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Clinical Trials: Gene Therapy

Healthcare

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2 Introduction

2.1 Report Scope

Gene therapy involves the delivery of complex treatments to patients. In recent years, there have been several promising clinical trial results within this field targeting an array of inherited neurodegenerative disorders, genetic diseases, and various cancers. Approvals based on these clinical trials have consequently encouraged interest in gene therapy from both industry and non-industry sponsors, and have boosted confidence in the therapeutic delivery of genetic material. This white paper investigates the changing clinical trial landscape for gene therapy clinical trials.

2.2 Methodology

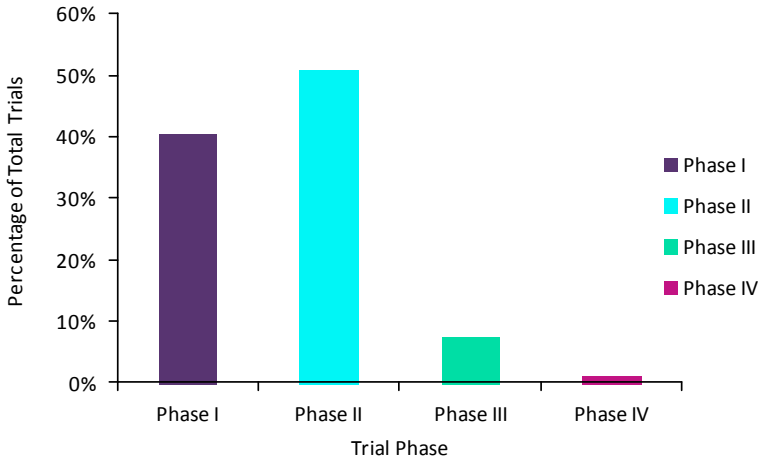
The data for these analyses are derived from GlobalData's clinical trials module on the Pharma Intelligence Center and include gene therapy clinical trials initiated from January 1, 1995 to December 31, 2019. The dataset was analyzed by the number of clinical trials by phase, year, top five therapy areas and indications examined in gene therapy clinical trials, proportion of industry and non-industry trials, top sponsors of gene therapy trials, top geographical locations of gene therapy trials, proportion of single-country/multinational trials, status, top drugs in the last five years, and top reasons for termination. In this report, a number of Phase 0, Phase I/II, Phase II/III, and Phase III/IV trials were combined with Phase I, Phase II, Phase III, and Phase IV trials, respectively.

3 Clinical Trials Landscape

3.1 Gene Therapy Trial by Phase

Of the gene therapy clinical trials with a start date between January 1, 1995 and December 31, 2019, the majority of studies were in Phase II (51.0%), followed by Phase I (40.5%). Phase III trials made up 7.4%, and the smallest proportion of trials was observed in Phase IV (1.2%). There is a large discrepancy in the number of trials in Phase II and III, highlighting that a significant proportion of clinical trials failed to progress to the final stages of clinical development.

