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2017-2023: state of the art of gene therapies in rare diseases in Europe: the dynamics of clinical R&D, new approved treatments and expected therapies in the pipelines

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Abstract

Aim: Gene therapies have been tested over the past three decades, and after a first market authorization in 2017, the field is starting to deliver. The study aims to analyze the current development dynamics of gene therapies for rare diseases using the GENOTRIAL database[®], which gathers information on gene therapy clinical trials and studies conducted between 2017 and 2023 in Europe.

Methods: The study involved extracting and filtering clinical trial data from the EudraCT database. Trials with the keyword "Gene Therapy" were selected and filtered using the "Rare disease" filter. Manual verification was conducted to ensure that the selected trial only concerned gene therapy treatments authorized in Europe for rare diseases in phases I to III. A total of 300 European country-related clinical investigations representing a total of 93 European-specific clinical studies were included in the GENOTRIAL database. The trials were classified by development phases, temporal status, sponsors and investigating countries, rare diseases with their related



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therapeutic area, and approval regulatory information of the identified gene therapies.

Results: Analysis reveals that rare diseases present a promising area for gene therapy development. On average, eight rare disease gene therapy trials are launched each year in Europe. The main sponsors of European clinical trials of gene therapies for rare diseases are from US, followed by the United Kingdom and France. The United Kingdom conducts the highest number of investigations in Europe, followed by France, Italy, Spain, and Germany. Nutritional and metabolic diseases are the most represented therapeutic area, followed by rare oncology, blood and lymphatic diseases, and ocular diseases. The analysis identifies 73 gene therapy medical products covering 35 diseases at various stages of development, with 12 new therapies approved in recent years for 8 rare diseases, while 15 other gene therapies are at an advanced stage of phase III in their development plan for 11 other rare diseases.

Conclusion: Gene therapy has shown significant progress and potential in treating rare genetic diseases. Europe has emerged as a promising region for gene therapy clinical trials in rare diseases. Efforts are now required to catch up with the USA and UK regarding the number of clinical trials sponsored by European groups.

Keywords: Gene therapy, rare diseases, research and development (R&D), Europe, state of the art 2023

INTRODUCTION

Although rare diseases, by definition, impact a small number of patients, it is estimated that they collectively affect approximately 400 million patients worldwide^[1]. Moreover, while the vast majority of rare diseases are characterized by Mendelian inheritance, the rapid evolution and application of sequencing technologies in recent years have revealed the causes and mutations associated with these diseases, enabling today the identification and differentiation of more than 6,000 to 10,000 types of rare diseases, depending on the source^[1-5].

In recent years, although considerable efforts have been put in place through regulatory and economic incentives to promote the development of therapies for rare diseases^[6], the momentum in the development of new therapies for these diseases remains low today^[7], with most rare diseases still lacking specific treatments and only a few hundred treatments approved today^[1,6]. As a result, this issue continues to be a major concern for regulatory and economic researchers, physicians, and affected patients.

If the clinical industry has traditionally focused on the development of small molecule drugs, in the context of rare diseases, they tend to act on the management of symptoms more than on the cure of these pathologies^[7]. However, advances in molecular biology and genomics over the last few decades have broadened the possibilities of new therapeutic approaches, notably with the appearance of innovative therapies including cell therapies, biotherapies (proteins, peptides, and antibodies), therapies based on antisense oligonucleotides or small interfering RNAs (siRNAs), as well as cell therapies and gene therapies at the center of this study^[7].

In addition, gene therapies represent a therapeutic approach relatively suited to the context of rare diseases. They broaden the scope of potential drug targets to encompass targets and mechanisms that are typically difficult to address with small molecules and proteins, which include targets of transcription factors and compensation of dysfunctional intracellular proteins linked to DNA alterations. These alterations can be stopped or reversed, including by supplying cells or tissues with a functional copy of the mutated gene^[7,8]. In this sense, gene therapies have the potential to correct the underlying genetic defects, offering a cure rather than just symptom management. Thus, successful gene therapy may require only a single dose to confer

lifelong improvement, eliminating the need for ongoing, lifelong treatment^[9].

Gene therapy has thus been suggested as a possible treatment for inherited diseases since the 1970s^[10,11], and the first formal trial was initiated in the United States in 1990. The therapy consisted of a viral vector that delivered a functional copy of the adenosine deaminase (ADA) gene into the T cells of a patient with severe combined immune deficiency^[12,13]. The success of this first clinical trial has since fostered numerous trials in gene therapies tested in thousands of clinical trials over the last 30 years, but only a handful of therapeutics have been obtained in recent years^[8]. However, the precise assessment of the R&D dynamics and the current synthetic status of available or under-development gene therapies in rare diseases remains a complicated exercise.

METHODS

Extraction and filtration of trials via eudraCT database

The EudraCT database is a European clinical trials database maintained by the European Medicines Agency (EMA). It serves as a centralized registry for all clinical trials conducted in the European Union and the European Economic Area. This tool facilitates transparency and access to information regarding clinical trials conducted in “rare diseases” with a specific filter tool, ensuring that they are conducted and reported in line with EU regulations.

To gain insights into the current clinical development dynamics surrounding gene therapies for rare diseases in Europe, we utilized data from the “GENOTRIAL database”. Developed by the French infrastructure OrphanDev, a member of the F-CRIN national network, this database consolidates information on phase I to III gene therapy clinical trials for rare disease indications. These trials either were in progress, had been completed, or had commenced between 01/01/2017 and 01/01/2023. Although these trials might have European or non-European sponsors, the investigations were conducted in Europe.

