CERTARA

Moving Advanced Therapies to the Next Level:

Tackling the Key Challenges When Transitioning from Nonclinical to Clinical Development

by Oxana Iliach and Brenda Taylor

Introduction

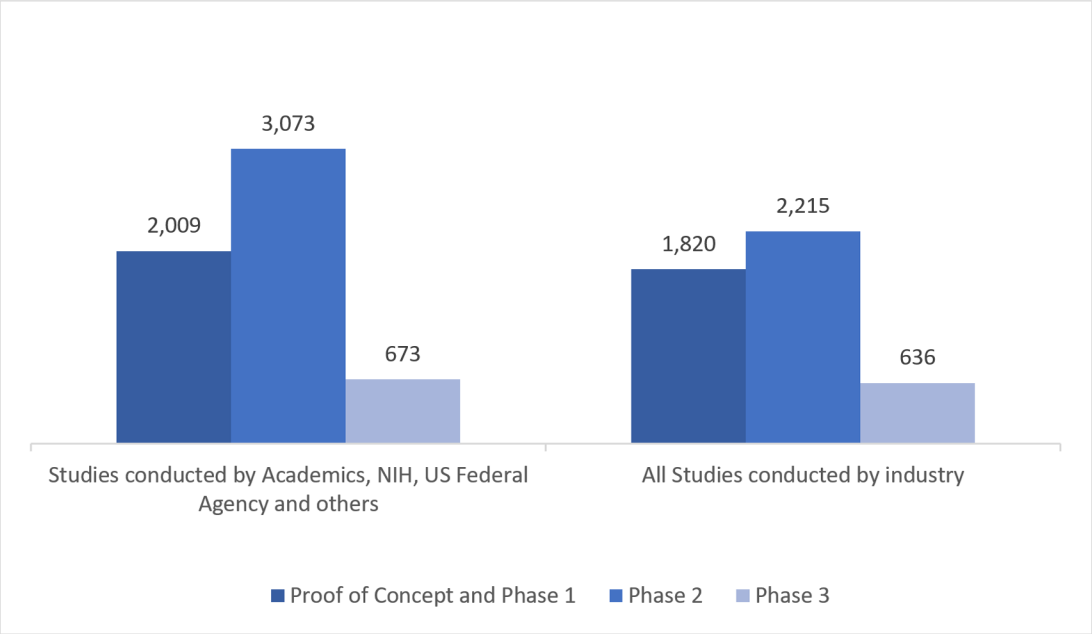
New advanced therapies are being developed with the goal of treating the causes of rare diseases. The definition of advanced therapies is broad and includes medicines that are based on genes, cells, or tissue engineering. This paper focuses on cell and gene therapies. Cell therapy products contain cells that were manipulated to either cure or prevent the disease. These cells may come from the patient (autologous) or a donor (allogeneic). Gene therapy works by introducing, removing, or changing a gene causing the disease. Development of cell and gene-based therapies poses specific challenges for sponsors. This white paper will explore the most common challenges that pharmaceutical companies face in developing these products and best practices for addressing them.

Overview of Advanced Therapies Development

The development of advanced therapy medicinal products (ATMPs or "advanced therapies"), which include gene therapies, somatic cell-based therapies, and tissue-engineered medicines, has recently exploded. There are approximately 1,195 advanced therapy developers worldwide (ARM, 2021). Most developers are in North America (594), followed by Asia-Pacific region (361) and Europe (209). What sets this treatment area aside from other types of treatments is that the developers are almost equally represented by industry and academia or publicly funded/not-for-profit organizations, especially for Phase 1 studies, as illustrated in Figure 1 and Figure 2. The number of ongoing Phase 1, Phase 2, and Phase 3 cell therapy studies conducted by industry are 1,820; 2,215; and 636, respectively (Figure 1). The numbers of studies conducted by academics and other organizations are somewhat higher 2,009; 3,073; and 673 for Phase 1, Phase 2, and Phase 3 studies, respectively.

Figure 1.