Figure 1: Gene Therapy Trials by Phase



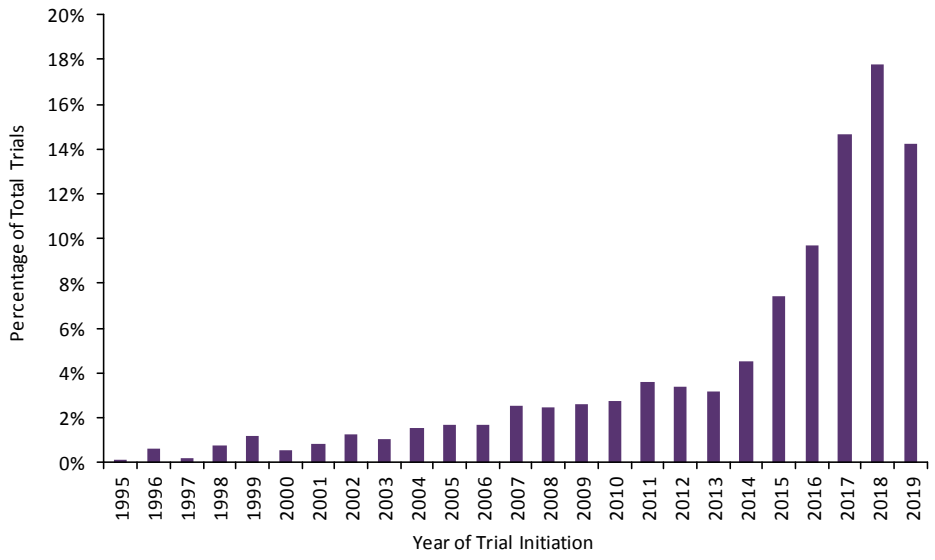
Source: GlobalData

3.2 Gene Therapy Trials by Year of Initiation

The clinical trials included in these analyses have start dates between January 1, 1995 and December 31, 2019. An increasing trend in the number of clinical trials initiated yearly was found, and was most consistently observed between 2014 and 2018, with the highest number of trials carried out in 2018. The approval of UniQure's Glybera (alipogene tiparvovec) by the European Medicines Agency (EMA) in 2012 may have sparked growing interest in the field, as the number of trials initiated in the following years incrementally increased, as detailed in Figure 2. The greatest increase from a previous year to the next was observed in 2017, when the FDA approved the first gene therapy agent, Novartis' Kymriah (tisagenlecleucel). Kite's Yescarta (axicabtagene ciloleucel), another gene therapy agent, was approved later that same year. Notably, the greatest decline in the number of gene therapy trials occurred in 2000, with the preceding year documenting the first death of a clinical trial participant in

a gene therapy trial. This may have resulted in loss of sponsor confidence in gene therapy clinical trials, leading to a temporary drop in clinical trials.

Figure 2: Proportion of Gene Therapy Trials by Year



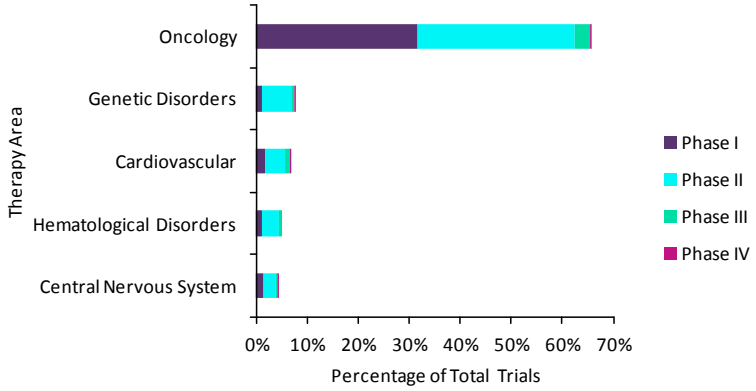
Source: GlobalData

3.3 Top Therapy Areas and Indication

As shown in Figure 3, oncology clinical trials account for the largest proportion of gene therapy studies (65.7%), greatly outnumbering the other top five therapeutic areas combined (24.2%), with the greatest proportion of studies in Phase I (48.3%). Genetic disorders account for the second highest number of studies and have the greatest proportion of trials in Phase II (71.9%). Cardiovascular studies take third place, followed by gene therapy trials targeting hematological disorders and central nervous system gene therapy trials. Gene therapy studies investigating hematological disorders is the only therapeutic area within the top five with no clinical trials in Phase IV.

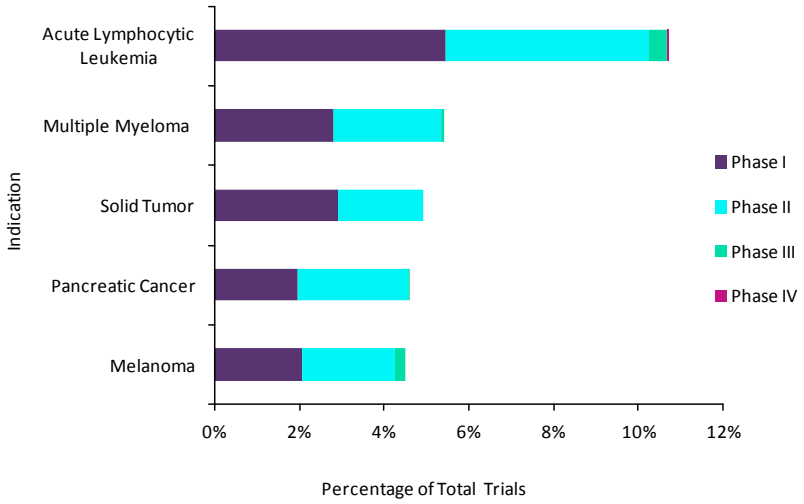
As expected, the top five indications all fall within the oncology therapeutic area, with blood cancers occupying three out of the top five indications. As shown in Figure 4, acute lymphocytic leukemia is the most frequently researched indication in gene therapy studies, almost double that of multiple myeloma, the second most commonly investigated indication. Additionally, acute lymphocytic leukemia is the only indication in the top five with a clinical trial in Phase IV. Solid tumors are the third most investigated indication and have the highest proportion of Phase I studies. Rounding off the top five are pancreatic cancer and melanoma.