For the extraction and filtration process, we conducted a search in the EudraCT database using the keyword “Gene Therapy”. This search was further refined by applying the “Rare Disease” filter for the timeframe from 01/01/2017 to 01/01/2023.

ClinicalTrials.gov, maintained by the US National Library of Medicine at the National Institutes of Health, is a database of privately and publicly funded clinical trials conducted worldwide. It provides access to information on study purpose, recruitment status, intervention methods, and outcomes.

Subsequent to the EudraCT search, a cross-manual verification was executed using ClinicalTrials.gov to account for any missing European countries linked to the identified studies.

From this methodology, 300 European country-specific clinical trials were identified, representing a total of 93 European clinical studies with a unique EudraCT number. Each of these studies was involved in testing phase I to III gene therapy treatments for rare diseases within the stated period. This collective data formed the content of the GENOTRIAL database, which was used extensively for the analysis and writing presented in this article.

Furthermore, all identified trials underwent manual distribution and were uniformly classified by therapeutic area and pathology. This classification was based on the Medical Dictionary for Regulatory Activities Terminology (MedDRA).

Integration of information on the status of the development of the identified gene therapies

To provide further clarity on the status of the identified gene therapies, a meticulous manual classification and standardization process was conducted. We examined the Food and Drug Administration (FDA) and EMA websites to ascertain the stage of development, regulatory status, and any recent potential approvals in the US or Europe.

The methodology is summarized in [Figure 1](#).

RESULTS

Gene therapies in rare diseases: contextualization of identified clinical trials and temporal assessment of recent years

Rare diseases: an important field of application in the development of gene therapies in Europe

From the database and based on the methodology described above, a total of 650 phase I to III clinical trials evaluating gene therapy treatments were identified, representing 5% of the 13 298 clinical trials, respectively, identified as ongoing, completed, or started between 2017 and the end of 2023 [[Figure 2A](#)]. Of these 650 trials, 300 were investigative gene therapy clinical trials for rare diseases, representing 46% of all identified gene therapy clinical trials [[Figure 2B](#)].

Moreover, between 2017 and 2023, when considering those country-related clinical investigations of gene therapy in rare diseases, the majority of trials identified in our database were in phase III (51%; $n = 153$) or phase II (45%; $n = 134$), followed by phase I (4%; $n = 13$) [[Figure 2C](#)]. This same analysis was carried out by focusing only on the clinical studies (based on EudraCT number) identifying 93 "gene therapy in rare diseases" related studies. These clinical studies accounted for 60% of Phase II trials ($n = 56$), followed by Phase III trials (33%; $n = 31$), and finally Phase I trials (6%; $n = 7$) [[Figure 2D](#)].

Gene therapies in rare disease: a growing temporal dynamic with encouraging therapeutic application

The analysis of the temporal dynamics of these clinical studies in gene therapies for rare diseases has shown that the number of clinical studies started per year in Europe had only increased from 2015 until 2018 (from 1 launched per year to 25 started in 2018) before decreasing drastically between 2018 and 2021 with only 5 studies having been launched last year. However, this trend seems to have reversed since 2022, with a new increase in the number of studies launched per year being equal to 9 [[Figure 2E](#)].

More specifically, between 2017 and 2023, among the 93 clinical studies identified, 22 (24%) were carried out, with an average of 3.7 per year, primarily phase II (13%; $n = 12$), followed by phase III (10%; $n = 9$) and phase I (1%; $n = 1$) [[Figure 2F](#) and [G](#)]. The outcomes of these studies have recently culminated in the successful marketing authorization and commercialization of several gene therapies targeting different rare indications, as described in the following.

In addition, 4% of these clinical studies were prematurely terminated ($n = 4$) [[Figure 2F](#)].

Finally, 67 of the 93 identified studies (72%) were still in progress at the beginning of 2023, mainly phase II (43%; $n = 40$), followed by phase III (24%; $n = 22$) and phase I (5%; $n = 5$). [[Figure 2F](#) and [H](#)].

European gene therapies development in rare disease: under the sponsoring and investigation of international dynamism

The US: sponsor of European clinical research in gene therapy for rare diseases. France in 3rd position

In order to establish the geo-economic situation of the actors financing the investigation of clinical studies identified as gene therapies in rare diseases, a survey of the sponsor countries was carried out. Following

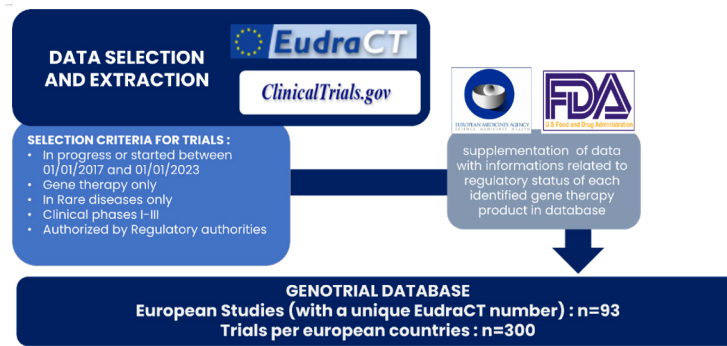


Figure 1. Schematic representation of the methodology used for the GENOTRIAL Database generation.

