UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FDA CBER OTAT Town Hall: Clinical Development of Gene Therapy Products for Rare Diseases

February 7, 2023

Note: This document is not official FDA guidance.

FDA CBER OTAT Town Hall: Clinical Development of Gene Therapy Products for Rare Diseases
February 7, 2023

DR. TEJASHRI PUROHIT-SHETH: Good morning, everyone, and welcome. Thank you all for joining us today for OTAT's town hall. Today's event is hosted by the Office of Tissues and Advanced Therapies, or OTAT, within the Center for Biologics Evaluation Research at the Food and Drug Administration.

My name is Dr. Tejashri Purohit-Sheth, and I am the Director of the Division of Clinical Evaluation and Pharmacology/Toxicology within OTAT, and I will also be your moderator for today's town hall. As you all know, today's town hall is focused on the clinical development of gene therapy products for rare diseases.

Before we begin, I want to mention the importance of today's topic. There are over 7,000 rare diseases affecting more than 30 million people in the United States. Many of these rare diseases are life-threatening and without available therapies. For many rare disorders, as there are no therapeutic options, gene therapies provide hope for potential therapies for these conditions. More than half of the investigational products evaluated in OTAT are for rare diseases, and many of these are gene therapy products. OTAT is committed to supporting the continued development of gene therapies, particularly for rare diseases, and to address the significant unmet medical needs, and that is why we are here today, to help answer some of your questions regarding clinical development of gene therapy products for rare diseases.

I want to share some background about the OTAT Town Hall series. OTAT launched its virtual town hall series to engage with product development stakeholders and researchers to discuss topics related to OTAT-regulated products. These town halls have a question-and-answer format, with the goal of providing regulatory information to stakeholders to help advance drug development.

Please note that this town hall is being recorded. The recording and event materials will be posted on FDA's website in the next few weeks. We will also be providing a transcript of the recording. Closed captioning for this event is available directly in Zoom.

This event is a question-and-answer format discussion. If you have a question, please type your question directly into the Q&A box in Zoom. The Q&A box can be found at the bottom of your screen in Zoom. We appreciate the questions submitted in advance and look forward to seeing your questions today during the live Q&A session. We will do our best to address as many as we can today, but please note that FDA is not able to comment on or answer questions regarding specific investigational products or drug applications. Also, we will not address any questions that we consider are out of scope for this particular event. Lastly, please use the chat box if you experience any technical difficulties during this OTAT town hall session.

I'd now like to take a moment to introduce you to today's panelists from OTAT's Division of Clinical Evaluation and Pharmacology/Toxicology. We have with us: Dr. Melanie Blank, who is a Clinical Team Leader in the General Medicine Branch 1; Dr. Elizabeth Hart, who is the Branch Chief for General Medicine Branch 1; and Dr. Lei Xu, who is the Branch Chief for General Medicine Branch 2. Thank you to all of our panelists today for taking time out of your day to sit on this panel and address the questions and answers for this town hall event.

We will now move to our Q&A portion of today's town hall. We will begin by answering questions submitted during the registration process, followed by responding to your questions submitted during the live Q&A event. As a reminder, you can submit a question for our panelists in the Zoom Q&A box at any time during the event. This is located at the bottom of your screen in Zoom. Again, we will try to address as many questions as we can today, but please remember that we will not be discussing any questions regarding particular products or particular applications that we may have. We will also not be able to discuss questions related to our draft guidance documents under public commenting period or under revision for final guidance document publication.

We hope you can stay on with us for the entire event but would also like to note that the town hall is being recorded, so you can visit the full discussion at a later point in time after the recording is posted on our website.

Let's go ahead and get started and begin with our first question that was submitted during the registration process. The first question is for Dr. Melanie Blank.

What factors should be considered when determining the study population for a gene therapy early-phase trial?

DR. MELANIE BLANK: Good morning. I'm Melanie Blank, and I'm very excited to be here today to be talking about gene therapy. Thank you very much, Tejashri, for introducing this town hall, and thank you all for being here today.

It's a very exciting time in gene therapy. We are seeing one or two new applications coming in every week for new gene therapies for different diseases. It's a very exciting time, and we're working very hard to expedite gene therapy development so that all of these programs can be successful.

In terms of the factors that should be considered when determining study population, the two main principles are benefit-risk analysis, where we try to optimize that, and also the ability for a patient to provide their consent.

The second is a little more straightforward, so I will discuss that first. An adult is able to provide consent, whereas the pediatric population, at best, can provide assent, and then there are the youngest children, who cannot even provide assent. When possible, if the disease affects an adult population, we always like to go first in adults and ensure that there's some preliminary safety before going into the children. Then, if there are children

affected, it's best to go first into ones who can assent before those who cannot assent, so the older before the younger, unless, of course, the disease only affects the youngest children. Then, of course, we have to adjust our thinking on that.

In terms of benefit-risk, we want to enroll a patient population who is most likely to benefit, because in the early-phase study, we don't understand what the risk is going to be of the gene therapy, so we really want to make sure that those who are first enrolled will have the greatest potential benefit. We also like to ensure that they're otherwise healthy, because of the concerns about toxicity to make sure that if there is a toxicity, that it's likely that they will be able to endure that toxicity.

So that's about it for this question. Back to you, Tejashri.

DR. PUROHIT-SHETH: Okay, thank you. The next question is for Dr. Lei Xu.