Figure 3: Top Therapy Areas Investigated in Gene Therapy Trials



Source: GlobalData

Figure 4: Top Indications Investigated in Gene Therapy Trials



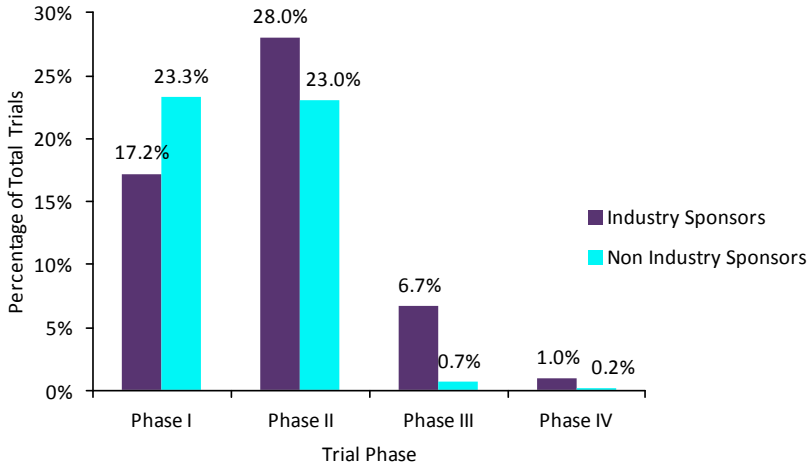
Source: GlobalData

3.4 Top Gene Therapy Sponsors

Industry-sponsored gene therapy clinical trials outnumber those of their non-industry counterparts in Phases II, III, and IV, while Phase I had 1.4 times more non-industry-sponsored trials than industry-sponsored trials, as shown in Figure 5. The most striking difference is seen in Phase III trials, where there are 9.7 times more industry-sponsored trials than non-industry trials. This may be attributed to industry sponsors acquiring the rights to the non-industry-sponsored products once the agents have demonstrated adequate efficacy and safety in the preceding stages of clinical development.

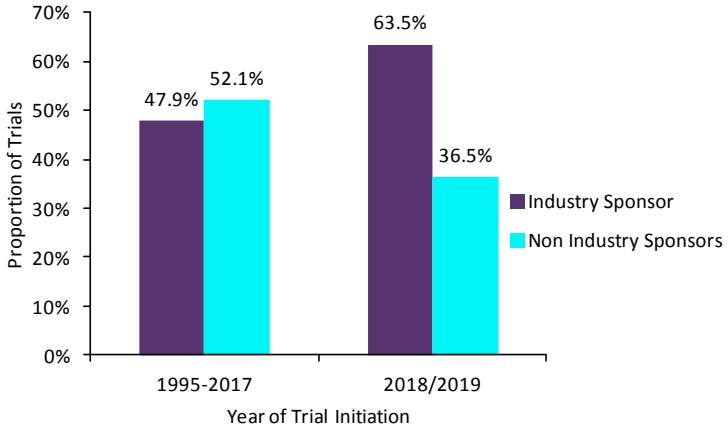
Figure 6 displays renewed industry confidence in gene therapy clinical trials, as highlighted by the 15.6% increase in the proportion of industry-sponsored trials following the announcement of Kymriah's FDA approval in 2017.

Figure 5: Industry versus Non-Industry Sponsors of Gene Therapy Trials



Source: GlobalData

Figure 6: Proportion of Industry and Non-Industry Sponsored Gene Therapy Trials, 1995–2017 versus 2018–2019



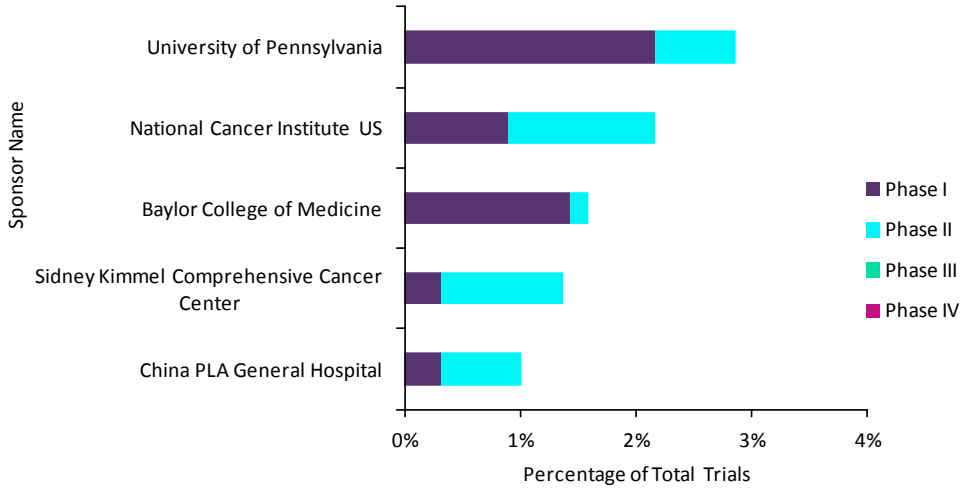
Source: GlobalData

Although industry-sponsored trials outnumber non-industry trials by 5.8%, overall four of the top five sponsors for gene therapy trials are institution-led. However when comparing the top five in each category, the top non-industry sponsors only have early phase clinical trials, whilst all of the top

