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Review

Clinical holds for cell and gene therapy trials: Risks, impact, and lessons learned

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The recent increase in cell and gene therapies being developed has been coupled with a disproportionate increase in Food and Drug Administration (FDA)-mandated clinical holds. Aiming to better understand causes and secondary effects of these clinical holds on biotechnology companies, we analyzed 33 clinical holds that were publicly announced from January 2020 to December 2022. Approximately 80% of the analyzed clinical holds were formally lifted by the close of our study after an average of 6.2 months, and several trials have had significant clinical success following a hold. CAR T cell therapies accounted for nine holds, Lentiviral and AAV-based gene therapies accounted for five and 15 holds, respectively, and other cell and gene therapies accounted for four holds. The most common trigger was an adverse event or patient death. To remove a hold, protocol amendments were the most requested resolution by FDA. While there is no way to guarantee a therapy will not be placed on clinical hold, especially following unexpected adverse events, some deficiencies are avoidable. Utilizing FDA-provided resources on regulations and expectations for cell and gene therapy investigational new drug applications, inclusion of an external safety monitoring board, and a proactive risk assessment plan may prevent a clinical hold or result in a shortened duration.

INTRODUCTION

The number of cell and gene therapy (CGT) clinical trials has increased sharply in the last several years; 10 years ago, approximately 1,800 gene therapy trials were ongoing or had been completed.[1,2] Today, there are over 5,000 gene therapy trials listed with the National Institutes of Health (NIH) including an increase in many new trials incorporating chimeric antigen receptor (CAR) T cell therapies and human genomic editing.[3] Unless they are eligible for an exemption, sponsors of gene and cell therapy products wishing to conduct a trial in the United States must submit an investigational new drug application (IND) to the US Food and Drug Administration (FDA) for review. An IND includes preclinical, chemistry, manufacturing, and controls (CMC), and clinical information, including the clinical protocol(s). Original IND submissions for CGT are primarily submitted to the FDA Center for Biologics Evaluation and Research (CBER). In 2020, CBER's Office of Tissues and Advanced Therapies (OTAT) (recently reorganized and renamed Office of Therapeutic Products), received over 350 new IND applications.[4,5] In 2021, application numbers dropped slightly to 299, potentially due to the COVID-19 pandemic. Overall, new IND applications during the last few years have approximately doubled from the 163 submitted in 2016.

Within 30 days after a sponsor files an original IND, the FDA conducts a multidisciplinary review of the application to determine whether the proposed clinical investigation can proceed. This is primarily based on safety considerations, as the Code of Federal Regulations states, "FDA will, unless patients are exposed to immediate and serious risk, attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order" (21 C.F.R. 312.42(c)).[6] Clinical trials may be placed on clinical hold if the review team identifies deficiencies as detailed in the Code of Federal Regulations.[6] As one would expect, the growth in clinical trials involving cell and gene therapies is accompanied by a growth in clinical holds; however, the increase in holds appears to be disproportionate to the increase in overall clinical trials.[7,8] NIH-listed CGT clinical trials total less than 2% of all listed clinical trials, yet they are responsible for approximately 40% of all clinical holds.[3,7]

This article summarizes clinical holds in the CGT sector issued between January 2020 and December 2022. This research was performed by conducting a retrospective search of the NIH clinical trials database at clinicaltrials.gov, a review of available information from biotech news outlets, and an examination of company-issued press releases. All information regarding a clinical hold, including communications and discussions between the sponsor and the FDA, is considered confidential. Therefore, our analysis of clinical hold data is limited primarily to press releases and other publicly available documents released by sponsors and does not include academic-sponsored, private company-sponsored, or any other trials in which a clinical hold may be deemed not material information. Currently, about 40% of all trials listed on clinicaltrials.gov are categorized as industry sponsored. The amount of information and details of the feedback from FDA is totally dependent on what the sponsor discloses about the specific issue(s) that led to the clinical hold. Despite this limitation and therefore small sample size, we believe that the examination of

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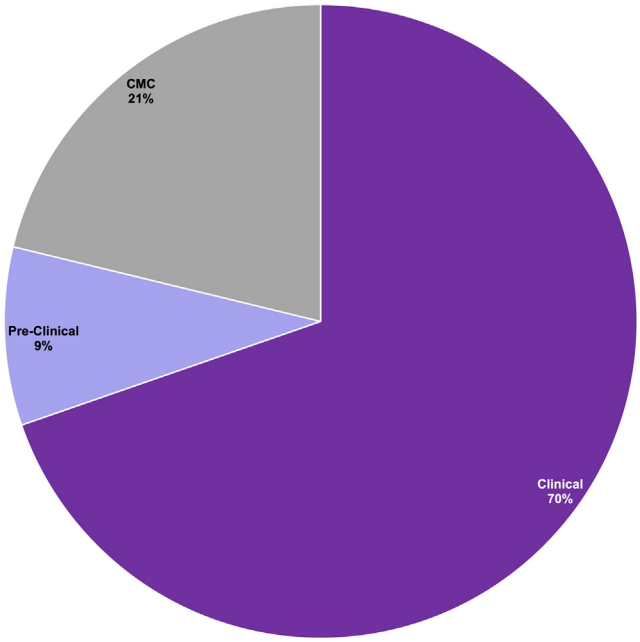

Figure 1. Reported causes of clinical holds

publicly available data on clinical holds provides insights into the reasons for these holds, how frequently they are encountered, and how they can be avoided and/or quickly addressed.