What are the conditions under which it may be appropriate to allow a single-arm externally controlled trial to provide the primary evidence of effectiveness for approval for a gene therapy?

DR. LEI XU: Good morning, everyone. I just want to echo what Dr. Blank just mentioned about our excitement to be here, and welcome to this OTAT town hall.

With regard to this question, and as you may be aware, regulatory approval of a drug or a biologic, such as a gene therapy, requires substantial evidence of effectiveness from adequate and well-controlled clinical studies.

Some of the features of an adequate and well-controlled clinical study include a valid comparison with a control to provide quantitative assessment of drug effect, a suitable method of assignment to treatment and control groups, such as a randomization, and adequate measures to minimize bias, such as blinding of the study participants as well as the evaluators.

As you may know, there are five types of commonly used controls: the placebo or sham control; the active concurrent control, by which I mean that an accepted alternative treatment will be used as the control; the dose-ranging concurrent control; no-treatment concurrent control; and external or historical control. Blinding and randomization are feasible when a concurrent control is used, especially for the placebo control, the active control, or the dose-ranging control. However, blinding wouldn't be feasible for the no-treatment control because the control is not receiving any treatment. The external control usually consists of data derived from patients outside of the clinical study — for example, data from a natural history study.

For us, the preferable type of control is one of the first three concurrent controls, which permit both randomization and blinding, making the study results largely free of bias and more interpretable. The no-treatment control is the next-best control because, although the study subjects will know if they are or are not receiving the investigational treatment, they

will be otherwise selected, treated, and assessed according to the same study protocol as those receiving the gene therapy.

Trials using an external control such as a natural history study rather than a concurrent control may be appropriate under certain circumstances for rare and serious conditions for the gene therapy trials. For example, if the disease which is studied has well-understood underlying pathogenesis, the disease course is well-documented, highly predictable, and can be objectively measured and verified, the study population and the external controls are suitably comparable, and the expected treatment effect is large, self-evident, and closely associated temporally with the gene therapy administration.

For example, we approved the first systemically administered AAV-based gene therapy, onasemnogene abeparvovec, also known as Zolgensma, for the treatment of patients less than 2 years of age with spinomuscular atrophy (SMA) based on substantial evidence of effectiveness generated from two single-arm externally controlled clinical trials in patients with infantile-onset SMA, because the natural history of this, infantile-onset SMA is well characterized and relatively consistent and the expected clinical benefit of this product — including survival benefit and ability to achieve major motor milestones such as ability to sit independently — is large, self-evident, and unlikely to achieve without intervention in this patient population.

In many situations, however, the likelihood of credibly demonstrating the effectiveness of a drug with an external control is low. That is why we recommend sponsors choose a more suitable design including the use of a concurrent control, regardless of the prevalence of the disease.

That's it for this question. Back to you, Tejashri.

DR. PUROHIT-SHETH: Thank you, Lei, for such a comprehensive response. I'd like to invite Dr. Hart to address this next question, please.

What are general guidelines on determining the length of clinical trials that are designed to provide evidence of effectiveness in gene therapy trials?

DR. ELIZABETH HART: Thank you. Before I address this question, I do just want to add to the welcome that you've already heard from Tejashri and Melanie and Lei. It's a very exciting topic, and I'm glad to be here to participate.

Given the large number of questions that have been submitted, to answer this, I would say that when we look at the duration of a clinical study, we think in terms of both the data that's needed for safety and efficacy. In general, for efficacy, it's important to understand the natural history of the disease and to understand what aspects of the disease a particular product will affect and when those changes would be expected in relationship to the timing of the administration of the gene therapy. Essentially, we are dealing with things that need to be individualized. This will be a common theme. No product development will be the same, because we're dealing with a bunch of different products and conditions. But in

general, when feasible, we recommend, from an efficacy perspective, that clinical trials are designed to demonstrate a clinically meaningful effect in how patients feel, function, or survive.

The duration needed to demonstrate this change compared to the controls will differ depending upon the condition and the product. In general, products that have a more rapid onset and for diseases that are more rapidly progressive, a shorter time will be needed to demonstrate efficacy compared to a disease that is more heterogenous, has slower progression, where there might be a long latency period between treatment and the development of the specific symptoms that the product is intended to treat.

Nonetheless, we do also recognize that there is a great medical need in rare diseases that are slowly progressive and whose severe and life-threatening clinical manifestations may take a while to manifest. Therefore, the good news is, we have flexibility that can be offered to speed drug development for these diseases. For instance, it may be possible to demonstrate a clinically meaningful effect on a validated biomarker in a shorter period of time instead of demonstrating a clinically meaningful benefit in how a patient feels, functions, or survives. We have tools and special programs and meetings to assist sponsors and other external stakeholders to develop and validate biomarkers.

FDA also has flexibility to approve products for serious conditions with unmet medical needs based on surrogate endpoints that are reasonably likely to predict clinical benefits or are based on an intermediate clinical endpoint, and by an intermediate clinical endpoint, I'm referring to a measurement of a therapeutic effect that is measured earlier than irreversible morbidity and mortality, that is considered reasonably likely to predict the therapeutic product's effect on irreversible morbidity and mortality, or some other clinical benefit.

This Accelerated Approval pathway can shorten the time required prior to receiving FDA approval. The length of the preapproval studies will depend upon the time needed to demonstrate a clinically meaningful effect on the surrogate or intermediate clinical endpoint. As all products approved under Accelerated Approval still require confirmatory trials to show that the product actually provides a clinical benefit, it's recommended that the studies still are designed to demonstrate a clinical meaningful benefit in how patients feel, function, or survive.