industry sponsors have at least one clinical trial in phase III. As Figure 7 shows, The University of Pennsylvania sponsored the largest number of gene therapy trials. In 2016, the institute formed in an alliance with Biogen worth up to $2B for the development of targeted therapeutics for the central nervous system, eye, and skeletal muscles. The National Cancer Institute is in second place followed, by Baylor College of Medicine, Sidney Kimmel Comprehensive Cancer Centre, and China PLA General hospital.

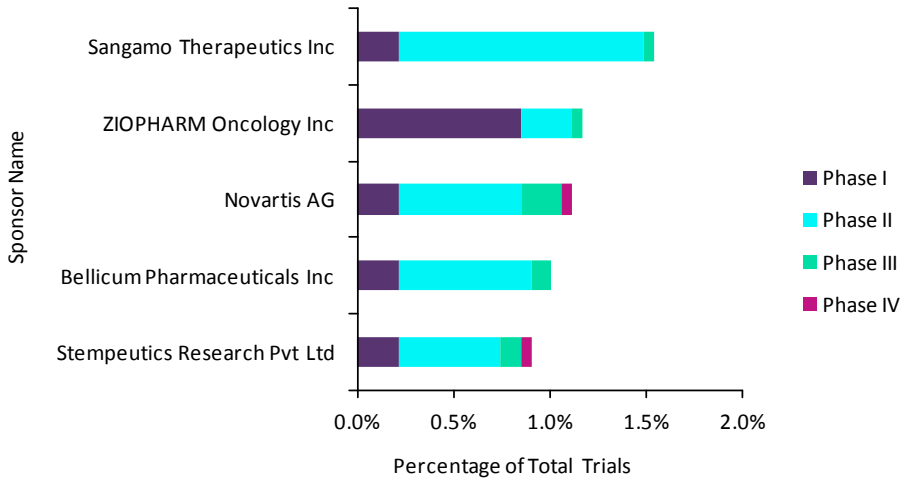
Among the top industry sponsors, Sangamo sponsored the largest number of gene therapy trials and sponsored the joint highest number of phase II studies across both sponsor types. ZIOPHARM Oncology is in second place and sponsor the largest number of phase I industry sponsored gene therapy trials. Novartis holds third place followed by Bellicum Pharmaceuticals Inc, and Stempeutics Research Pvt Ltd.

Figure 7: Top Non-Industry Sponsors of Gene Therapy Trials



Source: GlobalData

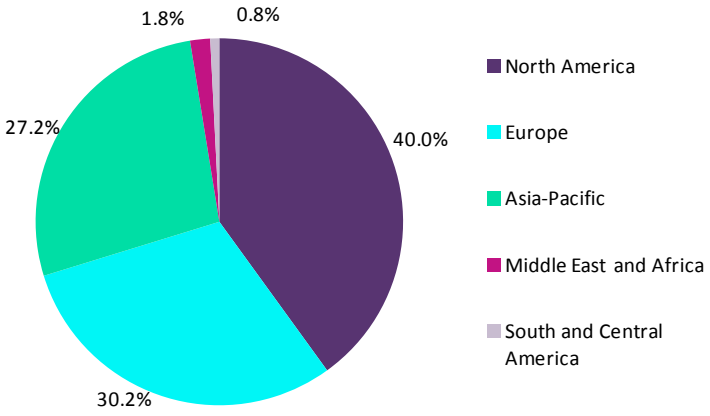
Figure 8: Top Industry Sponsors of Gene Therapy Trials



