MEMORANDUM OF MEETING MINUTES

Meeting type: C
PTS: PS007752
Meeting Date and Time: October 14, 2022, 9am-11am EDT
Meeting Location: Virtual

Indication: Friedreich's ataxia
Meeting Sponsor: Friedreich's Ataxia Research Alliance (FARA)

Meeting Chair: Wilson Bryan, MD
Meeting Recorder: FARA staff

FDA ATTENDEES
FDA's Office of Tissues and Advanced Therapies (OTAT)
Wilson Bryan, MD, CBER/OTAT
Kimberly Benton, PhD, CBER/OTAT
Wei Liang, PhD, CBER/OTAT
Anne Rowzee, PhD, CBER/OTAT
Denise Gavin, PhD, CBER/OTAT/DCGT
Kimberly Schultz, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Margaret Benny Klimek, PhD, CBER/OTAT/DCEPT
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Jennifer Hammer, MD, CBER/OTAT/DCEPT
Wiley Chambers, MD, CDER/OND/OSM/DO
Ramani Sista, PhD, CBER/OTAT/DRPM

FARA ATTENDEES
Jennifer Farmer, CEO
Barbara Tate, CSO
Ronald Bartek, President and Co-Founder
Elisabetta Soragni, Director of Research

Myriam Rai, Director of Global Relations and Initiatives
Layne Rodden, Director of Patient Engagement
Ruth Acton, Board Director, Mother of Ambassador Jack DeWitt
Brigid Brennan, General Counsel/Director of Advocacy/ Board Director
Tom Hamilton, Board Director
Thomas Brenninkmeijer, Board Director
Patrick Ritschel, Board Director
James Rusche, Board Director
Alex Fielding, Board Director, Ambassador
Shandra Trantham, Ambassador
Jack Dewitt, Ambassador
Joy Cavagnaro, Scientific Advisory Board
Massimo Pandolfo, Scientific Advisory Board
David Lynch, Scientific Advisory Board
Helene Puccio, Scientific Advisory Board
Maritza McIntyre, Consultant

INDUSTRY ATTENDEES

AavantiBio	Jessie Hanrahan, MS, MPH, PhD, Chief Regulatory Officer; Chris Wright, MD, PhD, Chief Medical Officer
Astellas	Diane Barnes-Glait, Senior Director, Regulatory Affairs; Jill Woloszynek, Director, Gene Therapy Program Management
CRISPR	Laurie Kelliher, Executive Director of Regulatory Affairs; Hari Padmanabhan, PhD, Principal Scientist
FA212	Tom Hamilton, Co-Founder; Thomas Brenninkmeijer, MBA, Co-Founder
Lacerta	Darin Falk, PhD, Chief Scientific Officer; Edgar Rodriguez, PhD, Chief Executive Officer
Lexeo	Jay Barth, Chief Medical Officer; Richie Khanna, VP and Head of Nonclinical Development
LifeEdit	Kathryn Woodburn, PhD, SVP Preclinical Development; Sally Kim, PhD, Scientist I, Preclinical Development
Neurocrine	Stephen Perry, PhD, Executive Director of Research; Amanda Richter, MS RAC, Executive Director of Regulatory Strategy

Novartis	Evgenia Dimova, NS & MSD, Global Therapeutic Area Lead, NS & MSD; Michelle L Krishnan, MD, PhD, Executive Medical Director, NIBR Translational Medicine
Pfizer	Laurence Whiteley, DVM, Nonclinical Safety/Pharmacology; Nicole Parker, PhD, Regulatory
Prime Medicine	Eric Zheng. PhD, Principal Scientist, Neuromuscular Diseases; Fubao Wang, PhD, SVP, Regulatory Affairs
PTC	Matt Klein, MD, MS, FACS, Chief Operating Officer; Bert Yao, MD, PhD, MHS, Vice President Clinical Development
Takeda	Gabriele Proetzel, PhD, Senior Director, External Neuroscience Innovation, Neuroscience Drug Discovery Unit; Edwin Addai, PharmD, RPh, Sr. Mgr. Regulatory Strategy
Tune	Luis Sanchez-Perez, PhD, Director of Preclinical Translation; Mike P. Hefferan, PhD, Director, Head of In vivo Pharmacology
Vesigen	Wendy Zhao, PhD, Principal Scientist; Joe Nabhan, PhD, Chief Scientific Officer