As I started with and as I will end with, this is complicated. There is not a "one size fits all," and especially if somebody is considering Accelerated Approval, it's really important to talk with us about the specifics.

Thank you. Back to you, Tejashri.

DR. PUROHIT-SHETH: Thank you, Elizabeth. Melanie, this next question is for you.

What is prospect of direct benefit, and why is it necessary to demonstrate prospect of direct benefit prior to testing gene therapies in children?

DR. BLANK: Thanks, Tejashri. This is a pretty straightforward question. We have regulations, specifically Title 21 CFR, Part 50, Subpart D, and it provides additional safeguards to children in clinical investigations. It stipulates that before an investigational product is tested in children where there's more than minimal risk to study subjects — which for sure there is with gene therapy — it first needs to be established through nonclinical or animal studies, or clinical studies with adults, that the investigational product has the potential to treat the targeted disease or disorder. That's what we call prospect of direct benefit. Once that is established, children may be studied. However, as previously stated, if feasible, adult safety should first be established.

Thanks, Tejashri. Back to you.

DR. PUROHIT-SHETH: Thank you, Melanie. Lei, this next question is for you.

Would it be appropriate to enroll healthy volunteers in a gene therapy early-phase study?

DR. XU: Thank you, Tejashri. With regard to this question, our thinking is that study of healthy adult volunteers may be reasonable for an early-phase trial for a product with short duration of action or in a class of products with a well-understood safety profile.

Unfortunately, for most of the gene therapy products, it's not the case. What we have encountered is that the risks of most gene therapy products include the possibility of extended or permanent effects, along with the risks of any invasive procedures necessary for the product administration. Therefore, for most gene therapy trials, the benefit and the risk profile is not acceptable for healthy volunteers to be enrolled in the early-phase study.

One exception so far to this is that in trials of patients with human immunodeficiency virus, also known as HIV, wherein volunteers who are well controlled on chronic antiviral therapies for HIV and who are essentially phenotypically normal have been allowed to participate in early clinical trials of gene therapies intended against HIV because of the community's strong desire to find a cure. Enrolling these HIV-positive healthy volunteers is associated with a range of ethical considerations, and this would need to be continually assessed as the technology advances.

Thank you, Tejashri. Back to you.

DR. PUROHIT-SHETH: Thank you, Lei. The next question is for Elizabeth.

How does FDA consider benefit-risk when evaluating a study population for an early-phase study?

DR. HART: So again, there are no absolutes here; it will depend. It will depend on a lot of different factors, such as the anticipated and potential toxicities of the product, underlying condition, anticipated benefit from the product based on preclinical proof of concept data, available therapies, et cetera, et cetera. The list goes on and on.

For products with significant risk, such as the gene therapy products that we're discussing today, it's usually prudent to enroll subjects with more severe or advanced diseases into these early-phase studies — essentially, patients who are out of options. However, there are cases where the therapy that is being developed is thought to primarily or only help patients with early or more moderate disease. Then it would be more appropriate to study that population in these early-phase studies.

Other factors often have to do with the general health of the subjects, the comorbidities. Essentially, a debilitated or a very ill person may not be able to tolerate the toxicities that an otherwise generally healthy person with only the underlying diseases being studied could tolerate. And in an early-phase study, we know less about the product, and so therefore we generally recommend, when feasible, to enroll subjects who have limited comorbidities in the first-in-human early-phase studies. The presence or absence of other disease-modifying therapies also needs to be considered. In general, if there are approved and broadly effective therapies, there's often a more favorable benefit-risk profile only for those subjects who are unresponsive or who don't tolerate the approved therapies.

There are a lot of different considerations to think about. These are just a few. And again, this needs to continue to be individualized for the specific development program. We recommend that sponsors discuss selection of the study population for an early-stage gene therapy trial with OTAT during the planning phases.

Thank you, Tejashri.

DR. PUROHIT-SHETH: Thank you, Elizabeth. We'll move on to our next question. Melanie, this one's for you.

Under what circumstances might it be appropriate to enroll pediatric patients in early-phase gene therapy clinical trials prior to testing a product in adults?

DR. BLANK: If there's no appropriate adult population in which to test the product first for safety and basically establish proof of concept, and the prospect of benefit is solely reliant upon animal data, children may need to be the first early-phase study subjects. We prefer this not to be the case, because they're a highly vulnerable population. But what we do there, again, is we look to see can we enroll the oldest pediatric population first, because, again, they can provide assent, which is better than enrolling a vulnerable patient population who really doesn't understand what they are going to be enduring. As we've said before, there are toxicities with these therapies and the first subjects are the most vulnerable, because often we don't see the toxicities in the animal studies, and then we are faced with them in the clinical studies. So we prefer not to enroll children first, but sometimes the disease is really only present in children and sometimes in the youngest, most vulnerable children. Basically, that's when we do it. Again, we need to have prospect of direct benefit established in the animals or in in vitro, if possible, but that's unusual, before we can proceed in children.

That's it for this question. Thanks, Tejashri.

DR. PUROHIT-SHETH: Okay, great, Melanie. This next question is for you, Lei.

What are the main concerns about relying upon single-arm, externally controlled clinical trials to provide the primary evidence of effectiveness for approval of gene therapies?