We discuss the common deficiencies reported and provide useful resources that can help sponsors avoid clinical holds and how to address the clinical hold issues expeditiously to allow clinical studies to proceed.

CGT clinical holds: Overview

A total of 33 clinical holds announced from January 2020 to December 2022 were identified. Of these holds, 5 (∼15%) were still active at the end of 2022, and 26 (∼80%) have been lifted. One of the clinical trials was permanently discontinued following the clinical hold due to safety concerns, and one was discontinued by the sponsor due to pipeline reorganization before the hold was lifted. Three other trials were halted shortly after the clinical holds were formally lifted. The average duration of a clinical hold was 6.2 months. For the holds that have been lifted, the length of time a clinical hold was in place ranged from 2 months to 19 months, with a median and mode of 5 months; however, there are a few ongoing clinical holds that have been in place for over 19 months. Per the CBER policy regarding administrative processing of clinical holds for IND applications, the FDA has 30 days after imposition of a clinical hold to issue formal hold comments and 30 days to review a complete response to the hold from the sponsor.[9] Because of these timelines, being on clinical hold for at least 60 days is likely and thus should be considered in discussions of hold length of time.

Overall, publicly provided reasons for FDA-imposed clinical holds can be placed into three main categories of concern: (1) clinical, (2) preclinical, and (3) CMC. The various categories of rates and reasons for clinical holds are provided in Figure 1. Of the 33 clinical holds, 70% (23 of 33) were the result of clinical concerns. Clinical concerns included 39% (13 of 33) of trials that reported a non-fatal adverse event, 27% (9 of 33) of trials that reported a fatal adverse event, and the 3% (1 of 33) of trials that reported no fatalities or adverse events, but the Agency requested clinical protocol amendments. Additional preclinical data were requested in 9% (3 of 33) of cases, and CMC concerns were the cause of 21% (7 of 33) of holds. About a fourth of holds (8 of 33) were put into place just after IND submission and prior to the start of patient dosing.

For the 26 clinical holds that were lifted, in about half of these cases (12 of 26), FDA requested protocol amendments that took an average of 4.8 months to resolve. The FDA requested amendments to CMC information or additional CMC data in about 25% (6 of 26) of lifted holds, which took an average of 8.4 months to resolve, and assessment of adverse event-related causes in approximately 25% (6 of 26) of cases, took an average of 6.5 months to resolve. Concerns regarding preclinical data were responsible for triggering 9% (3 of 26) of holds; however, only one has been resolved and was about 4 months in length.

When the 33 total clinical holds are broken down by product type, we find that 27% (9 of 33) were for CAR T cell-based therapies, 15% (5 of 33) for Lentiviral-based gene therapies, 45% (15 of 33) for AAV-based gene therapies, and 12% (4 of 33) for other cell and gene therapies (Figure 2). Triggers, solutions, and timelines for each product class are further elucidated in the following sections.

CAR T cell-based therapies

Examination of nine clinical holds on CAR T cell therapies ranging from January 2020 to December 2022 (Table 1) reveal that almost all the clinical holds in the CAR T cell field were triggered by a patient death or patient safety concern in an early Phase 1/2 clinical trial. There was one exception, where a hold was placed on the IND before the therapy was first administered to any patient enrolled in the clinical trial; in this case, additional preclinical information was requested.

Three of the nine holds were placed when there was a question about whether a death or adverse event was related to the therapy. Two of these three holds were eventually deemed unrelated to the investigational product, and the trial resumed after an average of 2.3 months. One trial was permanently terminated by the company due to two patient deaths, both due to neurotoxicity. Four holds were followed by requests for protocol amendments and were lifted after an average of 3.8 months; however, two of these trials have since been voluntarily terminated by the sponsor. The holds on CAR T-based therapies were lifted after an average of 4.1 months.

Three clinical holds were followed by other corporate implications for the sponsor. One sponsor lost support from a large industry partner.[26] Another hold on one particular CAR T cell trial also included

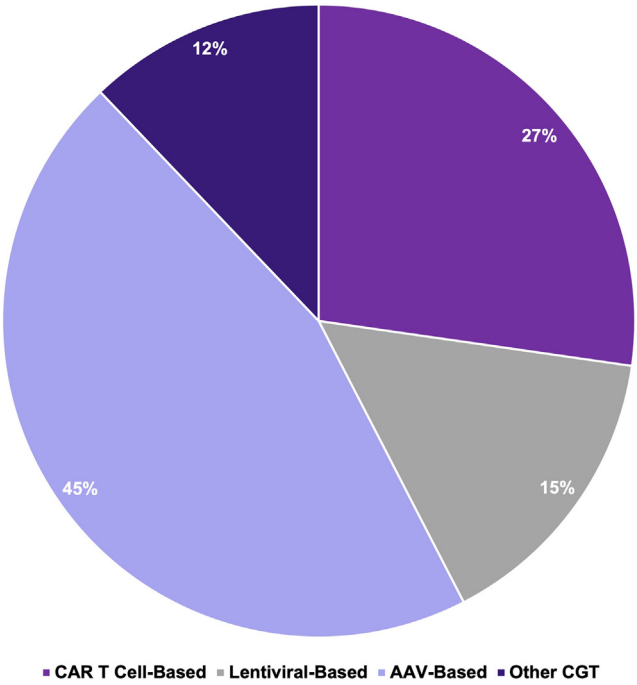

Figure 2. Distribution of INDs placed on hold by product type

a clinical hold on four trials of other CAR T cell therapies from the same sponsor, despite the concerns being specific to one clinical trial. Since then, an industry partner has cut ties with the sponsor returning partial rights to the therapy; however, it was not explicitly stated that it was due, in part, to the clinical hold.[27] Another clinical hold eventually resulted in termination of the clinical trial, and the sponsor then focused efforts on another drug candidate in their pipeline with the hope of an improved safety profile.