Active and Recruiting Cell Therapy Studies

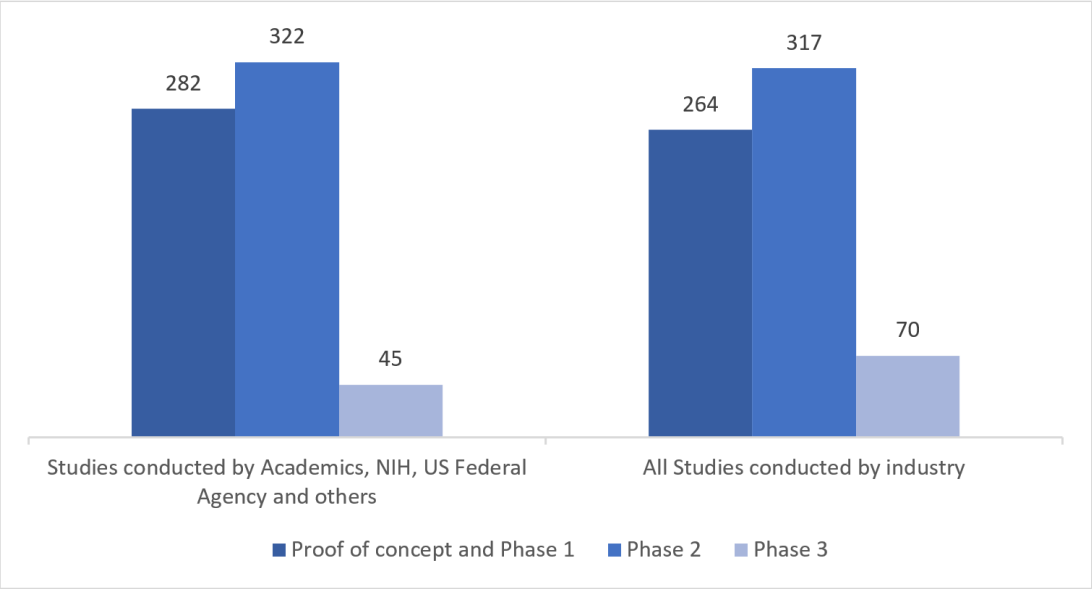


Source: ClinicalTrials.gov, August, 2021

Even though the number of gene therapy studies are about 1/10th the number of cell therapy studies, as presented in Figure 2, the distribution between studies conducted by industry versus academia or publicly funded/not-for-profit organizations is similar. Often, academic or non-profit organizations do not have the expertise to navigate the development challenges of bringing an advanced therapy through clinical development and regulatory approval. This can also be a challenge for small biotechnology companies.

Figure 2.

Active and Recruiting Gene Therapy Studies

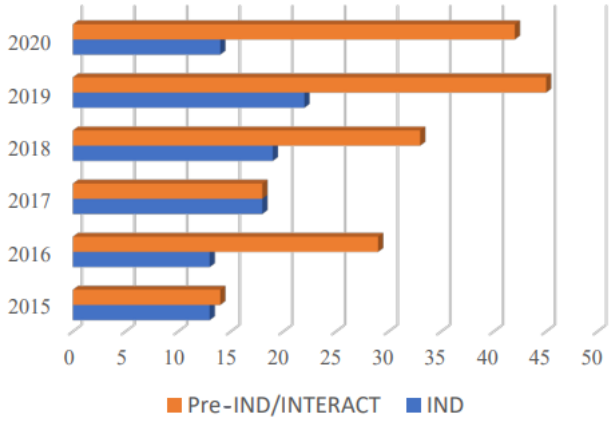


Source: ClinicalTrials.gov, August, 2021

From the regulatory perspective, there has been an increase in regulatory oversight and interaction with sponsors of advanced therapies in recent years. The latest numbers in gene therapy development were presented by the FDA during the Cellular, Tissue, and Gene Therapies Advisory Committee (FDA, 2021), using Adeno-Associated Virus (AAV) vector-based therapy as an example. As illustrated in Figure 3 the number of pre-IND /INTERACT (**IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on CBER produc**T**s) meetings has more than doubled since 2015, although the number of open INDs has remained steady.

Figure 3.

AAV Vector-based Gene Therapy Product submissions to FDA Office of Tissues and Advanced Therapies (OTAT)



One would expect that increase in the number of pre-IND/INTERACT meetings should translate into an increase in the number of INDs. However, this is not happening, based on the current numbers. The reason could be due to two major challenges that sponsors are facing: transition from nonclinical to clinical development and successful initiation of first- in-human (FIH) Phase 1 studies.

Transition from nonclinical to clinical development

Advanced therapies present specific safety issues due to their mode of action and the potential long-term consequences of gene insertion or manipulation. Safety issues, such as the risk of integrational mutagenesis of gene therapies, unexpected bio-distribution and ectopic tissue or tumor formation, require risk management that may need longer follow-up periods, as well as additional trials and registries post-authorization (Zabel, 2017).