DR. XU: Thank you, Tejashri. The purpose of conducting clinical trials of a drug or a biologic is to distinguish the effect of the product on the target condition from other influences, such as spontaneous change in the course of the condition to be studied, the placebo effect, or the biased observation.

When properly conducted, a clinical trial that includes random assignment of participants either to a treatment or to a concurrent control group to optimally promote the similarity of the comparative groups, and include appropriate blinding, can draw a conclusion as to whether differences in outcomes observed between groups can be attributed to the treatment of interest, such as a gene therapy, and meet the regulatory requirement of adequate and well-controlled investigations to provide substantial evidence of effectiveness for approval.

The main concern for a single-arm open-label externally controlled trial is that it may not be able to distinguish the effect of the product from other factors that impact the outcome of interest and meet regulatory requirements. First, because the externally controlled trials do not involve randomization of the study population to the treatment being compared, so the treatment and the control group may not be suitably comparable due to differences in known factors that can affect the outcome being measured, such as baseline characteristics, including demographic factors or comorbidities; the disease attributes, such as the severity and duration of the illness; and variability in disease manifestations and progression. The second reason is that the treatment effect may not be self-evident, so the planned outcome measures may be effort-dependent, such as visual acuity assessment. The amount of effort that subjects, the caregivers, and the evaluators put in in this externally controlled interventional study is unlikely to be similar to the external control, such as a natural history study. In addition, a lot of outcome measures are process-dependent, and as such, data generated from different studies may not be comparable.

Thank you, Tejashri. Back to you.

DR. PUROHIT-SHETH: Great. Thank you, Lei. So, Elizabeth:

How does OTAT incorporate the patient voice in clinical trials?

DR. HART: Such a great question. Patients and their families know about their diseases better than anyone else, and this is especially true with rare diseases. Therefore, it is so important for OTAT to hear directly from patients and their families and advocates. We recently held a patient-focused drug development meeting on gene therapies, there have

been multiple other individual disease-specific patient-focused drug development meetings, the office has reached out and held listening sessions in order to speak directly with patients and their families, and there are many pathways where patient advocate groups have reached out and spoken with us. The Office of Patient Affairs — formerly, the Patient Affairs Staff — in the Office of Clinical Policy and Programs are able to facilitate those interactions.

Basically, how does this information help? This information helps us to understand what are acceptable risks. We're looking at risks in the context of the individual disease and condition. This is one way that we can understand what is acceptable for different members of the disease community. It also helps us to understand what are the aspects of the condition that are truly bothersome, and which ones, and what are barriers to participating in clinical trials, and how can we essentially work together, because that's the only way that we're going to advance this. So in communications with sponsors who are developing these products to ensure that we can advance and design clinical trials that are going to give us the information that we need to approve products that will help patients with the aspects of the disease that are troubling and bothersome to them without putting them at risks that they do not see as being reasonable and ensuring that there is a reasonable effort and that the burden on these patients and their families is reasonable.

Thank you.

DR. PUROHIT-SHETH: Thank you, Elizabeth. Melanie, the next question is for you.

How can biomarker endpoints be best used in gene therapy clinical trials?

DR. BLANK: Thank you, Tejashri. This is an excellent question, but I first want to go back and restate — because I think it's worth restating — that for gene therapy we are held to the same standards that all drugs have, which is substantial evidence of efficacy based upon clinical investigations. For gene therapies, because they are long-lasting — basically, we don't know that they will ever go away; you've got them for life — efficacy generally means a substantial effect on irreversible morbidity or mortality.

Biomarkers are laboratory tests or imaging test results or other clinical measures that are indirect measures of physiological function or physical signs — like a blood pressure reading or an ECG reading — that can tell us something about the state of severity of a disease process and potentially about the activity of an investigational product on the disease process.

The utility of a biomarker and the decision regarding how best to use it in clinical investigations depends on how well the biomarker tracks with the disease process, how confident we are that a pharmaceutical effect on the biomarker would predict a clinically meaningful improvement on irreversible morbidity and mortality, and how confident we are in the assay used or imaging technique used to measure that biomarker. Scientific data are needed to provide confidence in the utility of a biomarker, and understanding the

natural history of the disease through a natural history study is the best way to explore the clinical utility of biomarkers. So that's why at the beginning of a clinical development program, when you're even thinking about studying gene therapy for a disease, it's really important to start your natural history study, so that you can decide what would be some good biomarkers to follow to be able to track disease activity and the effect of your product on that disease activity.

Some biomarkers, as Dr. Hart said, are validated and established, and we use them all the time for approvals. A good example that we have full confidence in is blood pressure measurement. We know that high blood pressure is predictive of future heart attack and stroke and that reducing the blood pressure will reduce that risk. We know that, as long as it's done in a standardized way, reducing the blood pressure will have a clinically meaningful effect on irreversible morbidity and mortality.

If there are data that provide full confidence in the predictive ability of the biomarker as currently measured for the disease process of interest, this would make the biomarker a validated biomarker that could support a traditional approval. Many drugs have been approved based on validated biomarkers, but we don't always have validated biomarkers. If there are data that provide intermediate confidence in the predictive ability of the biomarker as currently measured for the disease process of interest, this could lead to a decision to define the biomarker as a reasonably likely biomarker, which means that it could support an Accelerated Approval decision.

Accelerated Approval is a pathway that can occur when you have established an improvement on a biomarker that is reasonably likely to predict a subsequent improvement on the way a patient feels, functions, or survives. In the case of gene therapy, we really would like to see irreversible morbidity and mortality. Although there could be some exceptions to that rule, generally speaking, we like to see that — even if it's something like the burden of another treatment, that other treatment is preventing irreversible morbidity. So it really does boil down to that most of the time.