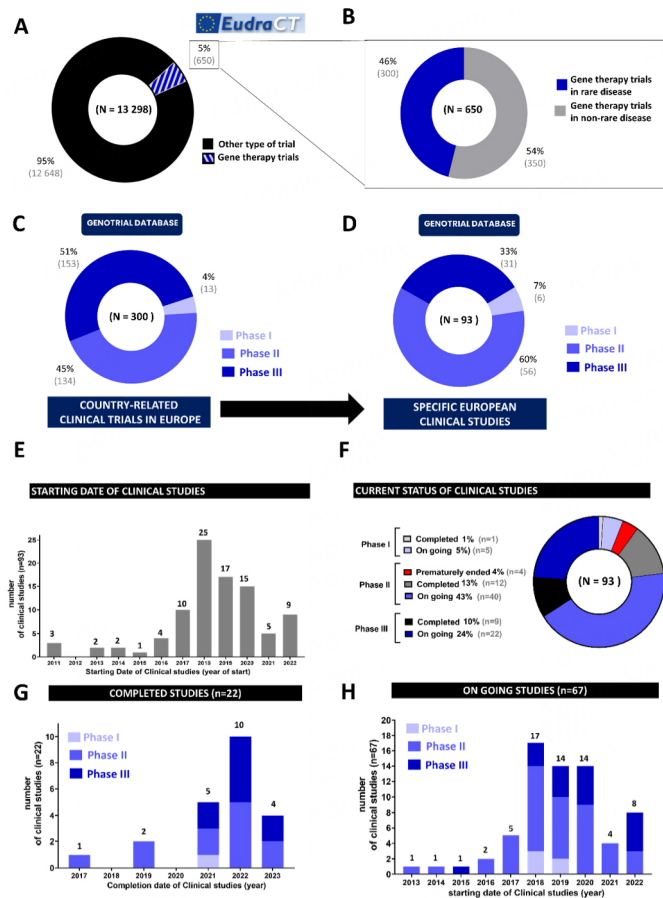


Figure 2. General distribution and temporal dynamic of clinical studies related to gene therapies in rare diseases in Europe from GENOTRIAL database. (A) Distribution of clinical trials considered as «Gene therapies» in EudraCT database from 01/01/2017 to 01/01/2023 ($n = 650$) vs. other types of clinical trials not considered as gene therapies ($n = 12.648$); (B) Distribution of clinical trials considered as «Gene therapies in rare disease» in EudraCT database from 01/01/2017 to 01/01/2023 ($n = 300$) vs. other trials Gene therapy ($n = 350$); (C-D) Distribution of 93 clinical trial phases from phase I to phase III, respectively, among (C) the identified 300 country-specific clinical trials or (D) their 93 associated clinical studies related to gene therapies in rare diseases from the constructed database; (E) Representative time charts of the number of clinical studies, including gene therapies, started between 2011 and 2022 ($n = 93$); (F) Distribution of current status of identified Phase I-III clinical studies, "ongoing", "completed", or "prematurely ended" ($n = 93$); (G-H) Representative time charts of the number of clinical studies including gene therapies (G) having been completed between 2017 and 2022 and started between 2011 and 2022, ($n = 22$) or (H) being currently still ongoing as of 01/01/2023 and having started between 2013 and 2022 ($n = 67$).

this analysis, it appears that the 93 identified clinical studies are financed by international actors from 9 different countries, mainly the US. (44%). In terms of European sponsors, the United Kingdom (19%) is in 2nd place, followed by France in 3rd place (15%). The remaining studies were funded by sponsors located in other European countries such as Switzerland (9%), Italy (5%), Spain (2%), Germany (2%), Belgium (2%) and Austria (1%) [Figure 3A and B].

The United Kingdom: European leader in clinical investigation of gene therapy for rare diseases. France in 2nd position

In order to establish the geographical panorama of the European countries participating in the investigation of clinical studies identified as gene therapies, an analysis was carried out on the database associating the information relating to the investigator countries associated with the 93 studies previously discussed. As a result of this analysis, it appears that the associated 300 European country-related clinical investigations identified are conducted in 19 European countries, mainly in the United Kingdom (20%), followed by France in 2nd position (16%), Italy (13%), Spain (11%) and Germany (10%). The remaining European countries participating in the clinical investigation of those studies are the Netherlands (7%), Belgium (6%), Sweden (4%), Denmark (2%), Austria (2%), Greece (1.7%), Norway (1.3%), Portugal (1%) and finally, in a less representative manner, Switzerland, Poland, Ireland, Hungary, Finland and Bulgaria [Figure 3C and D].

Gene therapies are investigated in numerous rare diseases

Rare diseases: which therapeutic areas are investigated by gene therapies?

Subsequently, the 93 studies qualified as "gene therapies for rare diseases" were divided by therapeutic area on the basis of the MedDRA classification.

According to this classification, 8 different therapeutic areas have been identified, with nutritional and metabolic diseases being the most represented area in the development of gene therapies for rare diseases in Europe (23%; $n = 21$). Similarly, 20%, 19%, and 13% of the studies identified in the database are classified in the therapeutic areas of rare oncology ($n = 19$), blood and lymphatic diseases ($n = 18$), and ocular diseases ($n = 12$), respectively. Finally, in a less representative manner, the last listed studies are classified in the therapeutic areas of immune system disorders (9%), nervous system diseases (8%), musculoskeletal disorders (5%), and finally connective tissue diseases (3%) [Figure 4A].

