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Non-clinical development

To help developers of gene therapy medicinal products (GTMPs) and cell-based medicinal products (CBMPs) navigate the most important regulatory requirements during the non-clinical development phase

Questions* to be answered during the non-clinical phase	**What to do** (justification required when not applicable)	**What you should know** to overcome common challenges
What are the potential risks associated with the clinical use of an ATMP?	Perform a risk based approach, including addressing any safety concerns from previous clinical studies of similar products	• Start at the beginning of non-clinical product development, update throughout product life-cycle. • **GTMP** and **CBMP**: Guideline on the risk-based approach (EMA/CAT/CPWP/686637/2011).
What is the intended patient population?	Identify specific patient eligibility criteria based on safety, pharmacokinetic and efficacy data	
What are the toxicological and safety effects?	Perform general safety and toxicity studies, including studies based on risk-based approach	• Duration of safety/toxicity observation should cover the duration of function and effect (**CBMP**) or gene expression and activity (**GTMP**) that is expected in the clinical trials. • **GTMP**: Quality, preclinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), Non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006); **CBMP**: Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006); **GTMP** and **CBMP**: Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018).
What is the therapeutic window? What should be the starting dose and dosing scheme in humans?		
What is the efficacy?	Carry out a proof of concept study	• In vitro and/or ex vivo cell/tissue based studies can be part of 'proof of concept' study, especially when there is no relevant in vivo disease model available. • **GTMP**: Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), section 5.3; **CBMP**: Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006). • **GTMP** and **CBMP**: Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018).
What is the mechanism of action?		

What are the pharmacokinetic characteristics?	Perform a pharmacokinetic study investigating, among others, distribution and persistence	• The rationale for the tissues selection for assessing biodistribution includes:
		  ▪ **GTMP**: the nature of the vector, the ability to transduce cells in other organs, location of application, risk of systemic exposure;
		  ▪ **CBMP**: depends on administration route and physical/structural containment of the cells.
		• **GTMP**: Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), section 5.4; **CBMP**: Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

	Investigate the inadvertent germline transmission	• Investigate inadvertent germline transmission in one species before starting the first-in-human study. Complete data before marketing authorisation. • **GTMP**: Guideline on non-clinical testing for inadvertent germline transmission of the gene transfer vectors (EMEA/273974/2005); ICH Considerations General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors (CHMP/ICH/469991/2006).

* These questions are based on the paper: Cohen AF, Burggraaf J, van Gerven JM, Moerland M, Groeneveld GJ. The use of biomarkers in human pharmacology (Phase I) studies. Annu Rev Pharmacol Toxicol. 2015;55:55-74. doi: 10.1146/annurev-pharmtox-011613-135918.

What you should know

Additional information applicable to all the above objectives

- Assess the relevance and suitability of animal models for each study endpoint. Take into account differences in species (structural, functional, immunological), immunocompromised animals, homologous models, in vitro assays, extrapolation to human situation. At advance stage of non-clinical development the animal should be suitable to receive the dose level to be administered in humans. Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014, section 5.2; Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials (EMA/CAT/852602/2018).
- Route and mode of administration in animal studies should mimic the clinical use. If this is not feasible in an animal model, another animal model can be used or an alternative administration route should be used in the non-clinical study. This alternative administration route should result in similar pharmacokinetic characteristics (e.g. biodistribution).
- Heterogeneous cell product: the composition of the product and the anticipated role and added value of each of the separate components should be clear.
- Pivotal non-clinical studies should use material manufactured using the clinical manufacturing process.
- Ask EMA for Scientific Advice during non-clinical development phase and/or prior to start of clinical studies.
- Analyse the dose-response relationship (not applicable to CBMPs).
- Pivotal toxicity studies are expected to be conducted under GLP. For more information check Support for advanced-therapy developers.
- In accordance with Directive 2010/63/EU, the principle of the 3Rs (Replacement, Reduction and Refinement) needs to be considered when selecting testing approaches to be used for regulatory testing of human medicinal products.
- For more information check Guidelines relevant for advanced therapy medicinal products.

Your checklist

- [ ] Perform a risk based approach
- [ ] Conduct safety and toxicity studies
- [ ] Address safety concerns from previous trials
- [ ] Conduct proof-of-concept studies
- [ ] Investigate pharmacokinetics
- [ ] Have a clear rationale for the tissues selection in the pharmacokinetics studies
- [ ] Determine intended patient population
- [ ] Assess relevance and suitability of animal model
- [ ] Use the same administration route as will be used in clinical studies
- [ ] Identify the role and added value of each of the separate components of the cell product
- [ ] Apply the same manufacturing process to the materials used in pivotal studies as will be used in clinical studies
- [ ] Ask for Scientific Advice

Regulatory support

ATMP certification: this procedure aims to identify any potential issues of quality and non-clinical data. For more information see Certification procedures for micro-, small- and medium-sized enterprises (SMEs)

ATMP classification: it is to determine if the product meets the scientific criteria ATMPs and consequently to clarify the applicable regulatory framework, development path and scientificregulatory guidance to be followed. For more information see Advance therapy classification

ITF: the innovation task force (ITF) is a multidisciplinary group that includes scientific, regulatory and legal competences. It was set up to provide a forum for early dialogue with applicants on innovative aspects in medicines development. For more information see Innovation in medicines

Orphan designation: medicines for rare disease are termed orphan medicines. Sponsors of designated orphan medicines can benefit from incentives. For more information see Orphan designation: Overview

Orphan similarity: check the Community register of orphan medicinal products to see if a similar medicinal product for the same therapeutic indication has been granted market exclusivity protection. For more information see Applying for marketing authorisation: orphan medicines

PRIME status: it allows support for the development of medicines that target an unmet medical need. For more information see PRIME: priority medicines

Scientific advice and protocol assistance: developers can be advised on the most appropriate way to generate robust evidence on a medicine's benefits and risks. During the non-clinical development phase and prior to the start of the clinical phase. For more information see Scientific advice and protocol assistance

SME status: the micro, small and medium-sized enterprise (SME) status can be used to benefit from regulatory and administrative assistance, and fee incentives. It is recommended to register as soon as possible. For more information see Supporting SMEs