Source: GlobalData

3.5 Geographical Locations of Gene Therapy Trials

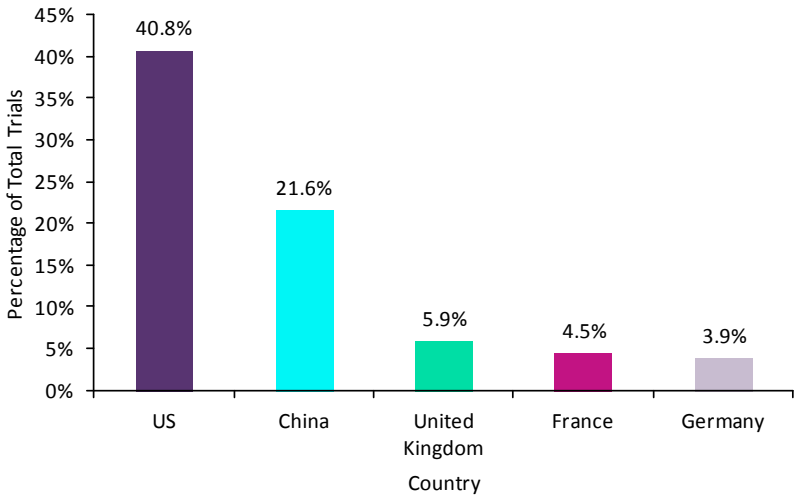
Figure 9: Top Geographical Locations for Gene Therapy Trials by Region



Source: GlobalData

North America has the largest number of gene therapy clinical trials, followed by Europe and Asia Pacific (APAC). Fewer trials were conducted in the Middle East and Africa and South and Central America, as shown in Figure 9

Figure 10: Top Geographical Locations for Gene Therapy Trials by Country



Source: GlobalData

Figure 10 show that the US dominates the research, outnumbering the combined number of trial locations for the remaining top five countries. China, the only APAC country listed in the top five, is in second place. The UK, which has the highest number of clinical trial locations in Europe, is in third place, followed by France and Germany.

3.6 Gene Therapy Trials by Status

Studies that are ongoing or planned make up a significant proportion of the overall trials (61.4%), highlighting recent interest in gene therapy research. Additionally, a significant proportion of trials are completed (28.4%). Withdrawn and terminated have the same number of studies and a similar phase distribution. The smallest proportion of the overall trials are suspended.

Figure 11: Gene Therapy Trials by Status

Source: GlobalData

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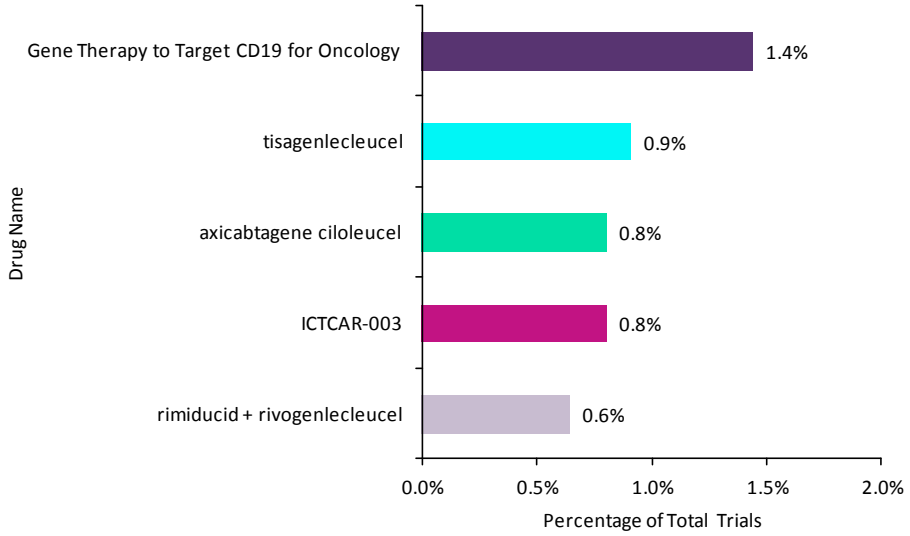
3.7 Top Gene Therapy Drugs 2014–2018

From 2014- 2018, four of the top five therapeutics frequently investigated in clinical trials are CD19-targeting agents, highlighting the promising nature of this strategy. CD19 remains an optimal target due to its wider range of expression relative to targets such as CD20 and CD22, as well as frequent expression across the vast majority of B-cell malignancies. Furthermore, its expression on normal cells is limited to the B-cell lineage. These top four drugs predominantly investigate hematological malignancies. Kymriah, Yescarta, and Innovative Cellular Therapeutics' ICTCAR-003 are all chimeric antigen receptor (CAR) T cell therapies in which a patient's T cells are extracted and implanted with CAR cells, producing a CAR T-cells. The CAR T cells are then replicated and delivered back to the patient via infusion.