CAR T cell therapies have transformed treatment of B cell malignancies but have faced multiple challenges when tested in other cancer indications.[28] Several mechanisms are being employed to overcome these existing and emerging challenges; these newer approaches, however, may present additional safety challenges. Almost all of the CAR T cell trials that were put on clinical hold were for observed patient safety concerns; several of these holds were coupled with requests for a more inclusive and detailed risk assessment plan in the IND.

Lentiviral gene therapies

Examination of five lentiviral-based gene therapy clinical holds since 2020 (Table 2) revealed that two of five were due to CMC issues and three of five were due to adverse events. One adverse event occurred in a patient under 18 years of age and there was one secondary cancer formation reported in an adult patient. All of the lentiviral-based product clinical holds were in trials that included a bone marrow harvest from either a patient or a donor, subsequent transduction of bone marrow cells with the lentiviral vector, followed by administration of the transduced cells to the patient. The FDA requested additional CMC information for two therapies, and for one, the hold was subsequently lifted after about 5 months. Three holds were lifted after an adverse event was deemed unrelated after an average of 10 months. One clinical hold, triggered by CMC concerns, is still ongoing. Three of the five holds were for clinical trials in Phase 1/2 stage of development, and two were in Phase 3.

One clinical trial in which a patient under 18 years of age showed persistent, non-transfusion-dependent anemia resulted in a partial clinical hold. In this case, the partial clinical hold was limited to patients under 18 years of age, but the study was allowed to continue for adult patients. The hold on this therapy was lifted in December 2022 after the adverse event was linked to a pre-existing genetic condition.[30] Two of the lentiviral gene therapy clinical holds, on beti-cel (Zynteglo) and eli-cel (Skysona), were lifted just prior to FDA approval for these products; in both cases, the approvals followed supportive voting from the FDA Cellular, Tissue, and Gene Therapies Advisory Committee in June 2022 stating that the benefit outweighed the risk of malignancy development for these gene therapies.[32,34] In the clinical trials of these lentiviral gene therapies, the development of myelodysplastic syndrome (MDS) occurred periodically post infusion. The FDA review and approval of Skysona indicated that the risk associated with MDS may be outweighed by the benefit of the therapy.[37]

The rest of the lentiviral gene therapy clinical holds (two of five) were triggered by CMC issues. However, the specific CMC issues associated with these submissions were not divulged by the sponsoring companies. The FDA has issued a draft guidance specific to CMC information recommended to be provided in IND submissions titled "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)" (January 2020 guidance). This guidance gives specific information that should be provided and the guidance should be closely followed to best avoid CMC-related clinical holds.[38]

Two of the five clinical holds associated with lentiviral vectors impacted other therapies at the same company. The original clinical hold on lovo-cel also included a hold on their beti-cel (Zynteglo) therapy. The hold on both therapies was lifted in June 2021; however, the second hold on lovo-cel, triggered in December 2021, was lifted in December 2022.[32,34] In August 2022, beti-cel (Zynteglo) was approved by FDA followed by eli-cel (Skysona) in September 2022.[39] Another company's clinical hold also resulted in a postponement of a Phase 2 trial of the same drug intended for use in a different age group.

AAV gene therapies

Fifteen AAV-based gene therapy clinical holds were examined (Table 3) and, similar to lentiviral gene therapies, none of the AAV gene therapy clinical trials were in the oncology field. Eleven of the 15 studies put on hold were Phase 1/2 trials and four were in Phase 3. It was noted that while 73% (11 of 15) were triggered by adverse events in patients or at least one patient death, 20% (3 of 15) were

Table 1. CAR T cell therapy clinical holds

Sponsor/Program/Trial identifier #	Target disease	Dates of hold	Reason for hold	Status/Conclusions
Beam Therapeutics[10] BEAM-201 N/A	T cell acute lymphoblastic leukemia (T-ALL) and T cell lymphoblastic lymphoma (T-LL)	July-22 – Dec-22	IND was submitted end of June 2022 and hold was placed prior to trial start. Insufficient information in the original IND to assess subject safety.	FDA requested: (1) additional control data from genomic rearrangement assessments; (2) further analyses of certain off-target editing experiments; (3) additional control data for a cytokine independent growth assay; and (4) an updated investigator brochure that includes information regarding any new nonclinical studies.
Legend Biotech[11,12] LB1901 NCT04712864	T cell lymphoma	Feb-22 – May-22 – Study terminated	First patient treated experienced low CD4+ T cell counts.	Company reported that FDA stated the IND does not contain sufficient information required by 21 CFR 312.23 to assess the risks to subjects. Legend Biotech voluntarily ended the trial in July 2022.
Atara[13] ATA2271 NCT04577326	Pleural mesothelioma	Feb-22 – Nov-22	Patient in higher dose arm died.	Clinical strategy reassessed as FDA recommended the sponsor run a clinical study with the commercial product as comparability had not been demonstrated.
Celyad Oncology[14–16] CYAD-101-002 NCT04991948	Metastatic colorectal cancer	Feb-22 – Aug-22	Two patient deaths with similar pulmonary findings.	Insufficient information to assess risk to study subjects. Hold was lifted after changes were made to eligibility criteria.
Allogene[17,18] ALLO-501A NCT04416984	Non-Hodgkin lymphoma	Oct-21 – Jan-22	One patient showed evidence of chromosomal abnormality.	Determined abnormality was not related to CAR T (no abnormality in manufactured product or any other patient).
Tmunity[19] PSMA-TGFbRDN auto NCT03089203	Prostate cancer	Jun-21 – Stopped	Two patient deaths due to neurotoxicity from over-reactive immune response.	Permanently stopped clinical trial—working on development of another similar therapy designed to have an improved safety profile.
Bellicum[20,21] BXP-601 NCT02744287	Pancreatic and prostate tumors expressing prostate stem cell antigen (PSCA)	Dec-20 – Jan-21	Death of a pancreatic cancer patient in the trial.	Concluded that patient death was unrelated to BXP-601.
Poseida[22,23] P-PSMA-101 NCT04249947	Prostate cancer	Aug-20 – Nov-20	Patient died from liver failure. Failure appeared to come from macrophage activation syndrome (MAS) that was exacerbated by patient noncompliance.	Protocol amendments intended to increase patient compliance and safety including modified inclusion and exclusion criteria and frequency of monitoring and laboratory testing.
Cellectics[24,25] UCARTCS1A NCT04142619	Multiple myeloma	Jul-20 – Nov-20	Patient suffered a fatal cardiac arrest after receiving the highest dose of the allogenic CAR T.	"Adjusted clinical protocol"; no specific details were provided.