Consequently, the requirements for a nonclinical development of AT should be more vigorous than for other biologics. This presents a challenge to the sponsor with regards to generating, evaluating, and presenting nonclinical data in a format acceptable by the FDA.

The FDA issued several guidances with general and specific requirements for nonclinical studies for cell and gene therapies (FDA, 2013). In general, the nonclinical program should incorporate a stepwise, multifactorial approach to achieve an understanding of the biological plausibility for use of the product in the intended patient population. Like the development of other biologics, in vitro and in vivo studies should be conducted prior to initiating clinical studies. However, considering that suitable animal models may not be available for AT, due to the nature of these treatments, the in vitro and in vivo studies should be extensive and should generate substantial data. In addition, a detailed assessment of the relevance of each animal species/disease-specific model used should be conducted, and a summary should be included in the regulatory submission.

The key nonclinical studies should ideally evaluate a version of the product that is identical to the product that is intended to be used in the FIH study. General principles of pharmacology and toxicology are applicable to cell and gene therapy products, but pharmacokinetic studies of Absorption, Distribution, Metabolism and Excretion (ADME) either do not apply or have a different approach. Another specific aspect of the AT nonclinical program is that carcinogenicity/tumorigenicity studies should be conducted at the early stages of product development.

The review of available literature, compilation, and presentation of data and identification of gaps in the program prior to the initiation of FIH study could be very challenging for the sponsor with limited regulatory expertise, such as academics or not-for-profit organizations. The support from independent experts with knowledge of nonclinical development and expertise in regulatory writing could help the sponsor to address this challenge and speed up overall product development.

A nonclinical program should include in vitro studies, proof-of-concept in vivo studies, toxicology studies, and biodistribution studies. In vitro and in vivo studies that are needed are presented in Figure 4.

Figure 4.

Outline of the Nonclinical Program

In Vitro Studies

- Functional assays
- Immunophenotyping of cells based on the types of antigens or markers
- Morphologic evaluation of cellular characteristics

Proof-of-Concept (POC) in Vivo Studies

- Investigate pharmacologically effective dose range (minimum to optimum)
- Optimize route of administration (ROA), ensure reasonable safety of ROA, confirm that product reaches the target
- Evaluate timing of product administration to onset of injury or disease
- Optimize dosing schedule
- Characterize mechanism of action (MOA) or expected biological activities

Toxicology Studies

- Evaluate proposed clinical indication
- Consider amount and quality of published nonclinical or clinical safety information for the specific cell or gene therapy (CGT) product under investigation or for a similar product
- Evaluate amount and quality of existing pharmacology (in vitro/in vivo) or POC data for the specific CGT product under investigation or for a similar product
- Include previous preclinical/clinical experience with the proposed clinical delivery device/delivery procedure or with any related device/procedure
- Ensure the biological responsiveness of the animal species to the investigational CGT
- Describe putative MOA and intrinsic properties of the CGT product
- Evaluate pathophysiology of the animal disease/injury model, if one is used
- Optimize study design: number of animals, control group, dose levels, dosing schedule, route of administraion, sacrifice time points and safety endpoints

Biodistribution Studies for Gene Therapy Products

- Assess the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target and non-target tissues, including applicable biofluids (e.g., blood, lymph node fluid, cerebrospinal fluid (CSF), as feasible.
- Determine extent of tissue transduction and transgene expression, evaluate whether expression is transient or persistent, which can guide the design of the nonclinical toxicology studies as well as the early-phase clinical trials

Additional Considerations for Cell Therapy Products

- Ability to reach the site for adminstration and delivery of a precise cell dose
- Immunogenic responses of animals to human cells
- Use of analogous cell products which may have different biological activites, molecular mechanisms, and contaminants
- Extent of manipulation and what happens to the cells after administration
- Scaffolds and biocompatability testing

Importance of chemistry, manufacturing, and controls (CMC) development

As outlined in the section above, the nonclinical program for cell and gene therapy is extremely important and requires special approaches. However, the most critical component of AT programs is the quality, or chemistry, manufacturing, and controls (CMC), development due to the complexity and novelty of manufacturing processes, and, often, the lack of CMC expertise in small biotechnology companies. The criticality of CMC in the cell and gene therapy program often becomes a rate limiting stage, because the early clinical trials, including FIH, are often expected to yield pivotal data, so sponsors need to front-load product characterization and control. Insufficient early quality control can jeopardize use of quality data for marketing authorization, e.g., due to lack of comparability with the commercial product (Reischl, 2020).

