Guide: Investigator´s Brochure for ATMP

Introduction:

In the absence of detailed guidance or a template for the content of the Investigator´s brochure (IB) for advanced therapeutic medicinal product (ATMP) development quality, this document has been created as an authoring guide for first in human (FiH) and early clinical studies where the focus is on safety. Efficacy aspects are more predominant in later development and have not been considered to the same extent.

This document may be used as a guide. However, the content should be adjusted to the nature of the product/process. Please, remember that each ATMP is unique and the information available is different for different ATMPs. The guide is based on the EMA Guideline: Good Clinical Practice E6(R1) chapter 7. The guide should preferably be used together with the Regulatory guide. With useful links to different documents important to consider in the creation of the IB.

For ATMP, the term dose should be defined according to the target product, e.g., milligram/kilogram, cell number.

The IB is usually the document that is show cased, propriety information could be presented in the IMBD. However, the IB is the basis for the future summary of product characteristics (SmPC) and thus a well-written IB will ease the later SmPC drafting. It is recommended that the content in the IB is a summary of the results and presented as conclusions.

This guide was created by:

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Final version of this guide was reviewed by the Swedish Medical Products Agency (MPA).

Disclaimer:

The following guide are produced and designed as a support for users within the ATMP-field.
The project group aims to ensure that the guide available on the website are up to date but cannot provide any guarantees. Users themselves are therefore responsible for checking that the content is correct and current with applicable regulations.

Document History:

Version number	Date	Revision description
1.0	2019-05-09	First version
2.0	2020-05-08	Second version includes control and correction of the text

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:

Research number:

Name(s): Generic (if approved)

Trade name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE for ATMP

For some section there will be limited information for the ATMP depending on the classification of the ATMP and available data. The IB is focused on the product, pre-clinical and clinical study results, and how to use the product. Details regarding the production process are presented in the IMPD.

Edition number:

Release date:

Replaces previous edition number:

Date:

Signature(s) of the developer/company and date of the signature [if electronic signature, this is to be informed and IT-praxis to be explained, eg. as a foot note]

Confidentiality Statement

Foot note: each page is to have information in line 'Investigator's Brochure: product name, company/developer, version number, date

SUMMARY OF SIGNIFICANT CHANGES IN UPDATED INVESTIGATOR'S BROCHURE

The lay out can be as following:

Product name
Version number and date
Replacing Version (the old version number and date)

The main changes (summarized below) in this update of the Investigator's Brochure are as follows:
[a table form is favorable to list the sections for changes and to explain shortly the changes from previous version of the Investigator's Brochure]

TABLE OF CONTENTS

NB: References to:

1. Publications

2. Reports

These references should be found at the end of each chapter

Appendices (if any) *Guideline for Good Clinical Practice*

TABLES:
List tables in the IB

ABBREVIATIONS AND ACRONYMS
List the abbreviations that will be used during the document (only some examples listed below).

ATMP	*Advanced therapeutic medicinal product*
CAR-T	*Chimeric antigen receptor (T-cell)*
DP	*Drug product*
DS	*Drug substance*
FiH	*First in human*
GTMP	*Gene therapeutic medicinal product*
IB	*Investigator Brochure*
IMPD	*Investigational medicinal product dossier*
MoA	*Mode of action*
MSC	Mesenchymal stroma cells

1. Summary

A brief summary (preferably not exceeding two pages) should be given (a suggestion):

- Scientific rationale
- Composition of the drug product: Describe the drug product and the container.
- General properties: Brief description of properties (physical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, pharmacodynamic/metabolic properties and function of the product). For an ATMP, especially in the early stage only limited information may be available.
- Stability: Describe the condition and timeframe that the product is stable.
- The target indication: Describe the disease and summaries the existing therapies available.
- Available non-clinical data: main conclusions on non-clinical pharmacology, pharmacokinetics and distribution in animals, toxicology and safety pharmacology
- Available data on clinical experience: A brief description of clinical data (from related studies, possibly hospital exemption data) focusing to clinical pharmacology, safety and efficacy.

2. Introduction

A brief introductory statement should be provided that contains the generic and trade name(s), when approved), of the investigational product(s), the active ingredients, the investigational product'(s) ATMP-classification). Background information of the targeted disease(s), current therapies and justification of the unmet medical need. The scientific rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s) should be presented. An overview of the clinical development results and conclusions are to be included.

It is also necessary to include the risks associated with the administration procedure, long-term safety issues specific to ATMPs such tumorigenicity, immunogenicity/immunosuppression, and risks related to infection with vectors used in gene therapy medicinal products. A risk-based approach should be applied. Information should also be provided on the potential impact of previous, concomitant and foreseen later treatments. The effect of future therapies typical for the diagnosis or treatment of the targeted disease on the product (e.g. an immunoglobulin treatment later in life that could impact the expression of an introduced gene by antibody interaction) should be discussed. The risks of treatment failure should also be addressed, where appropriate. Finally, the introductory section should provide the general approach on especially the pharmacovigilance requirements and efficacy outcome to be followed in evaluating the investigational product.

