Questions and Answers from Webinar May2, 2012
Focus on the Eye

Questions	Answers
1. Can the ACT participants comment on the duration of long-term follow-up to be conducted on patients enrolled in the Phase 1 trial?	ACT response: Long-term follow up will be 14 years after completion of the 1st year.
2. ACT - Were the clinical doses tested in the Stargardt's and Dry AMD patients selected for safety or was there a therapeutic expectation at all doses tested?	ACT response: The doses were chosen for safety.
3. What types of immune monitoring (systemic vs local) would be useful to assess preclinically or clinically for the eye?	FDA Response: The immune-mediated risks of cell therapies for retinal disorders can be addressed in human study subjects through general safety and adverse reaction surveillance and specific monitoring for an immune response. It has been suggested that this can be done by observing a local cell response with slit lamp biomicroscopy or indirect ophthalmoscopy, as well as by systemically monitoring the T cell and antibody responses. Additionally, staggered subject enrollment, adjusted administration intervals, and immunosuppressive therapy may be useful. However, the value of each of these strategies has not been well established.
4. What are the panel's thoughts about re-treating patients that experience sub-optimal yet safe responses to an initial treatment?	FDA Response: Because most retinal diseases affect both eyes and binocular vision depends on bilateral refractive input, clinical development programs typically include plans to treat both eyes. However in addition to general safety concerns with any novel agent, there exist potential safety concerns related to subsequent administration of the product into the second, or contralateral eye, or repeat administration into the first eye. Data from animal studies suggest that the immune response can vary secondary to a number of factors including: the animal species and immune status, the specific product administered, the administration procedure, the timing of the second or contralateral administration relative to first administration, and the use of immunosuppressive agents. These immune-mediated risks can be addressed in human study subjects, but the value of the various strategies to do so has not been well established. We are interested in learning more about the immune response after contralateral or repeat administration as part of the clinical development program where factors such as specific monitoring for an immune response and immunosuppressive therapy can be considered and controlled.

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5. How do you know when you're ready to approach the FDA for a pre-pre-IND? For example, what animal studies should you already have?	FDA Response: Due to the complex nature of products regulated by the Office of Cellular, Tissue, and Gene Therapies (OCTGT), a pre-preIND telecon interaction offers sponsors the opportunity to present preclinical data and discuss their preclinical program with the Pharmacology/Toxicology reviewers prior to submitting an IND for a first-in-human clinical study. Sponsors receive substantive scientific and regulatory feedback when they are able to provide some preclinical (in vitro and in vivo) activity/proof-of-concept and safety data and they are in planning stages for additional more definitive preclinical studies (toxicity/safety and proof-of-concept) necessary to enable administration of the product to humans. The feedback provided by OCTGT on specific protocol designs for preclinical studies can be helpful in preparing the Pharmacology/ Toxicology sections of the preIND meeting package. For more information regarding the pre-preIND process and how to request such an interaction, please contact Mercedes Serabian, Chief of the Pharmacology/Toxicology Branch at: mercedes.serabian@fda.hhs.gov
6. Is it the FDA's expectation that the cells to be transplanted will be 99% the target cell?	FDA Response: While it is optimal to maximize the purity of final products, FDA has no set standard of minimum acceptable purity for cell therapies. The significance of the amount and the type of impurity would be individually assessed for each product during the review process. Viability of the target cell population may also be a part of review consideration.
7. How does a patient get approved for clinical trials, i.e., is it health status, based on blood tests, based on severity of macular degeneration, is it age?	FDA Response: The study sponsor determines who is eligible for the clinical trial. While there may be overlap, eligibility criteria are individualized for each study, based on the study objectives. For studies of retinal disorders, eligibility criteria often consider age, disease severity, overall health status, and a variety of other factors. The study sponsor can provide information regarding participating study centers where volunteers could be assessed for inclusion into a study. Also, ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, who may participate, study locations, and phone numbers to obtain more detailed information.

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8. Would HLA matching be needed - i.e., with H9? Was immunosuppression used? If so, for how long? Or is this not an issue for these eye diseases? Could the patient develop an immune response to the cells?	ACT response: ACT does not use H9. Patients are immunosuppressed initially and then weaned off, or can remain on immunosuppression if the investigators see positive signs. Initial immunosuppression is for three months but may be continued at a decreasing dose out to one year. Whether or not the patient develops an immune response to the cells is part of the safety and tolerability study and will be determined. Humayun response: For pre-clinical studies done by the group, HLA matching has not been used. Immunosuppression has been used in preclinical studies for the duration of the experiments, which have varied from a few months to one year. Because animal studies are xenografts, we do need immunosuppression. While the subretinal space has been shown to be immunoprivileged in some studies, it is still possible for the patient to develop an immune response to the cells. This may depend on the specific ocular pathology involved.
9. ACT question: How does your cell dose compare with the # of cells that are lost or damaged in the diseased eyes? (e.g., are you looking for replacement or supportive effects?)	ACT response: This is to be determined as we get preliminary data and make further determinations.
10. Are there differences in the risk of immunogenicity or infections based upon the delivery approach e.g., intravitreal, subretinal, other?	FDA Response: Results of animal studies suggest that the immune response can vary secondary to a number of factors, including the animal species and immune status, the specific product administered, the site of product administration (e.g., intravitreal vs. subretinal space), and the administration procedure. Furthermore, a more invasive procedure like subretinal administration is technically more challenging and has higher rates of complications, including infection.

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11. In the ACT animal model experiments, how was injected cell repolarization measured or quantified?	ACT response: We do not believe polarization of the cells is necessary, we believe they will orient themselves appropriately.
12. Are there any unique features for assessment of a nonbiodegradable vs biodegradable scaffold?	FDA Response: There are certain device-type of considerations when using an implant that combines a scaffold with a biological product. Such considerations include the mechanical impact of the implant occupying space and the implant's effect on nutrient transport between cells or tissues. Also, biocompatibility of the scaffold should be assessed prior to use in humans. It would be optimal to assess the impact the device component alone has on in vivo safety in animal studies. However FDA recognizes that such an assessment might not always be possible, since implanting the device component alone, without the biological component that is thought to provide primary mode of action for the final combination product, might only cause adverse effects not related to the final combination product. The sponsor should provide justification for not also evaluating the device component alone in the animal safety studies. When a biodegradable scaffold is used, it is important to fully characterize the safety and functional parameters of the combined product to be implanted and to understand how these parameters vary with time. Depending on the specific product design, this may involve significant biological and mechanical changes during the manufacturing process and/or after implantation. Potential toxicity and functional changes to the implanted construct due to gradual long-term modification of the scaffold, as well as its impact on surrounding tissues, should be considered during product development. This should importantly include the fate and potential migration of the cellular component that may be released as the scaffold component degrades and remodeling occurs. Humayun response: One advantage of the non-biodegradable substrate is that it can be monitored using conventional ophthalmic imaging and therefore makes it easier to follow the area of the graft.