due to CMC issues, and 7% (1 of 15) were due to preclinical data safety concerns.

Of the 15 holds, 73% (11 of 15) were lifted by the end of 2022. Of those lifted, 47% (7 of 15) required protocol adjustments and took an average of 5.7 months to resolve, 27% (3 of 15) of the holds that were lifted were due to CMC issues and were resolved after an average of 5.3 months. The remaining 9% (1 of 15) were triggered by an adverse event that was determined to be unrelated to the therapy after a 5.2-month hold. Three holds were ongoing at the end of 2022. For one therapy, both primary and secondary endpoints of the trial had been met by the initiation of the hold, and the results of the trial have been published.

Three clinical holds on AAV-based gene therapies may have impacted other aspects of the company sponsor. Following a hold for a Phase 3 trial, one company also chose to voluntarily pause another Phase 3 gene therapy trial that used the same vector for a different indication. Another company cited significant financial consequences, due in part to the clinical hold, as a reason for abandoning several other programs at the company including one clinical stage gene therapy program treating Duchenne's muscular dystrophy (DMD).[52] Another company has since withdrawn their study due to lack of participants, and the company-initiated development of a second-generation product that is still in discovery (per pipeline on company website[63]).

Table 2. Lentiviral gene therapy clinical holds

Sponsor/Program/Trial identifier #	Target disease	Dates of hold	Reason for hold	Status/Conclusions
Mustang Bio[29] MB-207 N/A	X-linked severe combined immunodeficiency	Jan-22 – Present	CMC clearance failed post IND submission (IND submitted Dec. 2021)	Based on feedback from the FDA regarding CMC information. The company postponed the trial in May 2023.
Bluebird Bio[30,31] Lovo-cel NCT02140554	Sickle cell disease	Dec-21 – Dec-22	One patient under the age of 18 showed persistent, non-transfusion-dependent anemia.	Hold was only for patients under 18 years of age (partial hold). No evidence of malignancy or clonal predominance. Cause of anemia was determined to be an underlying genetic condition that will be screened for in future studies. This was the second hold for this therapy, the first 02/2021–06/2021 due to MDS diagnosis in a patient.
Bluebird Bio[32,33] ALD-104, (Eli-cel, Skysona™) NCT03852498	Cerebral adreno-leuko-dystrophy	Aug-21 – Sep-22	Multiple patients developed myelodysplastic syndrome (MDS).	Long-term safety and efficacy follow-up studies are being done. No events of acute or chronic graft-versus-host disease have been reported nor cases of graft failure, rejection, insertional oncogenesis, or replication competent virus (17 patients). Skysona was FDA approved September 2022.
Bluebird Bio[33,34] Beti-cel (Zynteglo®) NCT02906202	b-Thalassemia	Mar-21 – Jun-21	Placed on hold alongside lovo-cel after an MDS diagnosis. The two therapies use the same lentiviral vector.	Zynteglo was FDA approved Aug-2022.
Mustang Bio[35,36] MB-107 NCT01512888	X-linked Severe Combined Immunodeficiency in Infants	Aug-20 – Jan-21	CMC data issues	Hold lifted after review of comprehensive CMC data

Other cell and gene therapies

Other cell-based therapies include natural killer (NK) cell therapy, tumor-infiltrating lymphocyte, and stem cell therapies; however, these programs still represent only a fraction of cell-based therapies, as CAR T cell therapies are still dominant. From publicly available records, there were four clinical holds in the other CGT category (Table 4). All holds in this area applied to Phase 1/2 trials. Of the four clinical holds, none were related to adverse events or patient deaths. For one trial, donor eligibility requirements and CMC issues resulted in a clinical hold, though the hold was subsequently lifted 6 months later after amendments to CMC documents were made by the sponsor. One trial was on a partial clinical hold following the safety phase of the trial, and an improved potency assay was requested; this hold has since been lifted. Another hold was due to additional data being required before the next dose cohort could be initiated, and that hold was lifted after 2 months. The reason for one hold was disclosed as a request for additional preclinical data and is still ongoing. None of the CGT holds had a reported impact on other therapies being developed by these sponsors.

