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February 2026
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Regulatory guidance for the writing of the Investigator´s Brochure for a clinical trial application with an Advanced Therapy Medicinal Product

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Guidance for Investigator´s Brochure requirements for clinical trial applications with an ATMP

Introduction

This guidance document is drafted by the Danish Medicines Agency and is intended as a regulatory support during the writing of the Investigator´s Brochure (IB) for the clinical trial application of an advanced Therapy Medicinal Product (ATMP) in the early phase First-In Human / Phase I.

A specific format is not mandatory. However, the content should cover the listed topics. Specific templates for cell therapy based ATMP or gene therapy based ATMP is in the preparation and will be linked to here, when available.

The format and standard text are derived from Appendix A from ICH Guideline for Good Clinical Practice ICH E6 R3. Introduced text is in [] with reference to the source.

ICH E6 R3 is intended to cover all types of medicines incl. small molecules. Therefore, not all text is relevant for ATMPs. Use the relevant sections for the ATMP description and provide a short justification for not addressing non-ATMP relevant issues.

Elements from the publicly available IB guide from ATMP Sweden (from 2020) is also included.

Reference is given to the EMA Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials.

The guideline has the focus on the requirements for the early phase, exploratory trials. The sections 5 and 6 provides guidance to the non-clinical and clinical topics that should be covered in the clinical trial application documentation´s Study Protocol and IB, with respect to the specific product type and indication.

Guidance to the content and format of the IMPD, including a Q&A, is provided on the LMST homepage regarding ATMP regulation (Direct document link here).

Template based on Appendix A. INVESTIGATOR'S BROCHURE from ICH E6 R3

A.1 Introduction

The IB is a compilation of the clinical and non-clinical data on the investigational product(s)[1] that are relevant to the study of the product(s) in human participants. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for and their compliance with many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures.

[1] For the purpose of this template, the term investigational products should be considered synonymous with the ATMP. Please see EMA homepage for optional classification (Advanced therapy classification | European Medicines Agency (EMA))

A.1.1 Development of the Investigator's Brochure

Generally, the sponsor is responsible for ensuring that an up-to-date IB is developed. In the case of an investigator-initiated trial, the sponsor-investigator should determine whether a brochure is available from the product license/marketing authorisation holder. If the investigational product is provided by the sponsor-investigator, then they should provide the necessary information to the investigator site staff. Where permitted by regulatory authorities, the current scientific information such as a basic product information brochure (e.g., summary of product characteristics package leaflet, or labelling) may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that might be of importance to the investigator. If an authorised medicinal product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared unless there is a rationale for only one IB. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's documented procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. Relevant new information may be so important that it needs to be communicated to the investigators and possibly to the institutional review boards/independent ethics committees (IRBs/IECs) and/or regulatory authorities before it is included in a revised IB.

A.1.2 Reference Safety Information and Risk-Benefit Assessment

The reference safety information (RSI) contained in the IB provides an important reference point for expedited reporting of suspected unexpected serious adverse reactions (SUSARs) in the clinical trial. This RSI should include a list of adverse reactions, including information on their frequency and nature. This list should be used for determining the expectedness of a suspected serious adverse reaction and subsequently whether reporting needs to be expedited in accordance with applicable regulatory requirements (see section 3.13.2(c)).

The IB also provides insight to support the clinical management of the participants during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician ICH E6(R3) Guideline or potential investigator to understand it and make their own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should be involved in the generation of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

A.2 General Considerations

These considerations delineate the minimum information that should be included in an IB. It is expected that the type and extent of information available will vary with the stage of development of the investigational product.

[Risk-based approach [From EMA/CAT/22473/2025]

Risk-based approach Throughout the development of an ATMP, a risk-based approach can be applied[1]. The extent of the quality, non-clinical and clinical data can be adapted having regard to the identified potential risks. In particular, the sponsor can perform at the beginning of product development an initial risk analysis based on existing knowledge on the type of investigational product and its intended use. Aspects to be taken into consideration include for example the origin of the cells, the type of vector and/or the method used for the genetic modification, the manufacturing process, the non-cellular components and the specific therapeutic use as applicable. As per European Pharmacopoeia (Ph. Eur.), the risk-based approach may also

be applied to justify alternative approaches to the quality requirements of the Ph. Eur. gene therapy monograph. The risk analysis should be updated by the applicant throughout the product life cycle as new data become available. Key points relevant to the understanding of the product development approach chosen, should be summarized in the IMPD.

In deciding on the appropriate measures to address the identified risks, the priority should be the safety of subjects enrolled in the trial. The guideline on strategies to identify and mitigate risks for First-inHuman Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/294648/2007) excludes ATMPs but its principles are nevertheless also useful in the design of first-in-human (FIH) trials with advanced therapy investigational medicinal products. The increasing regulatory expectations along with advancing clinical development are discussed in the document.

The extent of quality, non-clinical and clinical data to be included in the clinical trials submission should be commensurate with the level of risk. The application of a risk-based approach can facilitate compliance with the guidelines on good clinical practice specific to ATMPs but does not obviate the applicant's obligation to support the quality and safety of the product to enable the generation of reliable and robust data. It likewise does not replace appropriate communications with the authorities.

