Human Gene Therapy for Retinal Disorders

Guidance for Industry

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I. INTRODUCTION

This guidance provides recommendations to sponsors developing human gene therapy (GT)[1] products for retinal disorders affecting adult and pediatric patients. These disorders vary in etiology, prevalence, diagnosis, and management, and include genetic as well as age-related diseases. These disorders manifest with central or peripheral visual impairment and often with progressive visual loss. This guidance focuses on issues specific to GT products for retinal disorders and provides recommendations related to product development, preclinical testing, and clinical trial design for such GT products. This guidance finalizes the draft guidance of the same title dated July 2018.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

[1] Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include nucleic acids (e.g., plasmids, in vitro transcribed ribonucleic acid (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing, and ex vivo genetically modified human cells. Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings (see Federal Register Notice: Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products (58 FR 53248, October 14, 1993), https://www.fda.gov/media/76647/download).

II. CONSIDERATIONS FOR CHEMISTRY, MANUFACTURING AND CONTROLS

There are multiple GT products being studied in clinical trials in the United States for retinal disorders. GT products are commonly delivered by intravitreal or subretinal injections through a medical delivery system. In some cases, the GT products are encapsulated in a device to be implanted intravitreally.

The general chemistry, manufacturing and controls (CMC) considerations for product manufacturing, testing and release of GT products for retinal disorders are the same as those described for other GT products (Ref. 1). For early-phase clinical trials, a sponsor should be able to evaluate the identity, purity, quality, dose, and safety of a GT product. A potency assay to assess the biological activity of the final product, with relevant lot release specifications, should be established prior to the initiation of clinical trials intended to provide substantial evidence of effectiveness for a marketing application (Ref. 2). To support licensure of a GT product, manufacturing processes and all testing methods for product release must be validated (21 CFR 211.165(e)). Sponsors developing GT products for retinal disorders are strongly encouraged to contact the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER) early in product development to discuss product-specific issues.

Sponsors of GT products for retinal disorders should take into account general CMC considerations for all GT products (Ref. 1), as well as CMC considerations specific to the products intended for treatment of retinal disorders, including:

- Consideration of the final product formulation and concentration for the expected dose and volume;
- The endotoxin limit for intraocular delivery should follow the specifications in USP <771> (not more than (NMT) 2.0 Endotoxin Unit (EU)/dose/eye or NMT 0.5 EU/mL);
- GT vector-based final products should be tested for particulate matter, and the test method and release criteria should follow USP <789>;
- Product testing and release should include testing of the final product configuration;
- Compatibility of the GT product and the delivery system(s) should be evaluated (Ref. 1).

III. CONSIDERATIONS FOR PRECLINICAL STUDIES

A preclinical program that is tailored to the investigational product and the planned early-phase clinical trials contributes to characterization of the product's benefit/risk profile for the intended patient population. The overall objectives of a preclinical program for a GT product include: 1) identification of a biologically active dose level range; 2) recommendations for an initial clinical dose level, dose-escalation schedule, and dosing regimen; 3) establishment of feasibility and reasonable safety of the proposed clinical route of administration (ROA); 4) support of patient

eligibility criteria; and 5) identification of potential toxicities and physiologic parameters that help guide clinical monitoring for a particular investigational product.

Further details for general considerations in preclinical studies are available in a separate guidance document (Ref. 3). The following elements are recommended in the development of a preclinical program for an investigational GT product intended for treatment of retinal disorders:[2]

- Preclinical in vitro and in vivo proof-of-concept (POC) studies are recommended to establish feasibility and support the scientific rationale for administration of the investigational GT product in a clinical trial. Data derived from preclinical POC studies may guide the design of both the preclinical toxicology studies, as well as the early-phase clinical trials. The animal species and/or models selected should demonstrate a biological response to the investigational GT product that is similar to the expected response in humans.

- Biodistribution studies should be conducted to assess the distribution, persistence, and clearance of the vector and possibly the expressed transgene product in vivo, from the site of administration to target ocular and non-ocular tissues, intraocular fluids, and blood. These data can determine extent of tissue transduction and transgene expression, evaluate whether expression is transient or persistent, and guide the design of the preclinical toxicology studies as well as the early-phase clinical trials (Refs. 3-5).