For tisagenlecleucel, Novartis sponsors the vast majority of clinical trials (53.0%) under the brand name Kymriah, with the majority of trials targeted against acute lymphocytic leukemia. For axicabtagene ciloleucel, the majority of trials (53.3%) are sponsored by Kite under the brand name Yescarta, with a focus on diffuse large B-cell lymphoma. For ICTCAR-003, Innovative Cellular Therapeutics is the main sponsor of the trials (40.0%), but its involvement as a collaborator with institutions (47.0%) outnumbers the instances where it serves as the main sponsor. ICTCAR-003 focuses primarily on acute lymphocytic leukemia. Bellicum Pharmaceuticals sponsors the majority of studies utilizing its rimiducid + rivogenlecleucel (83.3%), with a focus on improving outcomes in patients receiving allogeneic hematopoietic stem cell transplantation in the treatment of

hematological malignancies and inherited blood disorders. The drug aims to address the prominent causes of morbidity and mortality in patients without a human leukocyte antigen (HLA)-matched related donor.

Figure 12: Top Gene Therapy Drugs, 2014–2018

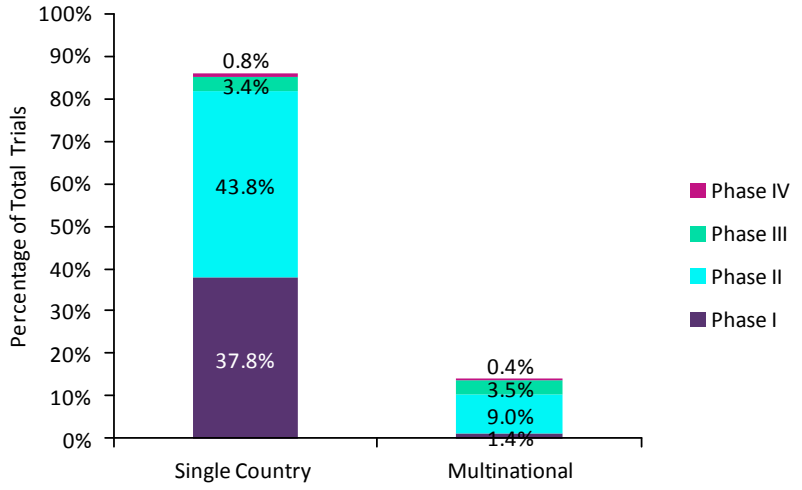


Source: GlobalData

3.8 Single Country versus Multinational Gene Therapy Trials

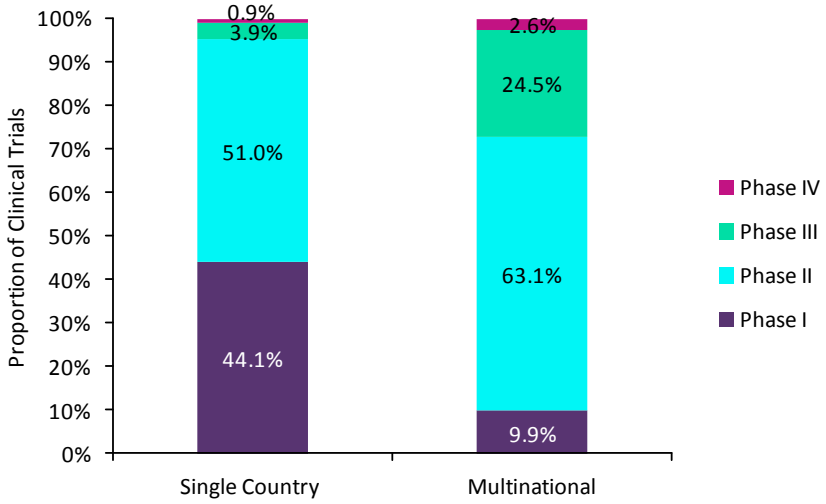
Single country trials represent more than six times the number of multinational trials, as highlighted in Figure 13. This may be attributed to the lack of Phase III clinical trials overall, because these studies are more likely to require multinational trials, as exemplified by the fact that single country trials outnumber multinational trials in all phases except Phase III. Single country studies also make up the greatest proportion of clinical trials in Phase I with 44.1%, compared to only 9.9% with multinational trials. For single country and multinational trials, the majority of clinical trials are in Phase II of clinical development. Although there is a similar number of multinational and single country trials in Phase III, there is a noticeable difference in proportion, with multinational trials having 20.5% greater proportion of trials in this phase. Phase IV trials make up the smallest proportion of trials for both single country and multinational trials, with 0.9% and 2.6%, respectively.