Moreover, there is a heterogeneous distribution in the stages of development of gene therapies, which is more or less important between the different therapeutic areas identified [Figure 4B].

What are the rare diseases targeted by these gene therapy developments?

To go further, a more detailed analysis was carried out on these therapeutic areas concerning the 93 clinical studies, to understand their specificities and identify the rare diseases that particularly benefit from the advanced dynamics of gene therapy development. This analysis allowed us to identify 35 rare diseases investigated within clinical studies for gene therapies and present a heterogeneous distribution between the different therapeutic areas with a more or less advanced stage of development [Figure 4C]. According to this analysis, rare gene therapies in development in oncology mainly concern hematological cancers such as lymphoma, myeloma, and leukemia, which represent 26%, 26%, and 21%, respectively, of the cancers studied with this approach, followed by other solid cancers such as sarcoma (16%), carcinoma (5%) and glioblastoma (5%) [Figure 4C].

Regarding the other identified therapeutic areas, several rare pathologies present an advance in terms of research and development of gene therapies, notably with phase III clinical studies in progress or completed

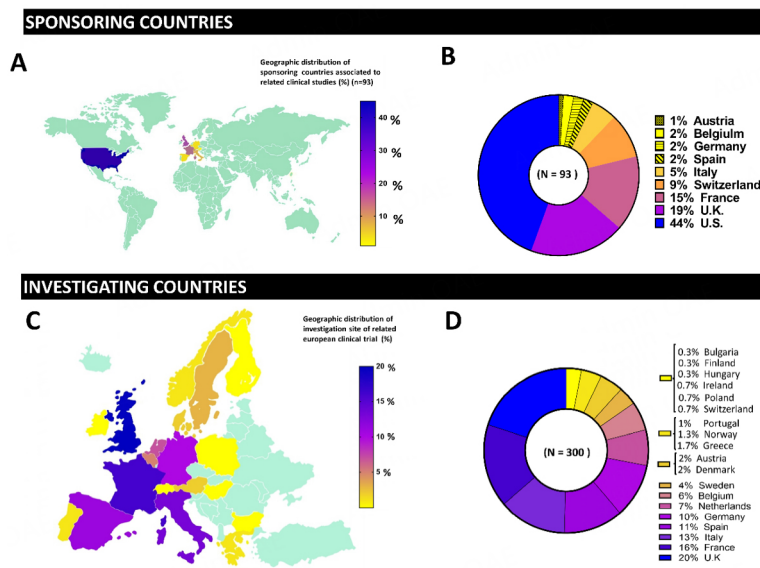


Figure 3. Characterization of sponsors and European investigator countries involved in the development of gene therapies in rare diseases. Geographical distribution (%) of (A-B) countries sponsoring gene therapy studies in rare diseases or (C-D) countries involved as investigators of those studies in gene therapy protocols in the field of rare diseases (A, C) as a map representation, or (B, D) as a pie chart representation showing associated percentages.

in recent years. Thus, the most studied pathologies and/or those in phase III of gene therapy development will mainly concern glycogen storage disease, mucopolysaccharidosis, and Wilson's disease, which represent 24%, 33%, and 5%, respectively, of the pathologies studied in the therapeutic area of nutritional and metabolic diseases [Figure 4C]. Similarly, sickle cell disease (22%), hemophilia A (22%) and hemophilia B (33%) represent the most studied pathologies in gene therapy in the field of rare blood and lymphatic diseases [Figure 4C].

Finally, other pathologies such as Leber's congenital optic neuropathy and retinitis pigmentosa (8% and 50% respectively in the field of eye diseases), Wiskott-Aldrich syndrome (50% in the field of immune system disorders), cerebral adrenoleukodystrophy and spinal muscular atrophy (43% and 57% respectively in the field of nervous system diseases), Duchenne muscular dystrophy (80% of musculoskeletal disorders) and epidermolysis bullosa (100% of connective tissue diseases) are other rare diseases that benefit from advanced stages of gene therapy development [Figure 4C].

New gene therapies in rare diseases: approvals and forecasts for therapeutic application

Finally, the last step of this overview consisted of identifying and categorizing the experimental gene therapy products developed for rare diseases in order to prioritize them in their respective stages of development from phase 1 to their marketing authorization. For this purpose, as described in the methodology section, a manual classification and standardization was performed on the Food and Drug Administration (FDA) and EMA websites in order to verify their stage of development, their regulatory status, as well as their potential recent approval in the United States and/or Europe.