Long-term financial impact

To date, the FDA has approved six CAR T cell therapies, five AAV-based gene therapies, and two lentiviral-based gene therapies. The sharp increase in IND submissions may lead to an uptick in approved therapies for patients with unmet medical needs. One challenge of clinical holds that may delay necessary therapies from reaching patients, especially for smaller companies, is the financial impact of a clinical hold. In the 7-day period following a clinical hold, when normalized to the Nasdaq index, stock prices fell an average of 1%. Stock prices continued to gradually decline on average to a level about 4% below the pre-hold stock price even 20 weeks later (Figure 3). Stock prices continued to decline for several months following a hold announcement; however, there were points were stock prices came close to the pre-hold price: 6 weeks and 13 weeks after a hold was announced.

After clinical holds are lifted, when normalized to the Nasdaq, there is almost no resurgence in stock price in the following weeks compared with the price erosion following the placement of a clinical hold (Figure 4). Interestingly, the lifting of a clinical hold has the greatest impact about 6 weeks later, but the rise in stock price only amounted to an average rise of less than 1% and does not appear to persist. By 6 weeks, the stock price has begun to fall again, breaking even and continuing to decrease for the next several weeks.

In an analysis of stock prices following the announcement of a clinical hold or hold lift, it is important to consider several other factors, including the overall biotechnology sector and stock price fluctuation. In January 2020, when our analysis began, the Nasdaq Inc Biotechnology Index (Nasdaq: NBI) reported value was around 3,715 and gradually increased throughout the next year when it hit a peak in

Table 3. AAV-based therapies clinical holds

Sponsor/Program/Trial identifier #	Target disease	Dates of hold	Reason for hold	Status/Conclusions
Astellas[40] AT845, FORTIS NCT04174105	Pompe disease-late stage	Jun-22 – Ongoing as of Dec-2022	A serious case of peripheral sensory neuropathy.	The FDA informed the company that it did not have sufficient information to assess the risks to subjects and requires additional information about the recently reported serious adverse event. Hold was lifted in January 2023.
LogicBio[41,42] LB-001 NCT04581785	Methyl-malonic Acidemia (MMA)	Feb-22 – May-22	Two patients (6 months–2 years) developed thrombotic microangiopathy. Serious adverse events appear to be limited to infants, but treating this age is necessary for maximum impact of the therapy.	Next patients will receive the same dose but will be continually assessed. Additional screening and monitoring requirements are in place. Trial will now include additional checks for complement activation and the use of a complement inhibitor if lab test reveals a potential case of thrombotic microangiopathy.
Homology Medicines[43,44] HMI-102 NCT03952156	Phenyl-ketonuria (PKU)	Feb-22 – Jun-22	Elevated liver function tests. All are resolved and none required hospitalization.	FDA requested modifications to risk mitigation measures. Clinical protocol adjustments made (inject a T cell inhibitor and steroids). Long-term follow-up is already being conducted (NCT04348708).
Pfizer[45,46] PF-06939926 NCT03362502	Duchenne muscular dystrophy	Dec-21 – Apr-22	Death of a young patient.	Cause of death was assumed to be more advanced disease and underlying cardiac dysfunction. FDA requested a potency assay and a protocol amendment, and the sponsor did both. Protocol amendment consists of closer monitoring of patients; there will be a 7-day hospitalization period after patients receive the therapy. Still determining strategy for non-ambulatory patients.
Pfizer[47,48] giroctocogene fitelparovec NCT04370054	Hemophilia A	Nov-21 – Mar-22	Some patients showed higher-than-normal factor levels which increases the risk of blood clots.	Adjusted protocol. Voluntary pause was maintained an additional 7 months (Sep-22) until sponsor had met all necessary conditions, including approval of updated study protocols by regulatory authorities.
Selecta[49,50] SEL-302, (MMA101 plus ImmTOR) N/A	Methyl-malonic acidemia (MMA)	Nov-21 – Mar-22	Trial has not been initiated yet—no clinical or preclinical issues.	FDA requested further data on CMC linked to the MMA-101 product candidate.
BioMarin[51] BMN 307 NCT04480567	Phenyl-ketonuria	Sep-21 – Ongoing as of Dec-2022	Clinical hold was based on interim safety findings from a preclinical non-GLP pharmacology study. Several mice developed tumors. Lower doses were administered in clinical trials. No issues in humans to date (over 3,000 patients treated).	FDA asked for more animal studies. Delay is expected to last "several quarters."
Astellas[52] AT132 (bilparvovec) NCT03199469	X-linked myotubular myopathy	Sep-21 – Ongoing as of Dec-2022	A total of four patient deaths. The first three received the higher dose and developed liver dysfunction and eventual liver failure. Most recent patient died who received a lower dose; cause of death has not been disclosed.	Patient who received this dose had abnormal liver tests despite a normal liver ultrasound and tests prior to dosing. This is the second time this therapy has been put on clinical hold. Hold was lifted in January 2023.
Rocket Pharma[53,54] RP-A501 (AAV9.LAMP2B) NCT03882437	Damon disease	May-21 – Aug-21	FDA requested modifications to the trial protocol and revised guidelines for patient selection and management.	Protocol modifications only.

