# 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 clinical development phase

| **Questions*** to be answered during the clinical phase | **What to do** (if not appropriate, justification required) | **What you should know** to overcome common challenges |
|---|---|---|
| Does the drug reach the site of action? | Investigate the feasibility of the route of administration and pharmacokinetic characteristics such as biodistribution and elimination | • Investigate pharmacokinetics such as biodistribution and persistence. **GTMP**: Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014); Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008 Rev. 1 - corr). **CBMP**: Guideline on human cell-based medicinal products (EMEA/ CHMP/410869/2006); Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009).<br>• **GTMP** and **CBMP**: standardize the administration procedure, also in case of surgical procedures. |
| Does the compound cause its intended pharmacological effects? And what are the undesired pharmacological effects? | Demonstrate the mechanism of action and off-target pharmacological effects | • **GTMP** and **CBMP**: the use of clinical endpoints relevant for the therapeutic indication and target population in pivotal trials is recommended (ICH guideline E8 General considerations on clinical trials; Reflection paper on stem cell-based medicinal products EMA/CAT/571134/2009). Other study endpoints should provide mechanistic understanding and be translatable into an effect on clinical outcome.<br>• **GTMP** and **CBMP**: secondary and/or exploratory endpoints included in a relatively short study might not be able to demonstrate significant treatment effects within this time frame. The data, however, are valuable as they strengthen the evidence at time of filing.<br>• **GTMP** and **CBMP**: in small populations, the efficacy based on the primary endpoint should be supported by the secondary endpoints. When the primary endpoint is 'reached', this does not necessarily make the study a success, if this is an isolated effect. Consistency of the effect across several endpoints is considered important.<br>• **GTMP**: factors such as promotor downregulation, toxicity caused by transgene overexpression as well as immune responses towards transgene or vector could all influence the durability of effect. In theory, even differences in transduction pattern within an organ (e.g. liver) could influence expression levels over time.<br>• **GTMP** and **CBMP**: describe how the effect of concomitant medication can be distinguished from the ATMP effect. |
| Does the compound have beneficial effects on the disease or its pathophysiology? | Investigate the effect on the disease and relevant pathophysiological systems | |
| What are the sources of variability in drug response in the target population? | Determine sources of variability in drug response (e.g. concomitant medication, disease status, prognostic factors) and if dose adjustment is required | |
| What is the therapeutic window? | Determine the starting dose of the first in human study and determine the optimal dose regimen based on all safety and efficacy data | • **GTMP** and **CBMP**: analyse the dose-response relationship and include this information in the rationale for dose selection and dosing schedule (ICH guideline E4 Dose response information to support drug registration). |
| Are there off-target pathophysiological effects? | Investigate safety and tolerability | • **GTMP** and **CBMP**: at least at the start of the study, the intra-patient interval should take into account the expected time that a safety event can develop.<br>• **GTMP** and **CBMP**: The duration of clinical follow-up observations should be sufficient to observe the subjects for risks that may be due to the characteristics of the product, the nature and extent of the exposure, and the anticipated time of occurrence of delayed adverse reactions. Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007); Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products (EMEA/149995/2008). |

* 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

- **GTMP** and **CBMP**: a small study population often requires a nonconventional study design, combination of multiple objectives in one study, and specific statistical approach. The following guidelines are recommended: Guideline on clinical trials in small populations (CHMP/EWP/83561/2005); ICH E8 General considerations for clinical studies; Points to consider on application with: (1) meta-analyses, (2) one pivotal study (CPMP/EWP/2330/99).
- **GTMP** and **CBMP**: the study population should support the therapeutic indication and/or target population of the product. Therefore, consider variation in disease stage, age, immune status etc within the study population. If the disease characteristics depend on gender and/or age, include enough patients per cohort to investigate the effect in sub-groups and investigate relevant adapted doses.
- **GTMP** and **CBMP**: usefulness of the external control group depends on the number of patients included, follow-up time, natural course of the disease, and how well the study population can be matched with respect to baseline characteristics such as age of diagnosis, genotype, disease stage, stage of affected organs and/or body systems, etc. Data of the external control group have to cover the study endpoints (ICH E10 Choice of control group in clinical trials).
- **GTMP** and **CBMP**: integrate post-authorisation studies in the development plan. Consider extension of clinical trials, separate post authorisation efficacy and/or safety studies, registries validated for this purpose, accompanied by appropriate statistical analysis plans. (Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products: EMEA/149995/2008; Guideline on follow-up of patients administered with gene therapy medicinal products: EMEA/CHMP/GTWP/60436/2007).
- Update the risk profile according to the risk based approach (Guideline on the risk-based approach: EMA/CAT/CPWP/686637/2011).
- Collect relevant data for the environmental risk assessment for **GTMP**s. The following guidelines are recommended: Guideline on scientific requirements for the environmental risk assessment of gene-therapy medicinal products (CHMP/GTWP/125491/06); Guideline on environmental risk assessments for medicinal products containing, or consisting of, genetically modified organisms (GMOs) (EMEA/CHMP/ BWP/473191/2006); Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP SWP/4447/00 corr 2).
- Other relevant guidelines: Guidelines relevant for advanced therapy medicinal products and Multidisciplinary guidelines
- Ask for Scientific Advice prior to start of clinical studies.

## Your checklist

- [ ] Apply the same manufacturing process to the materials used in clinical studies as has been used in pivotal non-clinical studies
- [ ] Route of administration should be similar in non-clinical and clinical studies
- [ ] Investigate the feasibility of the route of administration
- [ ] Standardize the administration procedure
- [ ] Demonstrate that the drug reaches the site of action
- [ ] Investigate pharmacokinetic characteristics
- [ ] Determine the optimal dose regimen
- [ ] Analyse the dose-response relationship
- [ ] Demonstrate the mechanism of action
- [ ] Investigate the off-target effects
- [ ] Demonstrate efficacy
- [ ] Investigate safety and tolerability
- [ ] Fit the study population with the therapeutic indication and target population of the product
- [ ] Include clinical endpoints relevant for the therapeutic indication and target population in pivotal trials
- [ ] Distinguish the effects of concomitant medication from the ATMP effect
- [ ] Determine sources of variability in drug response
- [ ] Update the risk profile according to the risk based approach
- [ ] Collect relevant data for the environmental risk assessment
- [ ] Integrate post-authorisation studies in the development plan
- [ ] 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