Guideline on Nonclinical Studies and Evaluation for Gene Therapy Products (GTP), China

Dr. Tian Xu

June18th, 2021

ICH regional public meeting

Expert Working Group in China

- Academia (6)

Dr. Tian Xu (Westlake University, Chair), Dr. Mingyao Liu(East China Normal University), Dr.Yan Liu (Shanghai Public Health Clinical Center), Dr. Jingsong Li (CAS) , Dr. Congjian Zhao(Central South University), Dr. Zhiwei Huang(Harbin Institute of Technology)

- Regulatory Agencies (6)

Dr. Qingli Wang (CDE), Dr. Xuan Ye (CDE, Co-Chair), Dr. Min Zhang (CDE), Mr. Chunming Rao (NIFDC), Dr. Shufeng Meng (NIFDC), Dr. Xingchao Geng(NIFDC)

- Industry (6)

Dr.Liqun Wang(Fosun Pharma), Dr.Zonghai Li (CARsgen Therapeutics), Dr.Yiping Li (JW Therapeutics), Dr. Kailiang Sun(GeCell Therapeutics), Dr. Hangwen Li(Stemirna Therapeutics), Dr. Su Xiao(Neurophth Therapeutics), Dr. Bin Chen(Fosun Lead, Secretary)

References

Gene Therapy Products Guidelines :

- ICH S12 draft: *" Nonclinical Biodistribution Considerations for Gene Therapy Products"*
- EMA (2018): "*Guideline on the Quality, Non-clinical and Clinical Aspects of Gene Therapy Medicinal Products"*
- PMDA (2019): "*Ensuring the Quality and Safety of Gene Therapy Products*"
- FDA (2013) : "*Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*"

General Guidelines :

- ICH M3 (R2)（2009） : "*Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*"
- ICH S5(R3)（2020）: *"Guideline on Detection of Toxicity to Reproductions for Human Pharmaceuticals"*
- ICH S6(R1)（2011）: *"Preclinical safety evaluation of biotechnology-derived pharmaceuticals"*
- ICH S9 （2009）: " *Nonclinical Evaluation for Anticancer Pharmaceuticals*"

Scope

Gene therapy products (GTP) work by transduction of transcription or translation of the genetic material, **including:**

- nucleic acids (such as plasmids, RNA),
- genetically modified microorganisms expressing specific genes (such as viruses, bacteria, fungi),
- in *vitro* genetically modified human cells[1],
- in *vivo* editing of the host genome (with or without specific gene transcription/translation),
- and microorganisms that express specific genes without genetic modification (such as oncolytic viruses),

excluding:

- chemically synthesized oligonucleotides and their analogs,
- preventive vaccines,

1. Refer to “Guideline on nonclinical Study and Evaluation for Genetically Modified Cell Therapy Products”

General Principles

- The guidelines should be continuously updated with technological development due to the diversity of GTP, now days limitations of understanding and rapid evolution of technologies.

- Non-clinical studies of GTP should provides sufficient information for clinical trials, which should be based on “risk-benefit” analysis, due to the huge differences between distinct GTPs, mechanisms of action, routes of administration, and safety risks, *etc*.

- Be assessed case by case for non-clinical research of GTP.

- Non-clinical safety research of GTP should follow GLP (Good Laboratory Practice) and 3Rs for animal usage.

Non-clinical Studies (1)

Relevant Animal Species

- GTP could be effectively introduced/exposed into relevant animal species, effectively transcribed/translated, and exert pharmacological activity.
- If using replicative vector, it should be able to replicate in relevant animal species.
- Communicate with regulatory agencies if no suitable animal model is available.

Test Article

- The GTP used in non-clinical studies should represent the products to be used in clinical trials.
- If the product undergoes major changes, like changes of carrier structure, expression elements, production process flow, etc., it is necessary to evaluate the need for bridging study or new non-clinical study.

Pharmacology： aims to study the mechanism and effect of product to the therapeutic target in vivo and in vitro.

- **Selection of animal models:** disease/injury models might be more suitable for“risk-benefit”analysis than normal healthy models; If no suitable animal model, using an alternative models (such as organoids) for non-clinical study is acceptable, which should provide scientific evidence for clinical trial design.
- **Proof of concept:** important, provide non-clinical evidence of feasibility and effectiveness for clinical trials, and provide information on possible biological mechanisms of action.
- **Safety pharmacology:** single dose, should consider mechanism of action of the introduced gene, the type of the vector, distribution, the route of administration, and the clinical administration plan, etc.

Non-clinical Studies (2): Pharmacokinetics

- **Exposure:** GTP should consider the actual exposure in non-clinical Study based on the specific characteristics of the product.

- **Biodistribution:** ICH S12, to assess the distribution, persistence and elimination of GTP at the site of administration, target tissues and non-target tissues in the body.

- **Shedding:** In addition to detect related nucleic acid, the shedding analysis should also consider the infectious ability of the excreted components. According to the result of study, corresponding risk management will be taken in clinical trials.

Non-clinical Studies (3): Toxicology

The study design should be based on risk. The assessment of potential risk comes from data of the POC of pharmacodynamic and biodistribution studies, **including:**

- **General Toxicology:** animal species selection, dosage, regimen, period, test Indicators and so on;
- **Immunogenicity and Immunotoxicity:** may be derived from the non-humanized components in the product, the expression product of the introduced, the vector, the unexpected peptide/protein produced by gene editing and other viral vector gene therapy products.
- **Reproductive toxicity:** refer to ICH S5(R3), ICH M3(R2), S6 and S9, the potential risk of reproductive/ developmental toxicity should be assessed based on the type, mechanism of action, toxicity, biodistribution, and patient population.
- **Genotoxicity:** transfer genetic material into host cells or integrate into host genome or edit host genome, and there is a potential risk of genotoxicity.
- **Carcinogenicity:** In the process of non-clinical development of gene therapy products, there is usually no need to carry out standard rodent carcinogenicity tests throughout the life cycle
- **Risk of Replicating Virus and Local Tolerance.**

Considerations for Conducting Clinical Trials by Non-clinical Study

- **Initial dose of the first clinical trial:** based on the safety and effectiveness characteristics suggested by non-clinical study, existing non-clinical data (pharmacokinetics, pharmacology and toxicology) with scientific demonstration, and selection based on a variety of methods； If no classic dose-effect relationship, then Minimal Effective Dose and Maximum Tolerable Dose might provide useful information for ratios of dose to exposure and activity to toxicity;

- **Pivotal non-clinical study to support clinical trials:** The non-clinical study of GTP should provide evidences to support clinical trials, and to evaluate of risks-benefits of the design of the clinical trial. Refer to ICH S9F for the non-clinical study of GTP intended for advanced cancer patients.