To clarify regulatory expectations for CMC, the FDA issued new and revised scientific guidances and also is working collaboratively with the European Medicines Agency (EMA) (Braun-Scherhag, 2020; EMA, 2019a; FDA, 2020, 2021, 2018 collaborative workshop). Recent quality topics addressed by guidances include CMC information required for gene therapy US INDs, good manufacturing process (GMP) for AT medicinal products (EU), and comparability requirements (FDA, 2020a; Hidalgo-Simon, 2020). Additionally, the EMA and FDA hosted a joint workshop in November 2018 with stakeholders to discuss how regulators can better guide and support medicine developers in generating quality and manufacturing data packages in the context of development support programs, such as the EU PRIME (priority medicines) scheme and the US Breakthrough Therapy program (EMA, 2019b).

Like the nonclinical program, the quality development of cell and gene therapy products is different from traditional biological dug product development. The high-level outline of these differences is presented in Figure 5.

Figure 5.

Specifics of CMC development for Cell and Gene Therapy Products

Critical Quality Attributes (CQA)

- Prepare list of CQA as early as possible
- Evaluate the number of product characteristics earlier in the development to help identify and understand CQAs

Drug Substance (DS)

- Define DS: Some gene therapy products may not have a distinct DS, others may consist of two or more different DS that are combined to make the DP
- Describe biological activity and proposed mechanism of action
- Evaluate shipping of DS (if applicable)

Drug Product (DP)

- Distinguish DP from DS
- Establish process for shipping, receiving, and handling of DP at a clinical site

Pharmaceutical Development

- Identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance, and DP quality

Manufacturing Process and Controls

- Define manufacturing run, batch scale, and quantification of DS
- Establish well controlled production of genetically modified cells

Deep understanding of regulatory requirements combined with CMC expertise and experience is essential to ensure the overall successful development of the cell and gene therapy products.

Clinical Challenges and Preparation for a FIH Study

Many of the diseases being targeted by cell and gene therapies are rare diseases. As such there may be no available treatments (precedent) or established clinical endpoints to determine efficacy and magnitude of clinically-relevant improvement. Also, the gold standard of a controlled, randomized, double-blind clinical trial may not be feasible or ethically justified, particularly for life-threatening diseases (Zabel, 2017).

Adaptation of established endpoints used in related diseases or de novo development of novel endpoints to establish clinical relevance will necessitate innovative trial designs and/or natural history studies to determine disease progression and relevant treatment effects. Natural history studies are particularly relevant when an active-comparator controlled study is not ethical or feasible, and the pivotal data is provided by a single-arm trial utilizing historical/external control arms to contextualize efficacy and safety of the new intervention (e.g., the pivotal data for the initial Yescarta and Kymriah CAR-T approvals were provided by single-arm trials).

Qualification of novel methodologies may be needed to establish the clinical relevance of novel endpoints or clinical trial designs. The FDA Clinical Outcome Assessment qualification process (FDA, 2020c) and the EMA Qualification of Novel Methodologies procedure (EMA, 2020) allow for assessment and qualification of new methodologies to be used for regulatory purposes.

Safety evaluation is paramount for the FIH study. This should include frequency and nature of potential adverse events and an estimation of the relationship to dose (FDA 2015). Dose-escalation protocols can be used to determine the highest dose that can be given with acceptable toxicity. In addition, a through benefit-risk analysis is crucial in the review of submission packages.

Development of the clinical program, and particularly design of a FIH study, is unique for each cell or gene therapy development program. The major differentiators are the lack of comparative treatments, difficulties in establishing end points and developing an appropriate biomarker, and the need for long-term follow-up. Like nonclinical and quality programs, it requires unique support with expertise and regulatory knowledge.

Conclusions

Regulatory authorities are supportive of these advanced therapies for high unmet patient need and offer enhanced scientific support and expedited regulatory review. To ensure speedy development of these life-saving therapies, it is essential that the sponsor leverages internal knowledge of the product, with external expertise and experience, while engaging in communication with FDA at the early stages of product development.

Certara can assist sponsors with many services that can enhance their cell and gene therapy development. These services include drug development and regulatory strategy; biosimulation consulting to optimize clinical plans; along with decision analytics and real-world evidence solutions to assist with value identification, pricing and market access. Our experts are ready to help you move your advanced therapy program to the next level.