An immature quality development may compromise the use of the clinical trial data in the context of a future marketing authorisation application (e.g. if the product used in clinical trials has not been adequately characterised). A weak pharmaceutical quality system may also compromise the approval of the clinical trial if deficiencies are apparent from the submission that pose a risk on the safety of trial subjects and the robustness of data.

[1] Specific guidance is given in the Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to ATMPs]

[General aspects on the non-clinical documentation (From EMA/CAT/22473/2025)

The non-clinical development pathway for ATMPs is significantly different from other medicinal products. The sequential non-clinical development in which the amount of data required and the duration of dosing increase by the phase of clinical development is not generally applicable for ATMPs. Instead, in many cases, most non-clinical data may need to be available before human exposure.

In general, the non-clinical dossier should provide information on the proof-of-concept and support the estimation of the safe and biologically effective dose(s) to be used in the first-in-human clinical trials, support the feasibility of the administration route and the appropriate application procedure, identify safety concerns and target organs for potential toxicity, and identify safety parameters to be followed in the clinical trials. This guideline intends to provide recommendations for the non-clinical data requirements before first dosing in humans and to give insights into the points where potential flexibility can be applied.]

The IB should include:

A.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name and trade name(s) where legally permissible and desired by the sponsor) and the release date. It is also suggested that an edition number and a reference to the number

and date of the edition it supersedes be provided along with the cut-off date for data inclusion in the version. Where appropriate, a signature page may be included.

A.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator and other recipients to treat the IB as a confidential document for the sole information and use of the investigator/institution, investigator site staff, regulatory authorities and the IRB/IEC.

A.3 Contents of the Investigator's Brochure

The IB should contain the following sections, each with literature references (publications or reports) included at the end of each chapter, where appropriate:

A.3.1 Table of Contents

A.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting:

The scientific rationale

The target indication; describing the disease and summarize available therapies.

General properties: significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic information available.

Available non-clinical data: main conclusions on non-clinical pharmacology, pharmacokinetics and distribution in animals, safety pharmacology and toxicology.

Available data on clinical experience if available: A brief description of clinical data (from related studies, possibly hospital exemption data) focusing to clinical pharmacology, safety and efficacy.

A.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s); all active ingredients; the ATMP classification of the investigational product(s); the scientific rationale for performing research with the investigational product(s) the anticipated prophylactic, therapeutic or diagnostic indication(s). The special risks related to an ATMP, including the administration procedure, should be highlighted.

Finally, the introductory statement should provide the general approach, especially the pharmacovigilance requirements, including long term safety issues, to be followed in evaluating the investigational product.

A.3.4 Physical, Chemical and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s), and a brief summary should be given of the relevant physical, chemical and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

A.3.5 Non-clinical Studies

Introduction

For this section reference is given to Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/22473/2025). Section 5.

The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results and a discussion of the relevance of the findings to the investigated product and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

• Species tested

• Number and sex of animals in each group

• Unit dose (e.g., gene copy number, cell number)

• Dose interval

• Route of administration

• Duration of dosing

• Information on systemic distribution

• Duration of post-exposure follow-up (Reference is given to the EMA guidelines Follow-up of patients administered with gene therapy medicinal products, Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products)

• Results, including the following aspects: - Nature and frequency of pharmacological or toxic effects

- Severity or intensity of pharmacological or toxic effects

- Time to onset of effects

- Reversibility of effects

- Duration of effects

- Dose response

Tabular format/listings[/illustrations] should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans and any

(a) Non-clinical Pharmacology

[Proof-of-concept with justification for the species tested]

• [Transduction/transfection and expression, integration studies, host-on-vector influences. See EMA/CAT/22473/2025 and (EMA/CAT/80183/2014 rev.)]

(b) Pharmacokinetics and Product Metabolism in Animals

[From EMA/CAT/22473/2025:

Pharmacokinetics for investigational ATMPs depend on the type of the ATMP and include biodistribution, as well as elimination parameters (persistence and clearance).

The need for biodistribution studies is dependent on the administration route as well as the structural or physiological containment of the cells. A globally harmonised view on expectations for biodistribution analysis of GTMPs and considerations for the dose, study design, assay methodology and vector modification has been described in the ICH S12 guideline.

The risk of germline transmission and modification should also be explored before use in humans (according to the Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005) and the above-mentioned ICH S12 guideline). The extent of studies will depend on the type of investigational GTMPs and its distribution to the gonads. For more detailed information, see the ICH General principles to address the risk of inadvertent germline integration of gene vectors (EMEA/CHMP/ICH/469991/2006). See EMA/CAT/22473/2025 Section 5.4. and ICH S12 guideline on non-clinical biodistribution considerations for gene therapy products (EMA/CHMP/ICH/318372/2021).]