Anyway, back to the Accelerated Approval: It may take a very long time to demonstrate the effect on irreversible morbidity and mortality with a gene therapy, as Elizabeth was saying; that some diseases are very slowly progressive, and that we really need to rely on a biomarker in order to get that product to market sooner. So that's when we rely upon a biomarker.

Sometimes we can rely upon an intermediate clinical endpoint, but that's not a biomarker. But just in terms of the Accelerated Approval pathway, we recently did approve a drug based on intermediate clinical endpoint, a gene therapy called Eli-cel, believing that the intermediate clinical endpoint did predict a subsequent clinically meaningful endpoint for the entire population.

So biomarkers can be used for approval; that's what most sponsors — by sponsors, I mean investigators and companies — are interested in. But we also really use biomarkers for

many different other things. We use them to assess safety, and that's very important early on in a trial, to see is this a safe product. We also use them to assess for pharmacodynamic effects to help with dose finding.

So I would say biomarkers are super important for your clinical development program, and it's best to start developing those early on.

Thanks, Tejashri.

DR. PUROHIT-SHETH: Thank you, Melanie. The next question is for Lei.

What are OTAT's recommendations on safety monitoring in a gene therapy clinical trial?

DR. XU: Thank you, Tejashri. Since there is so much unknown for these gene therapy products, comprehensive evaluation of safety is really critical for both early-phase and later-phase studies, so that we can collect data for the benefit-risk determination. For that reason, studies usually last 1, 2, or 3 years. We recommend both general and specific tests and that monitoring be incorporated in those clinical study protocols to look for both expected and unexpected safety issues.

General safety monitoring typically includes recording of symptoms and common clinical measurements, such as physical exams, routine labs, and other assessments appropriate for the condition that is being investigated. Specific monitoring would depend on multiple different factors, such as the nature and mechanism of action of the gene therapy product, the study population, the results of the animal studies, and any related human experience of the same or similar gene therapy products.

Another thing of particular interest is to monitor the immune response to gene therapy products because it may pose a very important safety risk, such as by damaging the tissues transduced with a viral vector carrying a therapeutic transgene. To monitor for systemic immune responses, we recommend sponsors perform immune assays measuring both cellular and human immune responses to the vector and also to the transgene, as applicable. To minimize immune responses, immune-suppressive treatment such as corticosteroids may be used before or after the product administration. We recommend sponsors provide justification for the immune suppressant regimen based on available clinical data for the investigational product or related products. Because immunosuppressants may carry their own risks, subjects should be closely monitored and treated as needed to minimize the risk of complications.

Thank you, Tejashri. Back to you.

DR. PUROHIT-SHETH: Great, Lei. The next question is for Elizabeth.

How does OTAT ensure that study patients or participants and their families are well informed of the risks associated with gene therapy, including newly emerging risks?

DR. HART: Thank you. For specific studies, the informed consent process is the primary method of communicating about risk. The IRB, or independent review board, of the institution where subjects are being treated are responsible for the informed consent. However, OTAT does consider and has the right to review the informed consent document and make sure that it fulfills all of the requirements as far as including all of the necessary information, making sure that it is informative, fair, and balanced as it pertains to the risks but also regarding the expectation or lack thereof for benefit, as well as what can be expected during the course of the study.

As we know, during the course of studies, sometimes there are new risks that emerge, and this is another time that OTAT gets involved. We can ask the sponsor to update their informed consent document both for subjects who have already received treatment as well as for future participants. Then in the broader sense, as far as making sure that patients who may consider participating in gene therapy are informed about what's going on, OTAT tries to publish and participate in dialogue about what are known risks of gene therapy. For instance, we had an advisory committee on AAV risk a couple of years ago, and we will continue to do that as well.

Thank you. Back to you, Tejashri.

DR. PUROHIT-SHETH: Thank you, Elizabeth. I'm going to invite Dr. Blank to address this next question.

When testing new gene therapies in rare diseases, should only safety be tested at first, or should efficacy also be evaluated in these phase 1 trials?

DR. BLANK: Thank you, Tejashri. I'd be happy to answer this question. Sponsorship carefully design their early-phase studies keeping in mind the context of the overall development program's objectives. In phase 1 studies, although they're primarily geared toward evaluating safety, tolerability, and dose exploration, efficacy endpoints should also be evaluated to ensure that the phase 1 study explores the proof of concept, different efficacy endpoints, and pharmacodynamic measures to help inform the design of later studies and enable those phase 2 and 3 studies.

Furthermore, it's important to follow all phase 1 study subjects in long-term follow-up studies, where clinical outcomes measures, not just safety, should also be assessed. Clinical outcome measures in these early treated subjects can often provide confirmatory evidence of efficacy eventually, so that's another reason. These are the first subjects that are treated, often, so they will be followed the longest, and so their efficacy data is very informative for our final decision regarding approval.

Thanks, Tejashri.

DR. PUROHIT-SHETH: Thank you for that. Lei, I'll invite you to address this one.

Can you address what is needed for short-term safety monitoring in gene therapy trials?