3. Physical, chemical and pharmaceutical properties and formulation

A description should be provided of the investigational product substance(s), including the structural formula (if applicable) and a brief summary should be given of the relevant physical, chemical and pharmaceutical properties.
To permit appropriate safety measures being 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.
Any structural similarities to other known compounds should be mentioned.
Keep this section brief; details will be presented in the IMPD.

3.1. Drug substance

Give a brief description of the drug substance (DS), including description of collection procedures of the starting material, e.g. apheresis, and concomitant medication required prior to collection of cells/tissue, e.g. lymphodepleting chemotherapy, antibiotics, if applicably.
DS is defined as an active ingredient that is intended to furnish biological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of a disease or to affect the structure or any function of the human body. For instance, it could be the purified/cell sorted starting material or complete efficacious material that will furnish pharmacological activity e.g. T-cells, mesenchymal stroma cells (MSC), modified cells (i.e. CAR-T), or the mRNA-sequence.

3.1.1 Manufacturing of drug substance

Give a brief description of the manufacturing process of the drug substance.

3.2. Drug product

Give a brief description of the drug product (DP).

The DP is defined as the final product in the final presentation e.g. pre-filled syringe with MSCs or CAR-T cells in a transfer bag. The DP shall be described as the finished dosage form that contains the DS, generally, but not necessarily in association with one or more other ingredients (e.g. excipients). The DP may require reconstruction or dilution prior to administration that is to be described here (alt. to be cross-referred to an IB section). Possible advanced administration steps needed are to be described, e.g. requirement of use of medical technical devise(s), surgical/radiological expertise and equipments.

3.2.1 Manufacturing of drug product

It is applicable only when the drug product is processed before administration.

3.3. Properties

Briefly describe the physicochemical and biological properties, impurity including also the storage conditions.

3.4. Formulation

Briefly describe the final formulation and container closer system.

4. Non-clinical studies

In some instances, this information could be summarized in the IB and in more detail in the IMPD, especially when propriety information needs to be contained in the more confidential IMPD. Preferably present the information using a table with details such as number, type, sex, age of animals used, study time duration, outcome/results related to the objective of the study and including number of drop-outs and reasons). The text can refer to detailed table information and focus to discussion and justification as well as the conclusions of non-clinical study outcome.

4.1 Introduction

The primary objective of the non-clinical study program during the development of ATMP is to provide sufficient information for a proper benefit-risk assessment for the use of such products in human. This section introduces the considerations of this program in supporting clinical trials and marketing authorisations for ATMPs. Features of ATMPs which are specific to this class of medicine and which impact on the requirements for gene therapy medical products (GTMPs) include the potential in vivo effects of the transgene or other recombinant nucleic acid sequences, the vector backbone (i.e. viral, bacterial or plasmid derived sequences) and of the excipients including any carrier or support medical device employed.

For ATMP there may be limited non-clinical data. Non-clinical development should be designed using a risk-based strategy identifying suitable safety endpoints. Likewise, it may not be feasible to conduct traditional preclinical pharmacokinetic or dose finding studies; the extrapolation of a potentially safe and possibly bioactive starting clinical dose from animal data will be influenced by for example species specificity and immunogenicity.

The ability of preclinical data to guide various aspects of the design of the early-phase clinical trial should be assessed on a case by case basis. Conclusions of chosen preclinical development strategy are to be discussed and justified.

The results of all relevant non-clinical pharmacology, toxicology, pharmacokinetic and investigational product pharmacodymanic/metabolism studies should be presented. Provided information of the methodology used, the results, and include a discussion regarding the relevance of the findings to the investigated therapeutic effects, as well as the possible unfavorable and unintended effects in humans.

Tabular format/listings 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, relevance to humans and any aspects to be studied in humans. If applicable, the effective and non-toxic dose findings in the same animal species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible,

comparisons should be made in terms of blood/other body fluid compartment, e.g. distribution in the CNS and spinal fluid/tissue levels rather than on a mg/kg basis.

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

- Species tested
- Number, age and sex of animals in each group
- Unit dose (e.g. milligram/kilogram (mg/kg), cell number)
- Dose interval based on unit dose
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- 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

4.2 Animal species/model selection

It is acknowledged that animal models may not always be capable of providing reliable information on the safety of the treatment due to the problems of incompatibility between humans and animal species. In some cases, testing the medicinal product in animals may not give sufficient meaningful information about the safety profile of the product in humans.