- Toxicology studies for an investigational GT product should incorporate elements of the planned clinical trial (e.g., dose range, ROA, dosing schedule, evaluation endpoints, etc.) to the extent feasible. Study designs should be sufficiently comprehensive to permit identification, characterization, and quantification of potential local and systemic toxicities, their onset (i.e., acute or delayed) and potential resolution, and the effect of dose level on these findings. For any abnormal ophthalmic findings or lesions, sponsors should determine the frequency, severity, potential cause, and clinical significance. Inflammatory or immune responses should be further characterized to assess potential attribution to the vector or transgene.

- Animal models of retinal disorders are frequently developed in rat or mouse strains (e.g., transgenic or knockout models) and these models are often utilized to generate POC data. However, due to differences in ocular size and anatomy in rodents as compared to the human eye, animals with more 'human-like' eyes, such as rabbits, pigs, or nonhuman primates, may also provide applicable safety information. Inclusion of the larger animals also facilitates relevant experience with the surgical procedures and delivery systems intended for clinical use.

[2] The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. We support the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VI of this document). We will consider if such an alternative method could be used in place of an animal test method.

- Differences between the immune responses of animals and humans are important considerations when interpreting preclinical data. Retinal disorders typically are bilateral and chronic. However, a second administration of a GT product to either the contralateral eye or to the same eye may not be feasible due to an immunologic reaction against the vector and/or the transgene product. Therefore, clinical data, rather than preclinical data, may provide the most relevant safety information for repeat product administration.

- As the clinical development program for an investigational GT product advances to late-phase clinical trials and possible marketing approval, additional preclinical studies may be indicated. Further testing may be necessary to address factors such as any significant changes in the manufacturing process or formulation, which may affect comparability of the late-phase product to product administered in early-phase clinical trials (Refs. 6 and 7).

- The preclinical program for any investigational product should be individualized with respect to scope, complexity, and overall design. Sponsors are encouraged to explore opportunities to reduce, refine, and replace animal use in the preclinical program. Proposals, with justification for any potential alternative approaches (e.g., in vitro or in silico testing), should be submitted during early communication meetings with FDA (see section VI of this document).

IV. CONSIDERATIONS FOR CLINICAL TRIALS

The fundamental considerations for clinical development programs of GT products for retinal disorders are similar to those for other biological products. Early-phase trials of GT products should not only evaluate safety and feasibility, but also gauge bioactivity and preliminary efficacy. Later-phase trials should be designed as adequate and well-controlled studies that can provide substantial evidence of effectiveness to support an application for marketing. For further details of general considerations for gene therapy clinical trials, please refer to relevant FDA guidance documents (Refs. 8 and 9).

The following important elements are recommended for consideration during development of clinical programs of investigational GT products intended for treatment of retinal disorders.

A. Natural History Studies

A thorough understanding of the natural history of a disease is an important element in all clinical development programs. Many degenerative retinal disorders are rare, and their natural history is often poorly characterized. Early in product development, sponsors should evaluate the depth and quality of existing natural history data. When such information is insufficient to guide clinical development, FDA recommends that a sponsor consider performing a careful natural history study to facilitate the product

development program, although FDA does not require these studies. Early interactions between FDA and sponsors are welcome regarding the design of natural history studies (Ref. 10).

B. Study Design

To facilitate interpretation of clinical data, inclusion of a randomized, concurrent parallel control group is recommended for clinical trials whenever possible. Administration of the vehicle alone may serve as a control. In general, while intravitreal injection of the vehicle alone is often feasible as a placebo control, it may not be considered ethically acceptable unless the physical properties of an injection in a closed space have a potential therapeutic benefit (e.g., creation of vitreous detachment). When ethically acceptable, such a control is especially helpful early in clinical development, to evaluate bioactivity of the investigational GT product and possibly to provide initial evidence of its clinical efficacy. However, FDA acknowledges the risks associated with intravitreal and subretinal injection procedures and vehicles; without any prospect of direct benefit, these risks may not be acceptable under certain circumstances, such as for pediatric patients (21 CFR Part 50, Subpart D). Other possibilities to vehicle controls include alternative dosing regimens, alternative dose levels, and existing products approved for the indication being sought.