Shedding

Information on shedding is normally needed for the environmental risk assessment. This information can be based on human data, published data and/or a justification. Non-clinical shedding studies are not mandatory for investigational GTMPs if sufficient information on potential sources of unintended exposure is available. For novel types of investigational GTMPs for which non-clinical or clinical shedding data are not available, non-clinical shedding studies may be required before clinical trials and will inform the timing and sampling of the clinical shedding testing. See also: ICH Considerations: General Principles to Address Virus and Vector Shedding (EMEA/CHMP/ICH/449035/2009).]

(c) Toxicology

[From EMA/CAT/22473/2025:

Normally, non-clinical safety or toxicity data are needed to support clinical testing. The need for additional toxicity studies e.g. genotoxicity, tumourigenicity, reproductive and developmental toxicity, and immunotoxicity studies should be determined on a case-by-case basis taking into consideration the risks related to the nature and characteristics of the particular class of ATMPs and the intended clinical use.

The safety studies should be designed to generate clinically meaningful and relevant data to support safe use of the product in the intended clinical indication and patient population. Safety studies in nonrelevant models may be misleading and are discouraged. For toxicology studies appropriate dose level(s)6, route and methods of administration should be chosen to represent clinical use. The mode and schedule of administration shall appropriately reflect the clinical dosing. If the first-in-human trial will include repeated dosing, this should be supported by repeat-dose toxicity data unless otherwise justified (e.g. advanced cancer indication or if immunogenicity restricts repeat-dosing in animals).

The duration of follow-up should take into account the time of persistence of administered product.

Safety data can be collected in toxicology studies as well as in proof-of-concept studies conducted in the disease model(s) provided that adequate safety endpoints are included. In silico, in vitro and/or ex vivo data can be used to substitute or supplement in vivo animal data. The overall safety evaluation should take into account cell persistence and biodistribution data. In the case that animal studies are conducted, one animal species is sufficient if the model is considered predictive. However, multiple animal species or strains may be needed to cover all relevant safety aspects on a case-by-case basis. Both sexes should be included unless justified.]

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

• Single dose toxicity

• Repeated dose toxicity

• Genotoxicity

• Carcinogenicity

• Reproductive and developmental toxicity

• Local tolerance

• Other toxicity studies

[From Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CAT/22473/2025)

GLP studies

GLP It is generally expected that pivotal non-clinical safety studies are carried out in conformity with the principles of GLP. However, it is recognised that, due to the specific characteristics of ATMPs, it would not always be possible to conduct these studies in full conformity with GLP. The considerations for application of GLP for ATMPs are described in the document: Good laboratory practice (GLP) principles in relation to ATMPs (EMA, 26 January 2017).] [For further guidance on the requirements for GLP documentation, see guidance at Heads of Medicines Agencies: Clinical Trials Coordination Group (CTCG).]

Please also see section 5.6 and 5.7 from EMA/CAT/22473/2025 regarding which non-clinical data are required as a minimum before First-In-Human studies and those that can be provided at a later stage of development.

At a minimum, the following information should be available before human exposure:

− support for the proof-of-concept in a relevant non-clinical model;

− support for the use of administration route, application procedure and application devices;

− support of the selection of safe and biologically effective starting dose;

− appropriate safety data.

A.3.6 Effects in Humans

Introduction

For this section reference is given to Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials. Section 6.

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial and ongoing trials where interim results are available that may inform the safety evaluation should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from clinical trials, such as from experience during marketing.

[From EMA/CAT/22473/2025:

Distinctive features to be considered for the clinical development of ATMPs include but are not limited

to:

- complexity of product characteristics and manufacturing considerations, e.g. difficulties in the collection and handling of source material and variability of starting materials, differences between allogeneic vs. autologous origin of the cells, bidirectional traceability of the materials from donor to recipient.
- cell procurement procedures, e.g. apheresis of haematopoietic stem cells after mobilisation into the peripheral blood.
- specific pre-treatment and concomitant medication, e.g. lymphodepletion, immunosuppression.
- treatment of specific adverse events related to the mechanism of action that impact on the efficacy of the ATMP.
- limitations to extrapolate from non-clinical data: starting dose, biodistribution, immunogenicity,
- on-and off-target effects and tumourigenicity.
- uncertainty about the possible persistence of the product and immunogenicity.
- uncertainty about potential malignant transformation, genotoxicity, tumourigenicity.
- risk of virus shedding and germ line transmission.
- the need for long-term efficacy and safety follow-up, based on prolonged biological activity and/or persistence of cells.
- administration procedures/delivery to target site.

- transportation and handling requirements.]

(a) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

• Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution and elimination)

• Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form

• Population subgroups (e.g., sex, age and impaired organ function)

• Interactions (e.g., product-product interactions and effects of food)

• Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s))

(b) Safety and Efficacy

For this section reference is given to Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials. Section 6.

(c) Marketing Experience

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response that was obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions, including information on their frequency and natures for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, adverse drug reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

A.3.7 Summary of Data and Guidance

This section should provide an overall discussion of the non-clinical and clinical data and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions and of the specific tests, observations and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous clinical and non-clinical experience and on the pharmacology of the investigational product.