4.3. Non-clinical pharmacology

A summary of the pharmacological aspects of the investigational product. A summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding and specificity) as well as those that assess safety (e.g. special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

4.4 Pharmacokinetics

Pharmacokinetic studies should focus on the distribution, persistence, clearance and mobilization of the ATMP and for GTMP they should also address the risk of germline transmission. Pharmacokinetic studies may be combined with non-clinical safety studies. For GTMPs, it is important to evaluate vector and virus shedding in the environmental risk assessment.

4.5 Pharmacodynamics

Pharmacodynamics studies should aim to support the claimed mode of action of the ATMP with the relevant clinical efficacy outcome measure.

4.6 Toxicology

For toxicology studies appropriate dose level(s), route and methods of administration should be chosen to represent clinical use with appropriate safety margins. A summary of the toxicological effects (including tumorgenic potential) found in relevant studies conducted in different animal species should be described under the following headings, where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

4.7 Drug interaction

As for any other medicinal products, the effects of co-medications should be investigated on a case by case basis since these can affect biological activity, i.e. clearance may be altered under an immunosuppressive co-treatment. Moreover, the ATMP may affect the liver metabolism of co-administered pharmaceuticals.

5. Clinical data

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on dose response, safety, efficacy and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than in clinical trials, such as from experience during marketing, individual named patient compassionate use and hospital exemption programs.

In the absence of clinical data from the investigational product, it is possible to referee to clinical data from 'similar' products. This is to include a description of 'similar' products, discussion on their characteristics and results to justify elements supporting the proposed data to be used in a specific aspect of the investigational product under development.

5.1 Pharmacokinetics

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

- Pharmacokinetics (including as appropriate, and absorption, plasma protein binding, but especially distribution, survival and elimination).
- Population subgroups (e.g. healthy subjects or patients with the target disease, disease stage, gender, age and impaired organ function).
- Interactions (e.g. product-product interactions).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s), extrapolation methodology when implemented).

5.2 Pharmacodynamics

A summary of information on the pharmacodynamics of the investigational product(s) should be presented. Focus is to be in the mode of action (MoA) and demonstration of association between the MoA and the claimed clinical relevant efficacy outcome, eg. protein production of a GTMP, partial or total repair of tissue engineering product, immune modulating effect of cell based medicinal product.

If available, study supporting the distribution of the DP to the targeted organ/area.

5.3 Clinical Safety

A summary of information should be provided about the product(s) safety, that were obtained from preceding trials in humans (healthy volunteers and/or patients). Information on short and long term safety issues particular to ATMPs such as infections, immunogenicity/immunosuppression and malignant transformation should be provided.

In cases where a number of clinical trials have been completed, safety should be summarized to provide a clear overview of the data and conclusions. Safety data is to include overview of adverse events, common adverse events, deaths, serious adverse events, adverse events of special interest, adverse events leading to discontinuation of study treatment and clinical trials. Safety section is to include a separate part on adverse drug reactions observed separating severe drug related adverse reactions, and presenting frequencies favorably in line with the product resume (i.e. 1/100,. 1/1000, etc). Important differences in adverse drug reaction patterns/incidences across over time and in various indications or subgroups studied should be discussed (see 6.2.1)

5.3.1 Reference safety information

Adverse drug reactions (ADRs) are to be presented from all available information, including data from the developers overall safety database, and data from ongoing clinical trials (*to be listed and possibly presented in table(s)*). Where applicable, information from other clinical studies and use in clinical praxis (*to be defined*) with the investigational product is to be considered.
All AE reports received from investigators participating in clinical trials dosing the investigational product are to be thoroughly reviewed by the developer for their severity, seriousness and causality and are to be included as ADRs with the respective seriousness and severity in Table (XX) [*the Table XX will be designed to have columns such as* MedDRA System Organ Class (SOC); Adverse Reaction; Nature; Serious (yes/no); Severity – presented in subgroups as following: life threatening/grade 4 (n, %), fatal/grade 5 (n, %), all grades (n, %), grade 3-4 (n,%); Overall Frequency – presented as a column Category –in terms as 'Very common', 'Common', etc… that are explained as a foot note to correspond 1/100, 1/1000 etc)] .

Table XX constitutes the Reference Safety Information (RSI) used for determination of 'expectedness' for single case SAE reporting to Health Authorities.

For the purpose of individual case safety reporting in clinical trials:

- Serious forms of ADRs indicated as non-serious in this table will always be considered unexpected.
- Adverse reactions with a higher severity than indicated in this table (with a "Yes") will be considered unexpected. However, fatal ADRs are always considered unexpected for reporting purposes.

5.4 Clinical Efficacy

A summary of information should be provided about the product(s) efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients).

In cases where a number of clinical trials have been completed, efficacy should be summarized to provide a clear overview of the data and conclusions.