BACKGROUND

Gene therapy and gene editing (GT/GE) approaches represent promising developments in the search for effective treatments for Friedreich's ataxia (FA) because of their potential to directly address the cause of FA: frataxin (FXN) deficiency. At the request of FARA, Dr. Bryan provided the opportunity to bring together industry sponsors to a listening session where issues of interest to all participants can be discussed with FDA, as a mechanism to advance these transformative approaches more rapidly and efficiently for this rare disease. The purpose was to discuss the field in general, and to provide general principles that will be helpful for sponsors. FARA coordinated with the sponsors in advance of the meeting regarding the issues of concern to them. In addition, FARA covered topics suggested by OTAT, including patients' perspectives on specific issues. Prior to the meeting, FARA provided a briefing document that included background material and the specific issues to be discussed at the meeting. The meeting represented a new format for communication with multiple sponsors developing therapeutics for FA. FARA will distribute the materials from this meeting (the briefing document and this Memorandum of Meeting Minutes) so that other sponsors and other disease groups may benefit from the discussion.

1. Special considerations for gene therapy or gene editing development programs for FA.

Friedreich's ataxia (FA) is a multi-system disorder, and no single delivery vehicle or route of administration can transduce all affected tissues. Therapeutic development programs likely will focus on a single or a few organ systems and employ multiple routes of administration.

Question 1.1:

FARA would like FDA to understand the patient perspective on the benefit/risk analysis of selected tissue-targeted GT/GE and receiving one lifetime treatment with a viral vector. Shandra Trantham provided comments for the FA community. The FA patient community is very well-educated; patients have the resources to make informed decisions. Patients need to know the following information from a sponsor to make an informed decision regarding whether to participate in a clinical trial: what organ systems and possible symptoms are being targeted? Is there sufficient evidence that the lowest dose is expected to be therapeutic? What are the risks of harm? If I receive this treatment, can I take part in other clinical trials, including gene therapy trials, in the future? Is there an immunosuppression protocol?

FDA Response to Question 1.1

FDA is very interested in better understanding the patient perspective in this regard, and appreciates the feedback that we receive from patients, caregivers, and patient representatives.

Question 1.2:

FARA suggests that assessment of frataxin toxicity in preclinical studies include the following: Frataxin levels relative to wild-type control should be determined and should not greatly exceed normal physiological levels. Because frataxin is an intracellular protein, the percentage of cells transduced/corrected in the target tissue should also be determined to provide context for the total FXN levels expressed. The rationale for duration of studies should consider the potential for delayed toxicity. Assessments should include evaluation of tissues for overexpression of frataxin leading to cellular dysfunction, including changes in mitochondrial structure and function.

FDA Response to Question 1.2:

FDA acknowledged the reports of toxicities associated with FXN overexpression (i.e., exceeding physiological levels) in animal models, particularly the safety signals in heart and liver, and agreed that expression should be assessed relative to wild-type levels. FDA recommended evaluating other disease-relevant endpoints including functional analyses and histology in addition to evaluation of vector transduction and resulting frataxin transgene expression and FXN protein levels. Sponsors should justify the method used for determining dose levels of the product that are associated with bioactivity and the method used for dose extrapolation. Sponsors should include a discussion of any differences between the preclinical model(s) and human disease, and the potential impact these differences may have on determining a clinical starting dose level.

Question 1.3:

Does FDA agree that interpretation of meaningfulness of changes in frataxin levels in tissues should be based on context of use? For example, in programs where disease-relevant tissues can be accessed (e.g., heart and skeletal muscle), measuring FXN expression and protein levels are highly relevant as pharmacodynamic/activity biomarkers.

FDA Response to Question 1.3:

FDA agreed that interpretation of meaningfulness of changes in frataxin levels in these tissues should be based on context of use. FDA had no objections to measuring frataxin levels or evaluating other biomarkers. However, outstanding questions remain regarding FXN protein levels needed for clinical benefit; the potential risks of FXN expression above physiological levels and how those risks can be mitigated; and how uniformly FXN protein will be expressed in target tissues. These factors are important for assessing whether measurement of frataxin expression is reasonably likely to predict clinical benefit.