After this analysis, from the 300 country-related clinical investigations associated with the 93 clinical studies concerning gene therapies in rare diseases, 73 gene therapy medical products were investigated, covering the 35 pathologies identified above and presenting more or less advanced stages of development ranging from phase I to market authorization. Of these, 62% are still in the early stages of clinical development (7% in

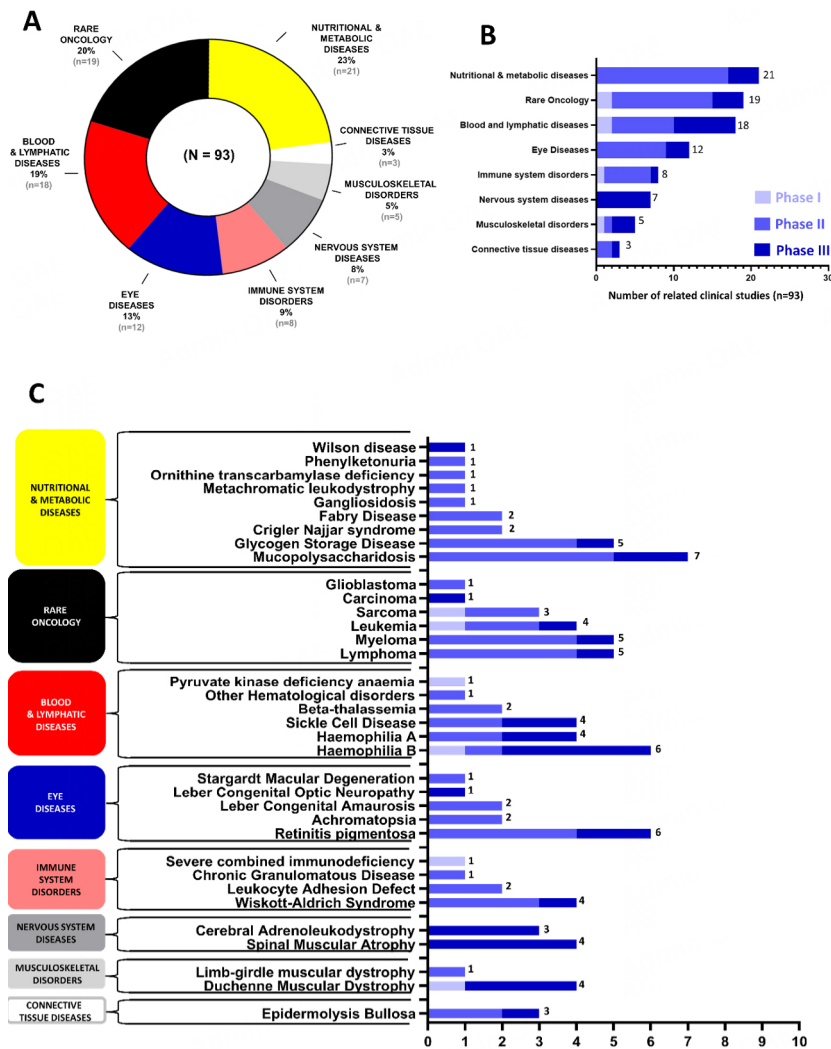


Figure 4. General distribution of therapeutic areas and related rare diseases among the identified studies related to gene therapies in Europe. (A) Distribution of therapeutic areas concerned by clinical studies considered as Gene therapies in rare diseases from 01/01/2017 to 01/01/2023 ($n = 93$); (B) Graphic representation of the absolute number of Clinical studies involved in each related therapeutic area from phase I to phase III. The absolute numbers of involved clinical studies are presented on the right of each diagram; (C) Graphic representation of the absolute number of clinical studies involved in each related pathology from phase I to phase III. Relative Therapeutic areas associated with pathologies are presented on the left. The absolute numbers of involved clinical trials are presented on the right of each plot.

phase I and 55% in phase II); 38% of them are at a more advanced stage in their development plans, with 19% of them in phase III and 19% of them having been approved for marketing in recent years between 2017 and early 2023 [Figure 5A].

The most advanced gene therapies in rare diseases today primarily encompass a total of 12 newly approved therapies between 2017 and 2022 in Europe and/or the US; these therapies are designed for 8 rare diseases, categorized across 4 therapeutic areas, including rare oncology ($n = 7$), blood and lymphatic diseases ($n = 3$), nervous systems diseases ($n = 2$), and nutritional and metabolic diseases ($n = 1$) [Figure 5B]. However, this is only the first wave of the wave to come. At the time of writing, many more new gene therapies could be approved in the United States, Europe, or both regions by the end of 2023 and in the years to come. Indeed, 14 additional gene therapies are currently in Phase III for indication in 10 rare diseases included in the