Figure 13: Single Country versus Multinational Gene Therapy Trials



Source: GlobalData

Figure 14: Proportion of Single Country versus Multinational Gene Therapy Trials



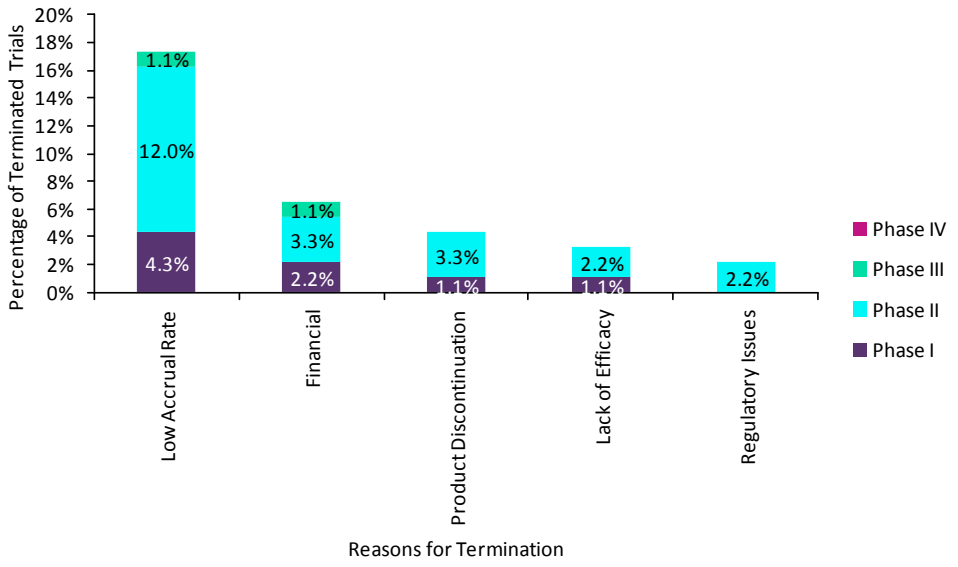
Source: GlobalData

3.9 Reasons for Termination of Gene Therapy Clinical Trials

Clinical trials terminated for “Other” and “Unspecified” reasons were omitted from this analysis. The most frequent cause of clinical trial termination across all phases was low accrual rate, which suggests that a failure to meet recruitment goals is a significant concern in gene therapy trials. This was followed by clinical trials terminated for financial reasons, likely due to the fact that gene therapy

clinical trials are costly and must comply with increasing regulatory requirements that impact financial burden. Furthermore, gene therapy clinical trials conducted within this therapeutic area must see highly significant and favorable results to generate returns on the cost of therapeutics and enrolment. Fewer trials were discontinued as a consequence of product discontinuation, lack of efficacy, and regulatory issues.

Figure 15: Reasons for Termination of Gene Therapy Trials



Source: GlobalData

3.10 Summary

GlobalData performed multiple analyses of gene therapy clinical trials spanning Phases I–IV in all trial statuses from January 1, 1995 to December 31, 2019. The majority of gene therapy trials are early phase studies (90.6%) with 51.0% of trials in Phase II and 40.5% of trials in Phase I. The biggest year for gene therapy trials was 2018 whereas the biggest increase in the number of initiated trials in a one-year period was seen in 2017 from 2016. This rise in gene therapy trials may be due to the first EU and US regulatory agency approvals of gene therapy agents, giving sponsors increased confidence that they can bring gene therapy products to market.

The top therapy area in gene therapy trials is oncology, followed by genetic disorders, cardiovascular disorders, hematological disorders, and central nervous system disorders. The top five indications are acute lymphocytic leukemia, multiple myeloma, solid tumor, pancreatic cancer, and melanoma. Industry sponsors outnumbered non-industry sponsors across all phases except Phase I. Following the

FDA's approval of Kymriah, the proportion of industry sponsors rose by 15.6%, indicating renewed industry confidence in gene therapy clinical trials. Even though industry-sponsored trials outnumber non-industry trials, the top five sponsors include four non-industry institutions and only one industry sponsor. North America dominated the gene therapy research space with the highest number of trials, and the US had the most clinical trials, followed by China and the UK.

Ongoing and planned trials make up the highest proportion of gene therapy trials (62.4%), followed by completed trials (28.4%). Trials with a withdrawn or terminated status account for the same proportion of trials (4.9%).

In the last five years, four of the top five drugs targeted CD19, demonstrating the significant research geared towards gene therapies against CD19. Single-country gene therapy trials strongly outnumber multinational trials. This is likely due to the lack of Phase III trials, which are more likely to require being conducted in multinational studies. The most common reason for trial termination is low accrual rate, followed by financial reasons. The surge in the number of gene therapy trials since 2014 highlights the increased interest within this sector, with every breakthrough and product approval offering new avenues for research. GlobalData expects this trend to continue to rise, as 2019 is on course to be the biggest year for gene therapy clinical trials yet.