DR. XU: Thank you, Tejashri. Because many gene therapy products are administered only once, the close monitoring in this peri-product administration period is really critical to ensure timely capture of those safety signals. This means that, during and immediately following the product administration, there should be intensive safety monitoring with frequent evaluation of vital signs and some of the different labs, depending on the types of gene therapy products. Then, patients should be very closely evaluated clinically during the first several weeks, at least, after the product administration. Also, there should be for early-phase studies very good stopping rules in place to avoid additional subjects being exposed to unknown but significant potential risks, so that, for example, if something particularly worrisome happens to a subject, the study will be paused temporarily to allow a third party or the sponsor and FDA to evaluate whether this adverse event is possibly or probably related to the product administration.

After the evaluation, there may be a change in the study protocol, such as change of the patient enrollment criteria, change of the safety monitoring procedures, and in rare cases it may have to lead to the termination of the study. But that's not the usual case. Well-designed stopping rules would allow sponsors to assess and address risks identified as soon as possible, and to assure the risks to subjects remain reasonable.

Back to you, Tejashri. Thanks.

DR. PUROHIT-SHETH: Thank you, Lei. Elizabeth, I'm going to turn to you for this one.

When a rare disease has multiple manifestations and there is considerably heterogeneity of presentation, can improvement on different endpoints in one clinical trial be considered? Multi-domain responder index, for example.

DR. HART: Thank you. Yes, it's a challenge when you have a heterogenous disease, and there are multiple different ways that you can possibly design the trial in order to demonstrate efficacy.

Multi-domain responder index is definitely one possibility, and it's quite attractive often because it allows subjects to be considered a responder if there is improvement in a specific domain and you can evaluate multiple domains for different subjects. The challenge is in choosing what those domains are, making sure that they are specific and appropriate to the population that you are studying. And again, like everything else, the devil is in the details, and so it's something that really should be discussed on a case-by-case basis.

DR. PUROHIT-SHETH: Great, Elizabeth.

Thank you to everyone who submitted questions during the registration process. It's greatly appreciated. We will now turn to the live Q&A session.

We will go ahead and start with the first question. Lei:

Please comment on the use of staggered enrollment in first-in-human clinical trials of gene therapies for rare diseases.

DR. XU: Happy to do that. When there is no previous human experience with a specific gene therapy product or related products, treating several patients simultaneously in the first-in-human study may represent an unreasonable risk to those study participants. To address this issue, we have asked the sponsors of most first-in-human clinical studies of gene therapy products to include adequate staggered treatment to limit the number of patients who might be exposed to an unanticipated safety risk. With staggered treatment, there is a specified follow-up interval between administration of the product to a subject or a small group of subjects and the administration of the product to the next participant or group of participants. For example, in a dose escalation study, the first several individual subjects within the first cohort might be staggered, followed by staggering between cohorts, and depending on the degree of safety concerns, the staggered treatment of individual subjects within each new cohort may be needed.

Regarding the staggering interval, either within a cohort, between subjects, or between cohorts, it is intended to be long enough to monitor for acute and sub-acute at-risk events before treating additional participants at the same dose or prior to increasing the dose in the subsequent subjects. The choice of staggering interval should consider the time course of acute and sub-acute adverse events that was observed in animal studies and in any previous human experience with related products. The staggering interval should also consider the expected duration of the activity of the product. However, the staggering interval should be practical in the context of the overall clinical development.

Thank you, Tejashri. Back to you.

DR. PUROHIT-SHETH: Great. The next question is for Elizabeth.

How does OTAT determine whether an advisory committee meeting is required for a biologics license application for a gene therapy product?

DR. HART: There are a lot of different factors that go into this, but in general, an advisory committee offers the opportunity for external public input and discussion. So if there is a great deal of uncertainty — whether that's because there's a specific issue related to safety, etc. — there has been flexibility compared to the usual ways that we demonstrate efficacy. Those may be reasons that we would seek an advisory committee.

DR. PUROHIT-SHETH: Great. Thank you, Elizabeth. Melanie:

How do we justify the risk of prophylactic or chronic immunosuppression in a placebo population?

DR. BLANK: Well, generally, we don't. When we think about a patient population that is the control group in a clinical trial, we want to try to preserve their safety as much as possible. An immunosuppressive therapy is sometimes required for the active arm because

of a wish to prevent autoimmune hepatitis that can occur with gene therapies, but then we're kind of stuck in terms of having a blinded study. We can sometimes have a sham arm for the placebo, where they're given immunosuppressive therapies. But occasionally, depending on the route of delivery, that may not be possible, and then we have to have an open-label study, which is still better than not having any internal control, but we do like to have a controlled study as we've mentioned before, and blinding is preferable. But sometimes there are situations where that can't be done.

So the answer is basically I can't think of a situation where we would give immunosuppressive therapy to a patient who's going to be receiving placebo. Maybe others have some comments on that.

DR. PUROHIT-SHETH: Thank you, Melanie. For the next question, Lei, this is a follow-up to one of the questions that was submitted during the registration process.

Can you comment on considerations for intrasubject control design when we are discussing single-arm trials?

DR. XU: Thank you, Tejashri. I would give it a try, and I would welcome Elizabeth and Melanie chiming in, if you'd like to. So I think the question which was asked about the intrasubject control is that the patients may be followed for a period of time before being enrolled into an interventional study, and this pretreatment follow-up period would be considered or would be used as a control to compare the effect following the gene therapy treatment.

In general, as I mentioned earlier regarding when it is appropriate to use an external control, to me, I still consider this as a single-arm open-label externally controlled study, because during this pretreatment time period for which we use it as a control, the patients know that they didn't receive the product — whenever you are doing assessment using a measure which could be subjective, that the reliability of the measure could be questioned, comparing to the period when they know they received the treatment.