Primary endpoint(s) used to support the claimed clinical indication is to be presented and discussed with conclusion. Secondary endpoints used are also to be presented and discussed with the supporting justification for the clinical indication. Exploratory endpoints are presented with results and conclusions with possible plans for future implementation.

Efficacy outcome data can favorably be presented in table form to list the relevant details, eg. trial population (trial design, volunteers, patients, disease stage, age, gender, numbers), dose, dose interval, administration form, evaluation time points, evaluation variables, trial duration, etc. Thus, results can be discussed and concluded in a shorter manner in the text body.

Results that support the suggested mechanism of action of the DP. It's important to present results to support the relevance of the used predefined potency assay and association of the outcome results with the clinical efficacy evaluation. It's to observe that the defined potency assay for the quality development of the investigational product is not necessary but can be the same assay as used for the evaluation of the potency/biological activity of the product in clinical trials.

5.5 Administration: Reconstitution and dosing

When the administration process is not standardized, detailed instructions for administration should be described in the protocol or in a separate document available at the site (e.g. handing instructions with their own version number and date), in which case a reference to such separate documents should be provided in the protocol (and to be clearly defined to be a part of the protocol including version number and date of the protocol). Instructions are to be presented as Appendixes to the IB.
Where appropriate, training should be provided to those involved in the process.

5.5.1 Dosing

Data on clinical dose-response studies are to be presented (favorably in table form for details) and results to be discussed to support the final dose regimen.
For ATMPs with complex dosing regimens, there should be adequate explanations for the rational to ensure an adequate level of understanding and compliance by the investigator and those involved in the clinical trial.

5.5.2. Reconstitution

When the ATMP requires reconstitution before it is administered to the subject, that should be described in the protocol. The sponsor should ensure that the detailed instructions of the reconstitution process (as validated by the manufacturer of the product during clinical trials) are transmitted to the sites where the product is going to be administered. Detailed instructions are laid down in a separate document available at the site (e.g. handing instructions), in which case reference to such separate documents should be provided in the protocol. The instruction is to include a version number and date as well as to inform which protocol version and date it belongs to). The instructions should be detailed and clear enough so as to avoid negative impacts on the quality of the product, i.e. when the reconstitution involves thawing, the rate of temperature change during thawing should be described. Instructions are to be presented as Appendixes to the IB.

Likewise, when the reconstitution requires the use of solvents and/or other materials these should be specified or, as appropriate, provided by the sponsor. When appropriate, training should be provided to those involved in the reconstitution process.

5.6 Traceability

Detailed information should be provided on the measures that should be followed to ensure traceability of the constituents contained in ATMPs (e.g. the cells, tissues, genes, medical device).

5.7 Risk benefit assessment

The risk-benefit (R/B) evaluation is to focus the investigational product's risks and benefits.

Clinical studies are expected to be adequately planned and to allow assessment of the feasibility and risks of the approach, carefully balancing the need for retrieving information with respect and protection for vulnerable patients. The foreseeable risks should be weighed against the anticipated benefit for the individual trial subject and other present and future patients (Directive 2001/20/EC).
The risk-benefit evaluation included in the IB is to focus on the IMP and thus, is different from the one in the protocol. In the trial protocol, the developer is expected to present a risk-benefit evaluation that includes elements related to IMP characteristics and mode of action, administration (especially if invasive using medical technical devices), the safety data identified during the non-clinical and clinical development, the target disease and patient population related risks including their co-morbidities, trial environment, uncertainties of long-term outcome etc. The collective risk-benefit evaluation but still focusing to IMP's characteristics and manufacturing procedure is to be in the IMPD that can refer to a clinical trial protocol but not vice versa.

5.7.1 Risk management

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 based on information from related products. There should be clear information on risk mitigation measures and pharmacovigilance requirements, such as precautions or special monitoring to be done as part of the investigational use of the product(s).

If sterility tests are not available at the administration there should be instructions on how to proceed if the product is contaminated, including instructions on how to contact the clinical trial subject if a health concern is identified.

5.8 Safe conduct of the clinical trail

Detailed information should be provided on product handling, containment and disposal, and the potential risks. For example, in case of ATMPs that contain infectious biological material, it is expected that detailed instructions for

handling and disposal are provided. For gene therapy products where there is a risk of viral shedding, adequate information on the measures to be implemented in order to address this risk should also be provided.

5.9 Marketing experience (if relevant)

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 and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or has been withdrawn from marketing/registration.

6. Summary of data and guidance for the investigator

This section should provide an overall discussion (with focus on safety) 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. The IB could be complemented with cross-references between previous sections and this one as well as vice versa, when applicable. 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.
The information could be organized in the following manner:

- Precaution for use
- Adverse events and adverse reaction in clinical studies
- Adverse events and adverse reaction that can be predicted from experience with previously approved ATMPs

7. Reference