Sponsors are encouraged to assess clinically meaningful outcome measures in the first-in-human (FIH) study, and to design the FIH study such that it is well-controlled (e.g., including randomization, a concurrent control group, and blinding of subjects and evaluators), in order to collect not only safety data, but also preliminary efficacy data. Results from well-controlled studies, including the FIH study, could provide evidence of effectiveness for a future marketing application.

Question 1.4:
Can FDA provide a comment on FARA's suggestion that evidence from toxicity studies of mild toxicity in preclinical models without a functional correlate should not be a sole factor that impedes clinical translation?

FDA Response to Question 1.4:
In general, FDA agreed that mild DRG toxicity, without a functional correlate, observed in preclinical studies should not impede clinical translation; however, such findings should be evaluated on a case-by-case basis, and the implications will depend on the overall safety profile of each specific product. The DRG and spinal cord should be evaluated at multiple levels as part of the pivotal safety study. In preclinical studies, in life and postmortem peripheral nervous system assessments may be needed. The extent of these assessments may vary based on serotype and route of administration.

FDA added that it is critical to assess patients' sensory functions at baseline and follow them throughout the trial, monitoring for changes in the neurologic exam. FDA is open to recommendations on other possible ways to monitor DRG toxicity.

Meeting discussion:
The neurologists in attendance at the meeting presented their understanding of the pathology in the spinal cord in FA. In their view, the DRG show impaired differentiation and development particularly of the large sensory proprioceptive neurons. These are also the same neurons that seem to be most vulnerable to the AAV9-mediated DRG toxicity. The global community of clinicians treating FA patients over the last twenty years, as summarized by FARA, report that at diagnosis, individuals with FA have already lost reflexes and do not have measurable somatosensory evoked potentials. Published studies have demonstrated that clinicians in a research setting were able to detect a signal from these neurons using magnetoencephalography (MEG), but this finding has not been replicated outside of the research setting. Therefore, the consensus view of neurologists with experience in FA is that

DRG toxicity monitoring is essentially not feasible using standard neurophysiological methods. Clinically, FA patients show a loss of deep sensation that can be measured with quantitative sensory testing, and in the context of a clinical trial, it may be possible to detect reversal of this finding, but worsening is unlikely to be demonstrated with this method, based on decades of experience of the clinicians. In summary, the neurologists stated that it is unclear how much DRG toxicity would affect FA patients clinically with such substantial loss already present at diagnosis.

2. Cardiac focused therapeutic approaches

2.1 Preclinical models

Question 2.1:

FARA presented data on the well-validated cardiac-specific mouse model (MCK knockout mouse) that closely mimics human disease. A treatment effect can be observed even when symptoms are advanced, and pre-symptomatic treatment prevents disease. In addition, studies in this model have informed percent transduction required for benefit, and consequences of overexpression or frataxin toxicity. **Can FDA comment on the utility of the proposed preclinical models to support IND-enabling studies?**

FDA Response to Question 2.1

A weight-of-evidence approach is recommended to support preclinical proof of concept (POC) and identification of an appropriate clinical dose level. For any model of disease, the sponsor should provide a discussion and justify the biological relevance of the model to the disease. This discussion should include a description of the progression of phenotype, the lifespan, and a comparison of similarities and differences between the model and the intended clinical population, regarding pathophysiology, biochemistry, functional changes, and affected anatomy. A rationale should be provided for the timing of administration of the product in animal models relative to disease progression, and how this timing compares to the clinical situation. For cardiac-specific models, the models should be appropriate to evaluate the parameters for the specific cardiac disease. The MCK model can also be used to evaluate cardiac toxicity, and safety endpoints should be included in these POC studies.

Question 2.2

MCK FXN conditional knockout cannot be used for preclinical GE programs; however, percent transduction in this model from can inform a benchmark for percent editing efficiency in heart. Considering the lack of humanized mouse models with repeat expansion and a functional cardiac phenotype to support GE, **does FDA have comments on the proposed utility of *in vitro* models for POC or other suggestions for preclinical studies to support FIH GE studies?**

FDA Response to Question 2.2

For any *in vitro* system, a sponsor should provide supporting data on the ability of iPSC-derived cardiomyocytes to recapitulate the FA phenotype. The sponsor should include a discussion and rationale for the method of dose extrapolation and how the resulting data support a starting

clinical dose level. The sponsor should also discuss the impact of species-specific differences in transduction and/or editing efficiency *in vitro* and how these findings affect dose extrapolation.