References

ARM (2021): Alliance of Regenerative Medicine, H1 2021 Annual Report. Accessed 15 Oct 2021 at: http://alliancerm.org/wp-content/uploads/2021/08/ARM-H1-2021-Report.pdf

Braun-Scherhag, 2020. Industry's perspective on ATMP development. Presentation to 2nd Joint DIA-EUCOPE Workshop on ATMPs, Innovative Gene and Cell Therapies in the EU. Session 1: Development of Advanced Therapy Medicinal Products (ATMPs) – Challenges and Opportunities from the Industry and Authority Perspective. 27 May 2020.

EMA Advanced therapy medicinal product. Accessed 9 Dec 2021 at: https://www.ema.europa.eu/en/glossary/advanced-therapy-medicinal-product

EMA 2019a. Meeting Report: Workshop with stakeholders on support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies), 26 November 2018. (25 July 2019 EMA/CHMP/BWP/812924/2018). Accessed 15 Oct 2021 at: https://www.ema.europa.eu/en/documents/report/report-workshop-stakeholders-support-quality-development-early-access-approaches-ie-prime_en.pdf

EMA, 2019b. Remarks from Guido Rasi, MD, Director General of the EMA, at ARM's Meeting on the Mediterranean. http://bit.ly/2vggBcj (April 2019).

EMA, 2020: Qualification of novel methodologies for medicine development. Accessed 15 Oct 2021 at: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0

FDA, 2013. Preclinical Assessment of Investigational Cellular and Gene Therapy Products. Guidance for Industry.

FDA, 2015. Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products. Guidance for Industry.

FDA, 2020a. Cellular & Gene Therapy Guidances. Access on 15 Oct 2021 at: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

FDA, 2020c. Clinical Outcome Assessments (COA) Qualification Program Resources. Accessed 15 Oct 2021 at: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/clinical-outcome-assessments-coa-qualification-program-resources

FDA, 2021. Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy, Cellular, Tissue and Gene Therapies Advisory Committee Meeting #70. Access on 15 Oct. 2021 at https://www.fda.gov/media/151599/download

Hidalgo-Simon, 2020. EMA's perspective on ATMP development. Presentation to 2nd Joint DIA-EUCOPE Workshop on ATMPs, Innovative Gene and Cell Therapies in the EU. Session 1: Development of Advanced Therapy Medicinal Products (ATMPs) – Challenges and Opportunities from the Industry and Authority Perspective. 27 May 2020.

Reischl, 2020. Regulatory Assessor' perspective on ATMPs. Presentation to 2nd Joint DIA-EUCOPE Workshop on ATMPs, Innovative Gene and Cell Therapies in the EU. Session 1: Development of Advanced Therapy Medicinal Products (ATMPs) – Challenges and Opportunities from the Industry and Authority Perspective. 27 May 2020.

Zabel et al. (2017) Regulatory, clinical and logistics challenges of Advanced Therapy Medicinal Products (ATMPs) in clinical research. Accessed on 8 July 2020 at: https://www.europeanpharmaceuticalreview.com/article/81122/regulatory-clinical-and-logistics-challenges-of-advanced-therapy-medicinal-products-atmps-in-clinical-research/

Authors

Brenda Taylor
Associate Director, Global Submissions

Brenda Taylor holds an MS in Biological Sciences and has over 20 years of experience in the biotechnology and pharmaceutical industry. She has led regulatory strategy and submission management activities to support pharmaceutical development and manufacturing. Brenda's research background in microbiology and immunology includes design and performance of nonclinical studies. Her therapeutic areas of expertise include oncology, immunology, cardiovascular, and anti-infective agents, spanning both small molecule drugs and biologics.

Oxana Iliach, PhD
Sr. Director, Regulatory Strategy and Policy

Dr. Iliach has more than 15 years of experience in the healthcare industry including the last 10+ years in regulatory affairs. She has expertise in developing and executing regulatory strategies for drugs for rare diseases, pediatrics, and biosimilars, with a focus on Chemistry, Manufacturing and Control (CMC). Oxana has experience with the FDA, EMA, Health Canada, and other smaller agencies. She has a MSc in Chemistry and PhD in Pharmaceutical Science. She is also a professor at Seneca College, Toronto, Canada, where she teaches a course on clinical trials regulations.

About Certara

Certara accelerates medicines using proprietary biosimulation software and technology to transform traditional drug discovery and development. Its clients include more than 1,650 global biopharmaceutical companies, leading academic institutions, and key regulatory agencies across 61 countries.

For more information visit www.certara.com or email sales@certara.com.