects have to be considered during the planning/set up of a FIH/early phase I clinical trial:

1. Choice of trial participants, study size and pre-defined cohorts (ICH GCP E6 (R2): 6.5.1-2, 6.6.1)

2. Adequate quality of the IMP (formulation) (ICH GCP E6 (R2): 5.13.1-2)

3. Justification and definition of the administration route, starting dose (availability of PK and toxicokinetic data relevant for the intended mechanism of action, standard core battery data, NOAEL/MABEL), maximal exposure and maximal duration of the investigational medicinal product (IMP) treatment in the protocol according to ICH M3, S3, S6, S7A-B, S9 (ICH GCP E6 (R2): 5.0.1, 5.4.1-2, 6.2.4)

4. Detailed description of dose escalation steps in the protocol (ICH GCP E6 (R2): 5.0.1, 5.4.1, 6.4.4)

5. The process of decision-making regarding the dose-escalation steps based on the data becoming available during the conduct of the trial has to be described precisely either in the protocol or a separate charter (e.g. responsibilities, if applicable: rolling review of the data, committee constitution, required quorum, quality control checks of data provided for review) (ICH GCP E6 (R2): 5.1.3, 5.3, 5.4.1; 5.5.1)

6. Clear definition of stopping criteria (ICH GCP E6 (R2): 5.0.1, 5.4.1, 6.4.6)

7. Process of ongoing safety evaluation, safety management plan i.e. monitoring of safety parameters, immediate information of investigators in case of new safety data and implementation of urgent safety measures by the sponsor if necessary (ICH GCP E6 (R2): 5.3, 5.16, 6.8.2)

8. Selection of a suitable FIH/early phase I clinical trial site by the sponsor via a quality control process (ICH GCP E6 (R2): 5.6.1)

3. Requirements related to investigator site personnel and facilities

FIH/early phase I clinical trials should be conducted by trained investigators and site staff which are experienced in conducting early phase trials. This type of trial should take place under controlled conditions and in appropriate facilities preferable in specialised phase1 units. Procedures and systems that encompass high standards for avoiding harm to trial subjects and for handling medical emergencies need to be implemented. (ICH GCP E6(R2): 5.6)

1. Training and experience
   The investigators and medical staff shall have training and experience in the conduct of early phase trials, immediate life support, the handling of medical emergencies, and GCP. They should also understand the specific characteristics of the IMP and of its target mode of action. (ICH GCP E6(R2): 2.8, 4.1.1, 4.1.2, 4.1.3, 4.2.4)

2. Supervision and resources
   FIH/early phase I clinical trials shall be conducted under standardised conditions with the possibility of close supervision of subjects as required by the protocol, e.g., inpatient care, continuous monitoring following dosing, adequate number of qualified on-site personal, on-call medical personnel. (ICH GCP E6(R2): 2.3, 2.7, 4.2.3, 4.2.5, 4.3.1)

3. Facilities and equipment
   The investigator site facility must have the necessary infrastructure and equipment to conduct the FIH/early phase I clinical trial and ensure that safety monitoring of the subject can be conducted in a controlled environment and according to the protocol, e.g., telemetry, pulse oximetry, observed areas for post-dosing.
   Investigator sites shall have immediate access to emergency medicine and equipment for stabilising and resuscitating individuals in an acute emergency, such as e.g., cardiac emergencies, anaphylaxis, convulsions. (ICH GCP E6(R2): 4.2.3, 4.11.1)

4. Emergency procedures
   The possibility to transfer subjects to a hospital with access to an intensive care unit shall be organised prior to start of the clinical trial. Procedures need to be established between the trial site and the intensive care unit regarding responsibilities and undertakings of the transfer and care of the patients, and to ensure that the treating physicians do have appropriate information about the IMP and the clinical trial.
   In case the transfer to an intensive care unit is not possible, access to the necessary emergency treatment must be ensured. (ICH GCP E6(R2): 2.13 and addendum, 4.2.6)