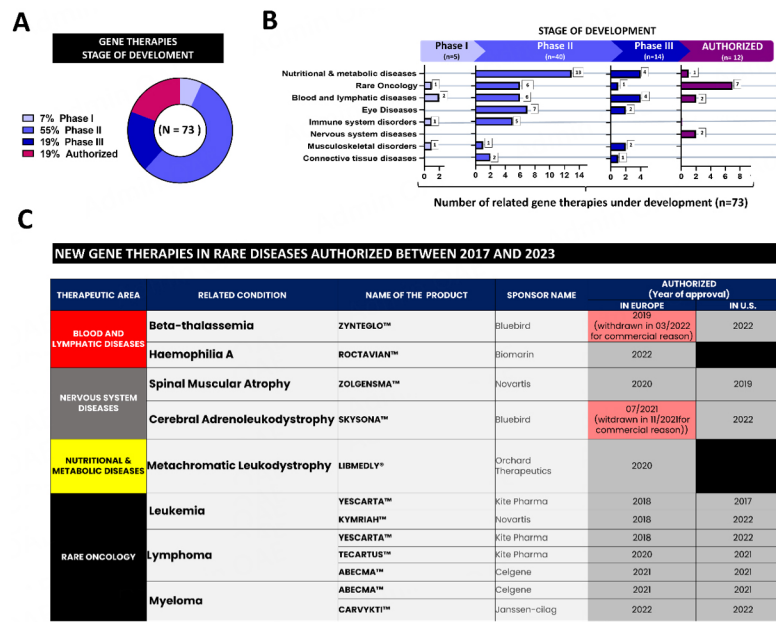


Figure 5. Gene therapies in rare disease - information about stage of development. (A) pie chart representation of development stages of the 73 identified gene therapies ranging from phase I, II, and III to market authorization; (B) Diagram representation of the absolute number of gene therapies in development associated with both their therapeutic areas and their respective stages of development (from phase I to market authorization (in Europe and/or in US)). The absolute number of individual therapies under development is presented to the right of each graph; (C) Table indicating information about new gene therapies for rare diseases authorized between 2017 and 2023; the information will cover associated therapeutic area, related condition, name of the product, sponsor name and year of approval (for authorized products), as well as the year of start or year of completion for gene therapies in stage III of development.

therapeutic areas of nutritional and metabolic diseases ($n = 4$), rare oncology ($n = 1$), blood and lymphatic diseases ($n = 4$), eye diseases ($n = 2$), musculoskeletal disorders ($n = 2$) and connective tissue diseases ($n = 1$) [Figure 5B]. Finally, a total of 45 gene therapies are still in the early stages of development (5 in phase I and 40 in phase II) for 30 rare diseases included in all the therapeutic areas identified above, excluding nervous system diseases [Figure 5B].

Identification of new gene therapies for rare diseases, European studies of which have been conducted for European approvals in recent years

Since 2017, from European identified clinical studies, 12 new gene therapies have been approved in the United States and Europe for 8 diseases in different therapeutic areas. For diseases of the blood and lymphatic system, two therapies have been approved: Zyngelo™ for Beta-Thalassemia (initially approved in Europe in 2019, withdrawn in March 2022 for commercial reasons and recently approved in the U.S. in 2022) and Roctavian™ for Hemophilia A (approved in Europe in 2022 and pending approval in the US). Moreover, in nervous system diseases, two therapies have been approved: Zolgensma™ for spinal myopathy (initially approved in the U.S. in 2019 and in Europe in 2020) and Skysona™ for cerebral adrenoleukodystrophy (approved in Europe in July 2021 but quickly withdrawn for commercial reasons in November 2021, it has been approved in the U.S. in 2022). In nutritional and metabolic diseases, Libmedly™ was approved in Europe in 2020 for metabolic leukodystrophy. Finally, seven new gene therapies were approved in rare oncology for myeloma, lymphoma and leukemia, including Abecma™ and Carvykti™ for myeloma (each approved between 2017 and 2022 in both the U.S. and Europe), Abecma™, Tecartus™, and Yescarta™ for lymphoma (each approved between 2018 and 2022 in both the U.S. and Europe), and Kymriah™ and Yescarta™ for leukemia (each approved between 2021 and 2022 in both the U.S. and Europe) [Figure 5C]

DISCUSSION

Since their first therapeutic consideration in the 1970s^[10,11,14] and three decades after the first gene therapy trials^[12,13], there have been few, if any, failures, which has boosted enthusiasm and increased funding for these new therapies^[15]. Optimism is encouraged by gene editing and other new or improved techniques, whose numbers seem to increase each year^[15]. While gene-editing approaches are still in their initial stages, follow-up times for many gene therapy trials have exceeded 10 years without major adverse events reported at clinical trials. Indeed, with over 2000 authorized clinical trials worldwide, it appears that advances in gene therapy may be ushering in a new era with an increasing number of products approved over the past decade worldwide^[14,16].

It is already described in the literature that gene therapies developed around the world cover many areas, largely including rare genetic diseases, oncology, and infections^[16,17]. This study provides an additional analysis of the current trends in the clinical development of gene therapies for rare genetic diseases. It compiles information from gene therapy clinical studies, ranging from phase I to III, 25 which were conducted, started, or completed in Europe between 2017 and 2023. Thus, as described above, 46% of gene therapy clinical studies conducted in Europe fall within the scope of rare diseases and represent a relatively promising and interesting field of application for the research and development strategy for this type of innovative therapy.

In 2020, globally, the United States and China dominated gene therapy clinical research and accounted for approximately 80% of all trials^[16]. Similarly, at the time of writing this paper, this analysis also reveals that the United States was the leading sponsor of clinical studies of gene therapies for rare diseases in Europe between 2017 and 2023, followed by the United Kingdom and France. In addition, analysis of the European investigating countries associated with the 93 studies identified in the database shows that the United Kingdom is the leader in country-based clinical investigations for gene therapy in rare diseases, followed by France, Italy, Spain, and Germany within Europe.

Similarly, the first European marketing authorization for a gene therapy product was granted in 2012 to Glybera™ as a treatment for hereditary hypercholesterolemia but was subsequently suspended for commercial reasons in 2017^[18]. The second such product to be approved in Europe was Strimvelis™ in 2016, whose marketing authorization has been recently transferred from Orchard Therapeutic to the Telethon Foundation for the treatment of immune deficiency due to adenosine deaminase deficiency^[19]. Moreover, the last gene therapy product that closed its clinical study before 2017 and was approved in Europe was LUXTURNA™ in 2018, indicated for patients with Leber's congenital amaurosis eye disease^[14,20]. Finally, although developed outside the European Union (and therefore not included in our study), Upstaza™ is also among the latest therapies developed in recent years and has been approved in Europe since 2022 as a treatment for aromatic L-amino acid decarboxylase deficiency^[21,22].