In addition, depending on how long the pretreatment follow-up period is, the disease progression during this pretreatment phase and the post-treatment phase may not be linear. In other words, the pretreatment period may not be able to predict the disease progression over the post-treatment period. So, because of those concerns, I think in many situations we still don't think this kind of intrasubject control is appropriate.

However, for us, when we are talking about intrasubject control, for example for the treatment of wounds, you may select two comparable wounds as one pair for each subject, so those wounds could be randomized and be blinded to either the active treatment or to a placebo control. In that situation, this term, intrasubject control, is acceptable, and it's quite efficient in detecting the local effect and the local safety problems. However, with this kind of intrasubject control, it may be challenging to assess the relatedness of a systemic effect to say whether it is due to the placebo or due to the active treatment.

Thank you, Tejashri.

DR. BLANK: I'd like to chime in a little on that, Lei. According to our regulations, 314.126, there is no such thing as a patient control. We do use baseline controls sometimes but it's really not a control. What's implicit in that is that we understand the natural history of the disease well enough to know that this change that is witnessed in the clinical trial would not occur otherwise.

So it really is an external control, not an intrasubject control. So I just want to make that clear. I think that that terminology should not be used, and we have a lot of concerns when we see, especially in single-arm studies, when you've got a run-in period and then the subject knows that they're going to be on active treatment, that knowledge of treatment assignment can influence the outcomes measures. And it becomes very hard to interpret the results, unless we really understand that natural history of the disease and know that that would not happen otherwise. So again, it's a plug for performing those natural history studies so we can understand the disease better.

DR. PUROHIT-SHETH: Okay, thank you. The next question is for Elizabeth.

What are the different strategies for optimizing dose finding in gene therapy clinical studies?

DR. HART: Great question. I just want to start by saying dose exploration is so important, and we recommend essentially that it happen as early in development as feasible, essentially, in those early-phase studies. As far as the dose selection itself, it should be informed based on all of the available sources of information, including preclinical data as well as clinical data from similar products.

The specific plans for dose escalation should consider the risks and activity associated with the change in dose. Within the clinical dose escalation studies, it is important to identify the maximum tolerated dose within the therapeutic target range. Usually clinical outcomes are delayed, so toxicity and biomarkers can be helpful for dose selection in subsequent product development.

DR. PUROHIT-SHETH: Thank you. Melanie:

How can an expedited program designation such as Fast Track, Regenerative Medicine Advanced Therapy designation, or Breakthrough Therapy designation help facilitate gene therapy development?

DR. BLANK: Thank you for that question, Tejashri. There are actually four expedited programs. We've already covered a little bit about Accelerated Approval — that's a separate type of expedited program because it's an approval pathway. The others are designations.

Because it's reliant upon a biomarker or an intermediate clinical endpoint, the Accelerated

Approval pathway is really a lesser standard for approval than what we have as traditional approval, which is a substantial effect on the way a patient feels, functions, or survives — and again, in this case irreversible morbidity and mortality is generally what we're looking for. So there needs to be an unmet medical need, and it needs to be a serious condition for us to consider Accelerated Approval, and that pretty much applies for the other programs as well. I don't mean to say that there's not substantial evidence, but it's evidence of efficacy on a biomarker or an intermediate clinical endpoint that is reasonably likely to predict — which means it's not clear yet — and that it can't be established until the post-marketing period. Basically, for that approval pathway to be accepted, there needs to be a confirmatory study that's done after approval that confirms that clinical benefit. We would not do that for a product where there's no unmet medical need or it's not a serious condition or there are other products for that. That would not be allowed.

So back to the other programs. The Fast Track program, to start, is the only program where the clinical data to support that designation can be animal data or in vitro data, and there's an approval process for that, basically. The sponsor has to submit a request for that designation and submit the data that are in support of the Fast Track designation. Once they get that Fast Track designation, their development program gets more attention from FDA, in the form of meetings and whatnot, and you can have a rolling review, which means that when it's time for the BLA submission, parts of the BLA package can be submitted in advance of the full submission when the clock begins. Also, there can be priority review, which changes the timing of the clock for us to review the application to decide whether or not we can approve it, and it's really pretty much cutting it in half, from 12 months to 6 months, which is an incredible benefit. So, what we're looking for there is that the animal data is sufficient to support that there is going to be a clinically meaningful effect in human subjects. Basically, we are trying to expedite bringing those products to market.

Breakthrough Therapy requires clinical evidence that this product is better than other treatments out there and can also meet this unmet medical need, so that's probably the highest standard that we have. When we do grant a Breakthrough Therapy designation, which also must be requested by the sponsor, then that gets all of the benefits of Fast Track and also gets attention from the higher FDA management. So there's a commitment to bring in our management to help facilitate the gene therapy development.

Same thing for the RMAT, or Regenerative Medicine Advanced Therapy designation. That basically means that once you give the therapy, or you give the course of it, you won't need to give it again chronically to keep the effect of it. Basically, it's able to cause a regeneration in that person —a pretty permanent or at least very long-term effect. And so that's a unique and our most recent designation of these three. If you get that — for which you also need to provide clinical evidence to support it — then you also get all of the benefits of Fast Track, as well as the attention of the higher management in the drug development process.

So that, I think, answers the question. Thanks, Tejashri.