Measurement of certain efficacy and safety endpoints such as visual acuity is subjective, and results can be influenced by effort on the part of the patient, leading to a potential source of bias in the clinical trial. For trials intended to form the primary basis of an efficacy claim to support a marketing application, concurrent parallel group(s) should be used as a control (placebo or active) to decrease potential bias.

To further reduce potential bias, sponsors should include adequately-designed masking[3] procedures. Masking can decrease the likelihood of biased observations, and decrease bias in assessments of outcome measure, particularly when the assessment includes subjectivity. Differences between the procedure used for product delivery and a sham procedure may enable patients to distinguish the eye which received the product from that which received the sham treatment (e.g., a sham intravitreal injection mimics a real intravitreal injection but does not penetrate the eye). FDA recommends multiple measures to reduce bias including at least two treatment arms, utilizing different doses but the same product administration procedures, and separation of clinical evaluators and personnel involved in product administration/sham procedure to minimize patients' ability to identify their treatment arm, in addition to a sham control group. In addition to facilitating masking, the second treatment arm has value as a dose-ranging control.

Although use of the contralateral eye to which the GT product is not administered as a control may potentially be considered, it is generally not recommended due to the following:

[3] In this guidance, the term "masking" refers to the process of keeping the study treatment group assignment hidden to patients, investigators, clinical evaluators, etc. after allocation.

- For most indications in which GT products are likely to be used, the treated eye and contralateral eye are often at different stages of disease at the time of trial entry. In addition, disease progression in the two eyes is not necessarily similar over the relatively short duration of the trial.

- When a patient is exposed to different procedures in the two eyes (e.g., one eye receives a GT product and the other eye receives sham procedure), it frequently leads to unmasking, which can confound the interpretation of the study results, particularly for endpoints where patient effort can make a difference, such as visual function measures.

C. Study Population

For clinical trials of GT products providing gene replacement, the correct genetic diagnosis is essential for identifying potential participants. Thus, confirmation of the genetic mutation prior to enrollment is recommended as an important element of the clinical trial. If there are no readily available, reliable means of obtaining the needed genetic diagnostic testing, a companion diagnostic may be needed and therefore should be strongly considered early in development. FDA encourages sponsors to discuss companion diagnostics early in product development. If an *in vitro* companion diagnostic is needed to appropriately select patients for study (and later, once the GT product is approved, for treatment), then submission of the marketing application for the companion diagnostic and submission of the biologics license application for the GT product should be coordinated to support contemporaneous marketing authorizations.

Patients with severe visual impairment, or a disease that is likely to progress to severe visual impairment, may be more willing to accept the potential or unknown risks of a novel GT product, and those risks may be more readily justified in this population. However, in some cases – for example, a GT product designed to restore function to remaining viable retinal cells – severely affected patients who have a minimal number of viable retinal cells may not benefit from administration of the GT product nor would use in these patients provide information about the effectiveness of the product. In general, first-in-human GT trials should enroll patients with severities of visual impairment that offer a favorable benefit-risk profile. If preliminary safety data supports further clinical development, sponsors may consider a broader patient population in future trials.

Many retinal disorders affect both children and adults, and therefore pediatric studies are a critical part of drug development. For diseases that affect both adults and children, trials in adult patients should be conducted prior to trials in pediatric patients, whenever feasible. It is important that clinical investigations in pediatric patients address ethical considerations for conducting investigations in vulnerable populations. FDA regulations at 21 CFR Part 50, Subpart D contain additional safeguards for children in clinical investigations. Clinical investigations involving no greater than minimal risk may involve children in accordance with 21 CFR 50.51. Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects may involve children as set forth in 21 CFR 50.52. An investigation involving

greater than minimal risk and no prospect of direct benefit to individual subjects, but which is likely to yield generalizable knowledge about the disorder or condition, may involve children as set forth in 21 CFR 50.53, which includes, for example, a finding by the IRB that the risk represents a minor increase over minimal risk. FDA's regulation at 21 CFR 50.54 also addresses clinical investigations not otherwise approvable and describes a process to follow to determine whether the investigation may involve children. In addition to the determinations required under applicable provisions of subpart D, adequate provisions must be made to obtain the permission of the parents and the assent of the child as described in 21 CFR 50.55.