Sponsors should demonstrate on-target specificity of their GE product. Off-target editing activity is a significant safety concern, and FDA recommends that sponsors reduce off-target cleavage and perform off-target analysis using unbiased and biased methods. FDA did not agree with the FARA statement in the briefing book (Appendix 3 Page 91) that "there are no specific concerns about gene editing relative to the editing of other genes when targeting frataxin." FDA thinks that this cannot be assumed.

FDA referred to the draft guidance document *Human Gene Therapy Products Incorporating Human Genome Editing* (available at fda.gov/media/156894/download). In addition to the *in vitro* data, the sponsor should justify the *in vivo* model selected for evaluating gene editing products and provide information to characterize product biodistribution and *in vivo* editing efficiency, and to support dose extrapolation.

2.3. Clinical Development
2.3 Patient Assessment of Risk Benefit

Question 2.3

Regarding the cardiac aspects of the disease, would FDA like any additional information on patient perspectives on benefit/risk of GT/GE for cardiac disease or appropriate populations for these treatments?

Shandra Trantham provided comments for the FA community. Cardiac disease negatively impacts quality of life and the community have lost friends to sudden cardiac events. Treating the cardiac disease must be a part of treating FA. The preclinical studies on gene therapy in mouse models was exciting news for the community. The community is also very familiar with and comfortable with cardiac biopsies and would appreciate the confirmation of increases in frataxin in cardiac tissue that might be demonstrated by cardiac biopsies.

FDA Response to Question 2.3

Patient perspective is very important to the FDA. Formal quantitative analysis of patient perspectives on benefit/risk would be especially helpful to understand the degree of risk patients at different stages of the disease are willing to accept for a given benefit.

Question 2.4

Given the inability to assess functional cardiac outcomes with certainty in less than 5 years, **can FDA comment on the proposed weight of evidence approach using well-validated cardiac biomarkers of cardiac structure and function to provide evidence of efficacy that could predict clinical benefit?**

FDA Response to Question 2.4

Since there are product-specific considerations for cardiomyopathy, the responses will depend on the stage of the disease (e.g., prevention versus reversal of damage). FDA's preference is direct measurement of a clinically meaningful endpoint. The biomarkers proposed have not yet

been validated to predict a clinically meaningful outcome. Cardiopulmonary exercise testing (CPET) could be considered a clinically meaningful endpoint if the change observed in treated patients compared to controls is clinically meaningful. For such effort-dependent endpoints, a randomized, blinded, controlled study is needed.

Patient-reported outcomes (PRO) measures are other ways to directly measure how a patient feels and functions but would need to be established to be fit-for-purpose (i.e., in terms of content and construct validity) prior to use as clinical efficacy endpoints. Sponsors should make sure to address whether other aspects of the patients' condition (e.g., depression or other non-cardiomyopathy-based symptoms, such as muscle strength or fatigue) could confound the results and reduce the ability of the PRO to detect an effect of the treatment on cardiomyopathy.

Biomarkers can be used:

- for eligibility criteria:
  For this use, the correlation to disease state does not require the same persuasiveness of data that is needed for a biomarker to replace a clinical assessment.
- for dose setting studies:
  Biomarkers can be used to assess a pharmacodynamic effect, although there is a risk that changes in the biomarker used to determine the dose will not predict clinical outcomes. If there is no alternative to assess the pharmacodynamic effect of the product, FDA recommended use of a biomarker.
- for safety monitoring
  FDA stated that for safety monitoring, understanding of pathophysiology of the disease, product-specific preclinical data, and information on class-specific properties and safety liabilities should be considered to determine the primary safety issues and use of biomarkers to monitor those potential safety concerns.

Using biomarkers as a primary efficacy assessment is challenging. In FA, there are currently no validated biomarkers to predict clinically meaningful outcomes for cardiomyopathy. FDA encourages development of biomarkers for this purpose. To develop a biomarker for this purpose, a sponsor would need to:

- show that an intervention causes change in the biomarker first, and is followed by a clinically meaningful improvement
- show a quantitative relationship between the biomarker and the clinical change; and
- show that the biomarker is associated with the causal pathway of the disease.

All the markers that FARA mentioned can be used for eligibility, safety and dose finding, but the current data do not support their use for efficacy.