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Table 3. *Continued*

Sponsor/Program/Trial identifier #	Target disease	Dates of hold	Reason for hold	Status/Conclusions
UniQure[55,56] AMT-061 (Etranacogene dezaparvovec) NCT03569891	Hemophilia B	Dec-20 – Apr-21	One patient developed hepatocellular carcinoma.	Determined not related. The patient had multiple risk factors making them susceptible to the cancer. No other adverse effects have been recorded.
Voyager[57,58] VY-HTT01 NCT04885114	Huntington's disease	Oct-20 – Apr-21 – Stopped	Hold placed following IND submission before trial was initiated due to CMC issues.	Updated CMC section of the IND (details vague). The study has since been withdrawn (no participants) and the company has initiated a second-generation product that is in discovery phase (per pipeline on company website).
Lysogene[59] LYS-SAF302 NCT03612869	Mucopolysaccharidosis Type IIIA (MPS IIIA)	Jun-20 – Ongoing as of Dec-2022	Observations in some patients of localized findings on magnetic resonance images at the intracerebral injection sites. The localized nature of the findings suggests a potential connection to delivery.	At the time of hold, 19 out of 20 patients have been treated, The primary and secondary trial endpoints are based on the analyses of these 19 patients already enrolled. Therefore, company reports that there is no anticipated impact on the current clinical trial timelines. Results of the trial were announced in November 2022. FDA has not approved the therapy and has not lifted the hold.
Passage Bio[60] PBGM01 NCT04713475	Infantile GM1	Aug-20 – Jan-21	FDA placed on hold and requested additional risk assessments of the biocompatibility of the proposed intra cisterna magna (ICM) delivery device.	No information about resolving the hold was given. Note that the hold was not regarding the therapy but the delivery device.
Voyager[61] VY-AADC NCT03562494	Parkinson's	Dec-20 – Stopped	Observation of MRI abnormalities in some RESTORE-1 study participants. The clinical implications of this observation are currently unknown and are being evaluated.	No longer in the pipeline. Program end was announced in February 2021.
Sarepta[62] SRP-9001-103 NCT03199469	DMD	Aug-21 – Oct-21	IND placed on clinical hold as it did not contain sufficient information required under 21 CFR 312.23 to assess the risks to subjects of the proposed studies. An unexpected serious adverse event was reported, of asthenia in a 9-year-old subject, requiring hospitalization and respiratory support after he received therapy in Study SRP-9001-103.	Few details are known as this hold was not disclosed until the FDA advisory committee in May 2023. This was the second clinical hold for this product, the first was in 2018 due to CMC deficiencies (3 months, June -Sept. 2018).

September 2021 at around 5,449. At the end of December 2022, the value was 4,213. The overall health of biotech companies should be considered in the larger picture when looking at effects of clinical holds on stock prices, alongside potentially disproportionate stock price erosion in the face of bad news.

Financial effects on companies are dissimilar for companies of different sizes; smaller companies that have one or two therapies in the clinical stage or pipeline may have a more difficult time surviving the financial effects of a clinical hold compared with a more established company that has multiple products in the clinical pipeline and possibly approved products that generate revenue. Regardless, stock prices appear to take a long-lasting hit in value that is not recuperated following the lifting of a clinical hold. For smaller companies, a long-term drop in stock value could be significantly detrimental. The long-standing financial effects of a clinical hold drive home the importance of avoiding a clinical hold as best as possible; however, the financial effects may not be justified, as a clinical hold does not mean the end of clinical development of a beneficial therapy—the majority go on to later phase trials or to be approved by the FDA. Lasting financial effects that are the result of a hold, therefore, may force companies to scrap otherwise promising programs to conserve cash and could possibly prevent some life-saving therapies from reaching patients who are in need.

Avoidance of clinical holds

Patient safety is a top priority for the FDA, and clinical holds are implemented to protect patients from serious safety risks. Proper planning in provision of required data to support an IND and clinical study can lessen the risk of a clinical hold. This may also avoid the chances for a delay or stopping further development of a potentially life-saving therapy for patients in need.

Table 4. Other Cell and Gene Therapies clinical holds

Sponsor/Program/Trial identifier #	Target disease	Dates of hold	Reason for hold	Status/Conclusions
Verve Therapeutics[64] VERVE-101 (Non-viral gene editing treatment) N/A	Hetero-zygous familial hypercholesterolemia (HeFH)	Nov-22 – Ongoing as of Dec-2022	FDA requests additional preclinical data relating to: (1) potency differences between human and non-human cells, (2) risks of germline editing, and (3) off-target analyses in non-hepatocyte cell types. The FDA also requested available clinical data from the ongoing heart-1 trial. In addition, the FDA has requested modification of the trial protocol in the United States to incorporate additional contraceptive measures and to increase the length of the staggering interval between dosing of participants.	Verve intends to submit a response as expeditiously as possible. No clinical trial number at this time.
Gamida Cell[65,66] GDA-201 (Cryopreserved NK Cell therapy in combination with rituximab.) NCT05296525	Follicular and diffuse large B cell lymphomas.	Oct-21 – Apr-22	FDA had requested modifications in donor eligibility procedures and sterility assay qualification (CMC).	Trial was put on hold after IND application and before initiation of dosing.
Vertex[67,68] VX-880 (Stem cell-derived, fully differentiated pancreatic islet cell replacement therapy) NCT04786262	Type 1 diabetes	May-22 – July-22	Clinical hold was a "surprise" to sponsor. To date, there have been no serious adverse events, and the first two patients treated with half the target dose established proof of concept.	FDA determined that there was not enough evidence to support increasing the treatment dose as planned. So far, evidence supporting product benefit in patients is strong. No serious adverse events.
Editas Medicine[69,70] EDIT-301 (HSCT edited cell therapy) NCT04853576	Sickle cell disease	Jan-21 – July-22	Partial clinical hold. Company passed safety phase but was required to develop and submit an improved potency assay prior to enrolling the efficacy phase.	Improved potency assay.