D. Study Use

For early-phase trials, dose-ranging study designs are recommended. Comparing a range of doses can identify potential therapeutic doses for a wider group of patients. The choice of an initial dose and dose regimen should be supported by preclinical studies and/or available clinical information. Such data should indicate that the initial dose is not only reasonably safe, but also has therapeutic potential, particularly when the administration procedure carries substantial risks.

Most retinal indications for which GT products are studied involve bilateral disease; consideration, therefore, should be given during product development to the planned administration of the GT product in both eyes. Because of safety concerns related to the product, administration procedure, and any ancillary medications, administration to each eye for an individual patient should be performed sequentially, rather than simultaneously. While the eye with more advanced disease often receives the GT product initially, a rationale should be developed for deciding which eye will receive the GT product first. This rationale should consider input from study investigators and patients. The time interval between administration in each eye should be carefully planned for each patient based on available human experience of the investigational product or similar products. For products intended for both eyes, the overall development plan prior to approval should include clinical trials in which both eyes receive the GT product.

To ensure consistency across study sites, sponsors should include in the study protocol a detailed description of the product delivery procedure and devices used for delivery.

A single administration of a GT product in each eye may not always be sufficient for a variety of reasons (e.g., a GT product has limited duration of effectiveness after single administration; or exposure to a GT product may be limited to a part of the target area in the eye with the initial administration and a repeat administration to the same eye may extend the treatment to additional parts of the target area for additional effect). In such cases, careful studies, especially trials in humans, are recommended to explore the feasibility of repeat administration in the same eye.

E. Safety Considerations

Intraocular administration (e.g., intravitreal or subretinal injection) may be the most efficient method to deliver GT products intended for treatment of retinal disorders. Risks of such procedures include intraocular infection, elevated intraocular pressure, media opacities, and retinal damage. Therefore, the procedure should be performed by individuals experienced in the method of planned delivery.

Safety measures and post intervention follow up schedules should be incorporated into the study design based on the anticipated potential for adverse reactions for the specific disease, target patient population and test article attributes.

Local or systemic immune responses to GT products may pose important safety risks. For certain GT products, such as those using various viral vectors to introduce therapeutic transgene(s) in vivo, immune reactions also may decrease transduction efficiency and thereby diminish the treatment effect. Biomicroscopy and optical coherence tomography are recommended to detect inflammatory reactions within the globe. To monitor systemic immune reactions, immunoassays should be performed to measure cellular and humoral immune responses to the vector and the transgene-encoded protein.

To minimize immune responses, immunosuppressants such as corticosteroids may be considered before and after product administration. Justification of immunosuppressant regimens should be based on available clinical data of the product or related product(s). Immunosuppressant drugs may cause increased intraocular pressure, cataracts, and other adverse events. Patients should be closely monitored and treated as necessary to minimize the risk of developing glaucoma, vision loss, and other complications.

F. Study Endpoints

Early-phase clinical trials typically focus on safety. However, for trials of GT products, early assessment of potential clinical benefit is also important, particularly for rare diseases with a limited number of patients available to participate in clinical development. To guide further clinical development, FDA encourages sponsors to explore a wide spectrum of potential clinical endpoints and other clinical effects in early-phase trials. For example, sponsors may include endpoints based on retinal imaging (optical coherence tomography, retinal photography, fluorescein angiography), visual acuity (low and high luminance), visual fields, color vision, contrast sensitivity, other measures of visual function (i.e., how well the eye and visual system function), and functional vision (i.e., how well the patient performs vision-related activities of daily living). For later-phase trials intended to provide substantial evidence of effectiveness to support a marketing application, primary efficacy endpoints should reflect clinical benefit, such as improvement in function or symptoms.