4 About the Authors

4.1 Analyst, Clinical Trials Database

Mohamed Abukar, MSc, BSc, is a Clinical Trials Analyst at GlobalData, where his primary responsibilities include the review and update of clinical trial information presented on GlobalData's clinical trials module, the maintenance of data quality through quality control and timely client support. Mohamed is also involved in producing analytical reports and insights, testing database releases and providing comprehensive conference coverage. He has a firm understanding of all aspects of clinical research, drug regulation and safety as well as marketing. Mohamed holds a Master's Degree in clinical drug development from Queen Mary University of London and a Bachelors of Science in Biomedical Sciences from the University of Westminster.

4.2 Associate Director, Clinical Trials Intelligence

Brooke Wilson, BSc Biotech (Hons), is the Associate Director of Clinical Trials at GlobalData in Washington, D.C., where she is responsible for the development and enhancement of the clinical trials and investigator database. Prior to GlobalData, Brooke was the Head, Lead Sheet at PharmSource for 12 years where she gained solid experience in every aspect of drug development, and drove the content and production of the Lead Sheet product. Brooke managed and trained analysts, and worked with software developers for product enhancements based on clients' needs. She has experience in interacting with clients and working with sales as a Lead Sheet technical expert. Brooke graduated from the University of Newcastle, Australia, with a BSc in Biotechnology, followed by an Honors degree in Biotechnology with a thesis focused on intestinal bacteria.

4.3 Global Director of Databases and Analytics

Revati Tatake, PhD, is the Global Director of Databases and Analytics at GlobalData in New York City, where she is responsible for the development and continuous enhancement of databases in the company's *Pharma Intelligence Center*. Revati has diverse experience, both in academic research and the healthcare industry, where she worked on several research, drug discovery, and competitive intelligence projects across many therapeutic areas. Before joining GlobalData, Revati worked at Citeline, where she was involved in competitive intelligence and analytics of clinical trials and products in the areas of Autoimmune/Inflammation, CNS, and Ophthalmology. Previously she worked at Boehringer Ingelheim Pharmaceuticals for over 10 years, where, as a Senior Principal Scientist, she led drug discovery projects involving traditional high-throughput screening, as well as innovative approaches for gene and cell therapies. She is a co-inventor on many issued US patents and

applications related to projects on cell and gene therapies. Revati holds a PhD in Tumor Immunology from the Tata Cancer Research Institute in Mumbai, India. She was also a postdoctoral fellow at the University of Connecticut Health Center.

4.4 Global Head and EVP of Healthcare Operations and Strategy

Bornadata (Bonnie) Bain, PhD, is the Global Head and EVP of Healthcare Operations and Strategy. Bonnie has almost 20 years' experience in the healthcare sector and a proven track record of developing innovative solutions on both the client and agency sides of the business. Bonnie was GlobalData Healthcare's first western analyst and under her leadership, the company launched a number of premium syndicated reports, analytical tools and databases in the pharmaceuticals and medical devices space. Prior to GlobalData, Bonnie was Vice President and Global Research & Analysis Director for Informa's Pharma Division, which includes Datamonitor Healthcare, Scrip Group, and Business Insight. Bonnie also worked for several years at Decision Resources as an Analyst and Project Manager. On the client side of the industry, Bonnie worked for several years as a Senior Manager in Marketing Strategy and Analytics at Boston Scientific where her work contributed to the successful commercialization of the first ever Access and Visualization Platform at the company. Bonnie has a PhD in Biochemistry and Molecular Biology from Purdue University and completed a Post-Doctoral Fellowship in Molecular Pharmacology at the University Of Miami School Of Medicine. She also has a graduate certificate in Applied Management Principles from Purdue University Krannert School of Management.

5 About the Pharmaceutical Clinical Trials Team

GlobalData's Pharmaceutical Clinical Trials Team focuses on ensuring that the company's records of clinical trials are accurate, inclusive, and comprehensive. The team works to make sure that the most up-to-date information on clinical trials is always available to clients through the Pharma Intelligence Center.

6 About GlobalData

GlobalData is a leading global provider of business intelligence in the Healthcare industry. GlobalData provides its clients with up-to-date information and analysis on the latest developments in drug research, disease analysis, and clinical research and development. Our integrated business intelligence solutions include a range of interactive online databases, analytical tools, reports and forecasts.

With an unmatched team of analysts, epidemiologists, and consultants, we provide high-quality, accurate, and transparent insight that can help you achieve growth and increase business value. Our analysis is supported by a 24/7 client support team, and our analyst teams are available to further address client-specific issues or information needs on an inquiry or proprietary consulting basis.

GlobalData has offices in New York, San Francisco, Boston, London, India, Korea, Japan, Singapore, and Australia.

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