DR. PUROHIT-SHETH: Thank you. So I just wanted to clarify for an approval pathway, whether it is Accelerated Approval or traditional, the statutory standards for effectiveness are the same.

Thank you so much, Melanie, for addressing the question. I will now move on to Lei.

Can you please discuss the use of real-world data for gene therapies in rare diseases?

DR. XU: Thank you, Tejashri. Real-world data usually refers to registries, electronic health records, and all medical claims. For gene therapies, as for other drugs or biologics, we are open to the discussion about the possibility of using real-world data.

I think one use may be as an external control, provided we have patient-level data from this type of database. Actually, FDA's CDER and CBER just released a draft guidance on the considerations to design and conduct externally controlled trials for drugs and biologic products. That draft guidance talks about how we can make real-world data be potentially useful as external control. Also, I think real-world data can tell us about clinical manifestations, disease progression, or what kind of endpoint may be most relevant to the condition, so that it could help us design clinical trials that would be adequate and well-controlled to provide evidence of effectiveness.

I think the appropriateness of the use of real-world data should be a case-by-case scenario, and I would encourage sponsors to talk to us early in development. As we have laid out earlier in our discussion about the limitations and potential issues associated with external control, I think the appropriateness of use of this kind of data really has to be considered on a case-by-case scenario.

Thank you, Tejashri.

DR. PUROHIT-SHETH: Thank you, Lei. Elizabeth:

Would you please comment on the challenges of incorporating diversity in small rare disease studies?

DR. HART: So often I actually think it's a question of when, because when you're dealing with a small rare disease, you have a limited population, so it really is about what you think the product is going to be designed to treat.

If you think that the product is designed to benefit the entire disease population as the product advances through the different stages of development, it would make sense to really work to enroll as much of the population as you can, such that it makes sense and it's feasible. If you are dealing with a population where it only makes sense to treat the early phases of the disease, then you should focus on just that subset, or if you have a product that is targeted to a specific manifestation. But I think, especially in the rare disease world, we're talking about collaboration, and we're often talking about

international studies and how we can bring the trials to the patient, versus just the patient to the trial.

DR. PUROHIT-SHETH: Thank you, Elizabeth. Melanie:

Can you please comment on how FDA interacts with other regulatory agencies such as the European Medicines Agency, or EMA?

DR. HART: Sure, Tejashri. Thank you for that question. We actually engage quite frequently with EMA and Health Canada. We have these meetings called clusters, where we come together and usually one agency or the other decides they want to discuss a clinical development program that is shared by all three of us. So one of us takes the role of presenting the clinical development up to the time and then poses their concerns, presents their concerns, and then poses questions. And it's very helpful for us to hear the thoughts and concerns of the other agencies, so we can collaborate, learn from each other, work together, and work toward expediting the development of these very important drugs for these rare diseases.

DR. PUROHIT-SHETH: Thank you, Melanie. Lei:

Can you comment on what would be an acceptable approach for inclusion of a sham-control arm in gene therapy studies that have an invasive route of administration, for example, intracerebral, ventricular, and concomitant immunosuppression? Can blinding truly be maintained with these sham-controlled trials?

DR. XU: Thank you, Tejashri. I will give this question a try. I think the purpose of including a sham control as a concurrent control is to try to maintain the blinding as much as possible. I have to acknowledge it is unlikely to maintain a perfect blinding, but some level of blinding can hopefully be appropriate enough to allow more reliable data collection regarding those efficacy assessments.

If including a sham control, we usually recommend it be as minimally invasive as possible. For the ICV, for example, you may just have the sham group receive sedation instead of general anesthesia, and you may just have the control group receive partial penetration of the skin — you don't have to penetrate through the dura.

Also, as Melanie has mentioned earlier, we do not ask the patients in the control arm to receive immunosuppressants — we have never required those. So again, although it may not be perfect blinding, some level of blinding together with the incorporation of the randomization we think would be helpful to generate more interpretable data to support effectiveness and also as a comparator for the safety.

Thank you, Tejashri.

DR. PUROHIT-SHETH: Thank you, Lei. So we are very shortly approaching the 1:00 p.m. mark. We will answer one more live question, and this one is for Elizabeth.

What is OTAT's guidance on long-term safety monitoring of gene therapies?

DR. HART: Thank you. So the good news for this one is we do have a guidance: it's called the Long Term Follow-Up After Administration of Human Gene Therapy Products. It has a lot of information — I highly recommend that you look at it — and it provides a lot of general recommendations, such as duration of follow-up, which is typically 5 years for AAV products, 15 years for lentiviral products. It has details about some of the follow-up, but obviously everything needs to be individualized for the product based on preclinical experience, experience with a specific product, and experience with related products, to maximize the knowledge and ensure safety for subjects.

Thank you.

DR. PUROHIT-SHETH: Thank you, Elizabeth, Lei, and Melanie.

We appreciate all of the questions that were submitted during the registration process and during the live Q&A session. Thank you all for attending today's OTAT town hall. We hope you found the session informative.

I would also like to extend a warm thank-you to our panelists for taking the time to address these excellent questions. As a reminder, a recording of today's town hall will be posted on FDA.gov in the coming weeks.

For more information, you can visit the FDA website to read the FDA guidance documents regarding clinical development of gene therapy products for rare diseases and find other valuable OTAT resources. Please note that we plan to host our next town hall meeting in April, and more information will be provided for this town hall in the near future.

Thank you again for joining, and have a great day. This concludes our OTAT town hall for today.