Examples of established efficacy endpoints that can be used to evaluate clinical benefit of GT products intended for treatment of retinal disorders include:

- Best corrected distance visual acuity, measured with the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart or other visual acuity charts with an equal number of letters per line and equivalent spacing between lines. A halving (or doubling) of the visual angle represented by a gain (or loss), respectively, of at least 15 letters on the ETDRS chart from baseline is considered clinically meaningful.

- Rate of photoreceptor loss, determined by measures such as optical coherence tomography or autofluorescence photography. The comparison should be made between the baseline and at least two subsequent area images, with intervals of 6 months or more between images. The best curve fit analyses demonstrating reduction in the rate of photoreceptor loss exceeding measurement uncertainty are considered clinically meaningful.

FDA encourages sponsors to develop and propose novel endpoints to measure clinically meaningful effects, or surrogate endpoints[4] that are reasonably likely to predict clinical benefit, in patients with retinal disorders. This can be especially pertinent to some rare retinal disorders for which the established efficacy endpoints may not be appropriate to assess clinically meaningful effect of an investigational product. Sponsors are welcome to engage FDA early in this process, and FDA is committed to working with sponsors to develop acceptable endpoints.

- For example, a novel primary efficacy endpoint measuring mobility under different levels of illumination was utilized to support marketing approval for voretigene neparvovec-rzyl (a recombinant adeno-associated vector (AAV) carrying the gene for human retinal pigment epithelium-specific 65 kDa protein). During the clinical trials, the sponsor worked with FDA to develop this clinically meaningful primary efficacy endpoint.

[4] According to section 507(e)(9) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 USC 357(e)(9)] "[t]he term 'surrogate endpoint' means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and—
''(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or
''(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c)."

G. Follow-Up Duration

The length of follow-up to provide additional information regarding the safety and efficacy of the GT product depends on many aspects of a GT product, including vector persistence, genome integration, and transgene activity, and the goal of the follow-up (e.g., safety vs. durability of clinical effect). In addition to monitoring for safety, long-term follow-up is recommended to evaluate durability of the clinical effect. More detailed discussion of long-term follow-up is provided in a separate FDA guidance document (Ref. 4).

H. Patient Experience

Patient experience data[5] may provide important additional information about the clinical benefit of a GT product. FDA encourages sponsors to collect patient experience data during product development, and to submit such data in the marketing application.

V. EXPEDITED PROGRAMS

There are several programs that may be available to sponsors of GTs intended to address unmet medical needs in the treatment of serious or life-threatening conditions. These programs, including regenerative medicine advanced therapy designation, breakthrough therapy designation, fast track designation, accelerated approval, and priority review, are intended to facilitate and expedite development of these therapies. For example, regenerative medicine advanced therapy designation and breakthrough therapy designation call for increased FDA attention to these potentially promising therapies, offering sponsors more frequent interactions with FDA on efficient trial design and overall drug development. Further information on these expedited programs is available in separate guidance documents (Refs. 11 and 12).

[5] As defined in the section 569(c) of the FD&C Act [21 USC 360bbb-8c], the term "patient experience data" includes data that are:

- Collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and
- Intended to provide information about patients' experiences with a disease or condition, including the impact (including physical and psychosocial impacts) of such disease or condition, or a related therapy or clinical investigation, on patients' lives; and patient preferences with respect to treatment of such disease or condition.

Additional information on Patient-Focused Drug Development can be found on this website: https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

VI. COMMUNICATION WITH FDA

FDA recommends communication with OTAT early in product development, before submission of an investigational new drug application (IND). There are different meeting types that can be used for such discussions, depending on the stage of product development and the issues to be considered. These include pre-IND meetings prior to submission of the IND (Ref. 13), and INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meetings, which can be used earlier in development to discuss issues such as preclinical development or manufacturing, so that the sponsor can obtain non-binding regulatory advice.[6]

[6] Going forward, INTERACT meetings will serve in place of pre-pre-IND meetings. For additional information about INTERACT meetings, please see https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products.

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*When finalized, this guidance will represent FDA's current thinking on this topic.