While the number of marketing authorizations for gene therapies and their diversities of indication were relatively low in 2017, the considerable progress made in the technologies of viral vectors used to deliver the genetic material and the evolution of regulations have to facilitate the implementation of clinical trials involving gene therapies^[15]. Therefore, our analysis reveals that rare diseases are an important field of application in the development of gene therapies in Europe, with many studies having been conducted between 2017 and 2023, some having already shown positive results in clinical trials and many others being at more or less advanced stages of development. This result suggests that while the clinical development of gene therapies remains an approach that is still underrepresented in the set of clinical trials proposed in Europe in recent years, rare diseases represent a relatively promising field of application and of interest for

the research and development strategy for this type of innovative therapy.

Moreover, when considering the state of development of those numerous projects, our analysis reveals that the majority of clinical studies for gene therapy in rare diseases will mainly concern advanced phase III or phase II. To illustrate these slight variations in phases, especially in the poorly represented phase I, it is interesting to note some of the specificities inherent in the development of treatments for rare diseases. Indeed, due to the low prevalences and resulting recruitment complexities, it is common for the development of therapies for rare diseases to be reduced to two clinical phases, including a merger of Phase I and II. These phase I/II typically collect safety and initial efficacy data simultaneously and may be followed by a phase III study, which is typically oriented towards finding strong evidence of efficacy^[23-25].

Regarding temporal dynamics, the analysis of clinical studies in gene therapies for rare diseases in Europe reveals a fluctuating pattern in the number of studies launched per year over the last decades. Between 2015 and 2018, there was a steady increase, but this was followed by a drastic decrease between 2018 and 2021. However, since 2022, there has been a reversal of this trend, with an increase in the number of studies launched per year. Overall, 22 out of the 93 identified studies were carried out between 2017 and 2023, primarily involving phase II and phase III trials. These trials have led to the marketing authorization and commercialization of several gene therapies for various rare indications. Some studies were prematurely terminated, while the majority were still in progress at the beginning of 2023. The fluctuating dynamic can be explained by socio-economic factors that disrupted the R&D economic climate, particularly between 2019 and 2021, and slowed down industrial sponsors in their clinical development plans for rare diseases. The increase in the number of studies launched in 2022 suggests a potential regain of dynamism in gene therapy trials for rare diseases in the future. The year 2021, marked by the COVID-19 pandemic, can be seen as a gap year in the clinical development of gene therapies. However, further research is needed to explore the specific socio-economic aspects influencing this fluctuating temporal dynamic and its correlation with the R&D climate.

Thus, the analysis reveals a diverse range of therapeutic areas being investigated. The most represented therapeutic area is nutritional and metabolic diseases, followed by rare oncology, blood and lymphatic diseases, and ocular diseases. The distribution of gene therapy development stages varies across these therapeutic areas, with a higher proportion of phase I to II studies in rare oncology, nutritional and metabolic diseases, immune system disorders, ocular diseases, and connective tissue diseases. On the other hand, other therapeutic areas such as diseases of the blood and lymphatic system, musculoskeletal disorders, and diseases of the nervous system have a more homogeneous distribution and a higher proportion of phase III studies. Within these therapeutic areas, several rare diseases are targeted by gene therapy developments. In oncology, hematological cancers such as lymphoma, myeloma, and leukemia are the main focus. For nutritional and metabolic diseases, glycogen storage disease, mucopolysaccharidosis, and Wilson's disease are among the most studied pathologies. Sickle cell disease, hemophilia A, and hemophilia B are prominent in gene therapy research for rare blood and lymphatic diseases. Other diseases such as Leber's congenital optic neuropathy, retinitis pigmentosa, Wiskott-Aldrich syndrome, cerebral adreno-leukodystrophy, spinal muscular atrophy, Duchenne muscular dystrophy, and epidermolysis bullosa also benefit from advanced stages of gene therapy development. Those results are in line with previous observations made in recent years^[14,16,17] and suggest the potential availability of new gene therapies in the short term and a paradigm shift in the management of these related rare diseases in the coming years.

In this sense, as described in detail in the previous sections, this study identified 73 gene therapy medical products at different stages of development, from phase I to market authorization, covering the 35 identified

rare diseases. Among them, 12 new therapies have obtained marketing authorization in recent years, between 2017 and early 2023, in Europe and/or the United States for 8 rare diseases. While our study primarily focuses on gene therapy clinical trials for rare diseases conducted in Europe between 2017 and 2023, it is imperative to underscore the significant role of the U.S. as the predominant sponsor, accounting for 44% among the leading European countries. Moreover, contrasting the market authorization statuses between Europe and the U.S. is insightful. Although the regulatory requirements often align, discrepancies may arise due to varying opinions of regulatory bodies or distinct territorial commercial interests held by the sponsors.