In our analysis of clinical holds issued to sponsors of CGT products between 2020 and 2022, AAV-based gene therapies and CAR T cell-based therapies were more likely to be put on hold, making up 45% (15 of 33) and 27% (9 of 33), respectively, of all clinical holds in this sector (Figure 2). Over 70% (23 of 33) of holds were triggered by clinical concerns, followed by 21% (7 of 33) triggered by CMC issues and with 10% (3 of 33) or less due to preclinical issues (Figure 1). On average, it took sponsors about 6 months to resolve the hold; however, clinical holds due to CMC issues took the longest to be lifted with an average duration of over 6 months. Guidance in the growing CGT field is evolving rapidly alongside the field. It is important to rely on current regulations and guidelines and correct gaps as soon as they are identified.

According to FDA, typical CMC deficiencies leading to a clinical hold include but are not limited to (1) compatibility with administration devices and containers, (2) stability during transport, (3) development of adequate potency assays, (4) comparability bridging studies, (5) substantive manufacturing changes, and (6) release specifications.[71,72] Additionally, lack of demonstration that the material used in the preclinical studies is representative of the material to be used in the clinical trial can also lead to a clinical hold. FDA provides many resources regarding IND regulations and expectations for CGT INDs. These include CFR Title 21, FDA guidance documents, FDA presentations and meetings with the agency, and FDA website learning presentations and videos. Guidance documents are non-binding agency resources that describe and clarify the FDA's current thinking related to regulatory issues and procedures. Unlike regulations and laws, guidance documents are not enforceable and should be considered recommendations. Nevertheless, some of the CMC deficiencies observed in this paper are addressed in a recently released FDA guidance specific to CMC issues for human gene therapy IND applications.[38] This guidance document should be closely followed to best avoid CMC-related holds, as these holds took the longest to resolve. Another CMC guidance on human somatic cell therapy INDs should also be reviewed, if applicable.[73] CMC issues resulting in clinical holds are not only problematic for those specific CGT products but can also be an issue for other products under development. Multiple studies looking at INDs submitted to the Center for Drug Evaluation and Research (CDER) found CMC issues to also be the leading cause for clinical holds within that center and noted that many of the holds could be avoided by following available guidelines for investigational product development.[1,71,74]

Most clinical holds noted in this assessment were due to an adverse event, including death, in a clinical trial. Although these adverse events may or may not have been expected, including a more inclusive and detailed risk assessment plan in the IND submission and

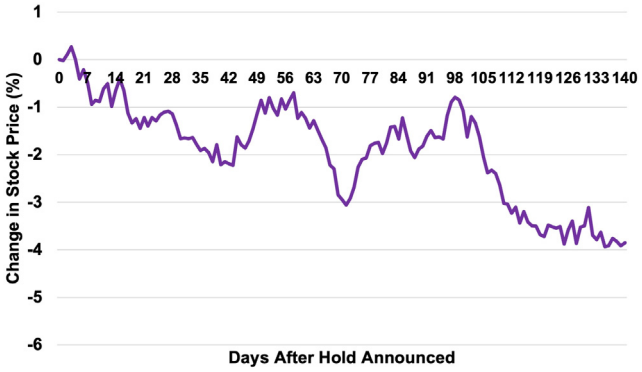

Figure 3. Average percent change in stock price following announcement of a clinical hold (Normalized to Nasdaq)

ensuring a sound clinical protocol with specific stopping rules for toxicity may have resulted in avoidance or shortening of clinical holds for some companies, as these were commonly requested protocol adjustments. Additionally, in the case of unexpected adverse events that could occur during a clinical trial, having an external safety monitoring board and developing a detailed and proactive risk assessment and management plan could shorten or prevent a clinical hold. For example, a patient death recently occurred in a clinical trial following the dosing of an investigational cell therapy product.[75] This event triggered a pre-specified, temporary stopping requirement by the sponsor and review by a data monitoring committee (DMC). After review of the patient's death, the DMC recommended that dosing in the trial continue. In this case, the proactive assessment by the DMC possibly prevented a clinical hold, though this ultimately may not preclude a clinical hold imposed by FDA. Quick and efficient communication, and a thorough systematic approach to examining all clinical trial documents is essential. A useful guidance for assessing unexpected toxicity, including tumor development and death, can be found in the FDA's guidance on long-term follow-up of gene therapy products.[76]

In our analysis, holds due to preclinical issues were the least frequent cause of a clinical hold. These may be reduced by carefully reviewing the results of each preclinical study conducted and satisfying the requirements outlined in 21 CFR 312.4 (b)(iv) by submitting sufficient information for the agency to assess the potential risks to the patient. This exercise should include identifying any safety findings, determining their relevance to the clinical study, and providing a mitigation and monitoring plan for potential safety concerns or issues in the clinical protocol. Potential off-target effects for genome-edited products (both *in vitro* and *in vivo* edited) need to be comprehensively studied and assessed for potential impact on patients to be enrolled in the clinical trials. As outlined in the above guidelines provided by FDA, a comprehensive and robust preclinical plan to evaluate potential toxicity, biodistribution, and minimum effective dose should be developed and ideally discussed with the agency prior to IND submission as CGT products are unique.

Minimizing the risk of any potential clinical hold should begin by collecting as much information and feedback from the FDA early in the IND process. An important way to anticipate the information FDA requires to be included in an IND is to carefully read through FDA-issued guidance documents relevant to the specific product type and/or indication. For the CGT sector, there are multiple guidance documents that may apply. With the uptick in clinical holds on gene and cell therapies accompanying the major increase in development of these novel therapies, it is highly recommended that developers carefully review two new FDA draft guidance documents that were released in the first quarter of 2022: "Considerations for Development of CAR T cell Products" and "Human Gene Therapy Products Incorporating Human Genome Editing."[77] These guidance documents provide FDA's recommendations regarding preclinical, CMC, and clinical information to be addressed in an IND for these specific products. The release of more guidance documents from FDA, hopefully, will further elucidate expectations and reduce the frequency of clinical holds in the CGT sector. After collecting as much information as possible from the FDA or other resources as to why a hold was placed, sponsors should request a Type A meeting. Per FDA, "Type A meetings are reserved for discussions necessary for an otherwise stalled product development program to proceed or to address an important safety issue." Requests for Type A meetings, including a briefing document, should be submitted as an amendment to the existing IND. FDA will respond to the meeting request within 14 days of receipt and schedule the meeting within 30 days of receipt.

Regarding AAV-based products, an advisory committee met in September 2021 to discuss emerging safety issues that were identified by the FDA.[78] The issues included oncogenicity risks due to vector genome integration, hepatotoxicity, thrombotic microangiopathy, neurotoxicity in preclinical studies, especially related to the dorsal root ganglia, and observed clinical neurotoxicity based on brain magnetic resonance imaging studies. For any AAV-based product planned for an IND filing, these risk factors should be assessed in preclinical studies as applicable to the product and proposed route of administration in addition to development of a safety monitoring plan for clinical trials.

Additional preparation for a successful IND application includes early communication with the FDA such as by requesting an INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs (INTERACT) meeting during early preclinical development stages, and/or a pre-IND meeting just before conducting definitive preclinical studies. An INTERACT meeting is intended to obtain feedback early in product development when the investigational product has been identified, and some preliminary, but not definitive, preclinical proof-of-concept studies have been conducted. Importantly, for an INTERACT meeting, no toxicology studies should be designed or conducted, for this may indicate to the FDA that product development is too far along to be appropriate for an INTERACT meeting. When proof-of-concept and preliminary safety studies have been completed but before definitive safety

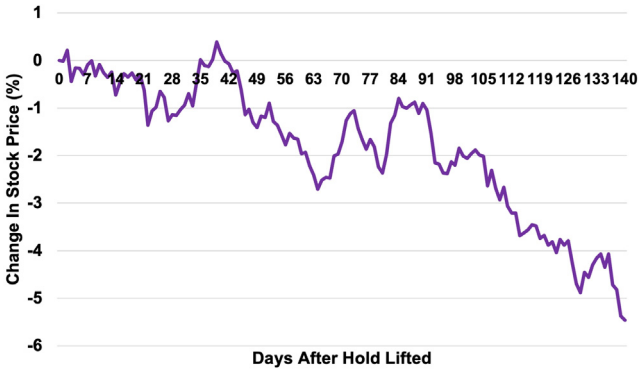

Figure 4. Average percent change in stock price following lifting of a clinical hold (Normalized to Nasdaq)

or toxicology studies are complete, a pre-IND meeting is suggested. A pre-IND meeting, like an INTERACT meeting, is intended for feedback on specific questions regarding study design, proposed studies, and test/model systems. More information is provided in the guidance document for meetings with the FDA.[79] It is essential that sponsors address each of the comments made from any FDA feedback in the IND as the FDA will check that pre-IND correspondence is addressed.

Conclusion

Clinical holds can delay and disrupt CGT development programs and may produce long-lasting adverse financial effects for sponsors; however, most trials put on hold resume activity within 6 months. We found adverse events to be the most common trigger of a clinical hold. While unexpected adverse events may result in an unavoidable clinical hold, inclusion of an external safety monitoring board, a proactive risk assessment or management plan, or by proactive institution of preventive therapies such as immunosuppressants may prevent a clinical hold or result in a shortened duration. Other deficiencies leading to a clinical hold can be avoided when sponsors understand and address FDA regulations and expectations for CGT INDs. CMC and preclinical concerns accounted for over 25% of CGT clinical holds that were analyzed. As the CGT sector continues to expand and new, unique modalities are developed, CMC information and a comprehensive preclinical plan to assess potential toxicity (on-target and off-target), biodistribution, and minimum effective dose will continue to be essential. Failure to address these preclinical or CMC expectations can result in a clinical hold prior to start of a clinical trial. As the CGT field continues to expand and introduce novel CGT products into clinical trials, sponsors and FDA will continue to face new challenges, so we may continue to see an increase in clinical holds in coming years. It is recommended that the FDA strongly consider alerting the industry early on regarding specific safety concerns they may be seeing for certain therapeutic classes of products that they may see under INDs, while maintaining confidentiality could mitigate the risk for clinical holds, as sponsors could plan to look for these events in the preclinical setting and define risk management plans to assess such adverse effects in the clinical trials. It is important to note that the majority of trials that were placed on clinical hold were able to resume activity within a few months, and that several therapies that have previously been on clinical hold go on to be FDA approved for the benefit of patients.

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DECLARATION OF INTERESTS

The content of this article represents the authors' opinion and may not necessarily represent the views of their employers. C.W. and R.P. are employed by Vor Biopharma. D.D. is employed by NDA Partners.

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