- Among these successes of new gene therapies identified as newly approved in rare diseases are CAR-T cell-based therapies indicated in rare oncology in certain hematological malignancies such as Leukemia, Lymphoma, and Myeloma. Two of them, Yescarta® (Kite Pharma)^[14,16,26,27] and Kymriah® (Novartis)^[14,28,29], received marketing authorization in Europe in 2018, followed by Abecma® (Celgene)^[30,31], Carvykti™ (Janssen-Cilag®)^[32,33] and Tecartus® (Kite Pharma)^[14,34,35] between 2020 and 2022. Moreover, all those products have also been authorized in US between 2017 and 2022. The principle of these immunotherapies consists of genetically modifying T lymphocytes in the laboratory, in order to equip them with a receptor (the CAR) that identifies cancer cells and destroys them. First, the patient's T lymphocytes are collected by leukapheresis, genetically modified to express the new CAR receptor, and then re-administered to the patient in a single infusion.

- Among the latest treatments developed in rare blood diseases is Zynteglo™ (Bluebird), initially approved in 2019 by the EMA (currently withdrawn for commercial reasons since 03/2022) and most recently in 2022 by the FDA for the treatment of Beta-Thalassemia. Roctavian™ (Biomarin) was also approved in Europe in 2022 for the treatment of Haemophilia A. The product consists of the transport of the factor VII gene into the liver cells, which is lacking in patients with hemophilia^[36].

- Libmeldy™ (Orchard Therapeutics), meanwhile, was approved by the EMA in 2020 for the treatment of Metachromatic Leukodystrophy, a rare inherited disease characterized by a mutation in a gene required to make an enzyme called arylsulfatase A, which breaks down substances called sulfatides^[37].

- At the level of the latest treatments developed in rare diseases of the nervous system, we find Zolgensma™ (Novartis), initially approved in 2019 by the FDA and then in 2020 by the EMA, for the treatment of Spinal Muscular Atrophy^[14,38,39], along with Skysona™ (Bluebird) for the treatment of Cerebral adrenoleukodystrophy which was approved by the EMA in July 2021 before being suspended for commercial reasons in November 2021, and it is also approved by the FDA in 2022^[40,41].

In the current perspective and as of the time of writing, in the pipeline, there are 14 other therapies in advanced phase III stages of development for 11 different rare diseases. This indicates their potential approval in either the United States, Europe, or both regions by the end of 2023 and in the coming years. This underscores the promising and swiftly growing domain of research in the development of gene therapies for rare diseases.

However, despite the enthusiasm and momentum surrounding these new therapeutic approaches, gene therapies are raising new economic, regulatory, and social concerns, particularly in rare diseases; the limited number of patients in such cases makes it challenging to meet the conventional requirements of pharmacological drug development, thereby impacting the commercial interest of the industry^[8,9]. Gene therapies do hold promise for potentially curative treatments in genetic diseases. Furthermore, there is a

pressing need for technical improvements, especially in the delivery of products to non-dividing cells), and their improved specifications to increase safety^[8].

Moreover, regarding the risk/benefit ratio of gene therapy therapeutic approaches, European regulatory issues appear to be resolvable and have not impeded the critical development of gene therapies in recent decades and even present a good efficiency of regulatory processes for market leadership^[9,42]. Notably, the orphan drug designation (ODD) seems to play a pivotal role in the status of clinical trials and marketing approval, as evidenced by the fact that 11 (92%) out of the 12 recently approved gene therapies have benefited from it during their development process (data not shown). This suggests that obtaining this designation could be crucial for the success of research and development of gene therapies targeting rare diseases. This is an important question, but it goes beyond the scope of this study.

However, while scientific research explores gene therapy treatments for a wide range of rare diseases, financial challenges for industries still threaten their accessibility and availability^[9,43-46]. Thus, new therapies must demonstrate cost-effectiveness to not only succeed but also to maintain their presence in the market^[45,46]. Moreover, while in Europe, centralized health systems tend to balance cost-effectiveness analyses often in favor of the therapy, these expenses become an additional burden for economically vulnerable patients in countries with limited health care assistance^[45,46]. Ensuring accessibility is a challenge for societies and the scientific community to guarantee equal treatment for all citizens.

Finally, this study did its best to be exhaustive, but a complex methodology had to be deployed because there is currently no simple and accurate way to qualify rare disease gene therapy clinical trials within public databases. There is, therefore, an urgent need to set up a guideline for coding these trials in clinical research databases in order to easily identify rare disease trials and studies with their therapeutic specificity and thus facilitate and accelerate the realization of analyses on this theme, such as the one presented in this document.

However, while significant effort was invested in ensuring the comprehensiveness and accuracy of our study, certain limitations persist. Notably, some trials that evaluate gene therapy treatments in rare diseases might not be labeled as "rare disease" or "gene therapy" within the EudraCT database. This oversight could potentially exclude them from our analysis. Our examination provides a multi-layered understanding, allowing us to identify and quantify the European countries associated with each clinical study. However, the exact count and details of investigator centers by specific countries that may have been involved in these clinical studies remain unidentified.

In summary, advances in scientific research and clinical studies of gene therapy promise great benefits in the long-term treatment of diseases, including rare genetic diseases. The field is advancing rapidly, and various approaches are being explored and/or are already under investigation. In the near future, companies and international agencies may need to re-evaluate and update current regulations as therapies evolve. Further improvements and adaptations require collaborative efforts by multidisciplinary teams (including governments and European authorities) to make breakthroughs accessible to all^[9].

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Author's contributions

Collection and Analysis of Data: Gicquel T

Discussion and writing of the manuscript: Gicquel T, Cortial L, Lutsyk K, Forget S, Braun S, Boyer PO, Laugel V, Blin O

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

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Not applicable.

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