To use composite endpoints for efficacy assessments, the sponsor would need to show that an improvement in a composite endpoint predicts an improvement in a clinically meaningful outcome like survival or function.

Meeting Discussion:
Published data demonstrates and the experience of FA clinicians attending the meeting confirmed that cardiac changes in FA are slow and clinical events occur late in disease after significant, potentially irreversible damage. Published studies have also noted that CPET testing can be a very confounded measure in FA because it reflects skeletal muscle biology. Decades of data support that structural biomarkers are the markers which determine the clinical course of cardiac disease in FA ; these biomarkers dictate the clinical care given to patients. In some cases, they are closely linked to clinically relevant events. FARA agreed that there is a need to better anchor them to known clinical events. FARA asked if there were any recommendations for other or better ways to use the imaging-based biomarkers of cardiac structure and function that we have.

FDA responded that requirements for drug approval include substantial evidence to support claims of effectiveness for new drugs, regardless of the clinical course or severity of the disease. FDA is willing to consider evidence to support the use of biomarkers that might predict clinical benefit. If the goal is accelerated approval based on surrogate endpoints, there must be adequate and well-controlled studies that provide evidence of an effect on the specified biomarker (i.e., proposed surrogate endpoint).

3. Nervous system-focused therapeutic approaches
Preclinical

Question 3.1

Can FDA comment on whether there are any concerns regarding the proposed preclinical models to support IND-enabling studies for gene therapy of nervous system manifestations of FA?

FDA Response to Question 3.1

FDA understands that the nervous system manifestations in animal models may differ from the clinical presentation of the human disease. Sponsors should explain these differences and discuss how these differences affect translation of the preclinical data to the clinical trial. The rationale for use of a model should be provided. FDA referred sponsors to the guidance document Human Gene Therapy for Neurodegenerative Diseases, available at fda.gov/media/144886/download.

Question 3.2

Can FDA comment on FARA's suggested plan to include *in vitro* evidence of increased frataxin expression and functional correction after gene editing, plus characterization of nervous system gene editing efficacy in an animal model?

FDA response to Question 3.2

FDA agreed with the general approach and recommended the discussion of these approaches at product specific INTERACT and pre-IND meetings. Appropriate steps should be taken to minimize potential bias for neurobehavioral assessments.

Clinical Development

Question 3.3

Could the FDA comment on the plan to initiate pediatric studies early in development if supported by safety in adults, and some evidence of activity as well as preclinical POC?

FDA Response to Question 3.3

FDA has no objection to enrolling pediatric patients early in clinical development if there are sufficient data to support the prospect of direct benefit to individual subjects based on available preclinical or clinical data, and the risks are adequately characterized.

If there are no or minimal efficacy data in adults, but safety is established in adults and data from the animal studies support prospect of direct benefit, enrollment of pediatric participants in the study could be justified.

To support prospect of direct benefit, POC studies should be conducted in a disease model to evaluate whether administration of the product using the intended clinical route of administration results in a durable improvement in relevant neurobehavioral parameter(s). Such evidence of bioactivity, along with safety data, should be provided to support the administration of dose levels of the product that have the potential to be clinically meaningful. A comparison between any treatments that are currently available for the clinical population to the investigational product should be considered when evaluating risk-benefit of the investigational product.

Sponsors should engage early with FDA to discuss their preclinical program is appropriately designed to collect evidence of prospect of direct benefit.

Question 3.4

FARA believes the neurological data in the Friedreich's Ataxia Clinical Outcome Measures Study (FACOMS) are informative for designing trials, providing outcome assessments, and providing a comparator arm for clinical trials, or at least to supplement placebo, e.g., employing Bayesian approaches to reduce size of placebo group in trial design. **Can FDA comment on the proposed utility of natural history data?**

FDA Response to Question 3.4

Natural history data is extremely valuable to inform study design, including establishing eligibility criteria, identifying endpoints, and establishing the clinical trial duration. FDA in general would not agree with use of an external control to replace a concurrent control group, because of concerns about the heterogeneity of disease and the comparability of an external control data set with that of the study population. Significant differences may exist between a study population and natural history data, due to issues like supportive care treatments that become available during the study but were not available at the time the natural history data were collected. Additionally, outcome measures are often process- and effort-dependent, which will likely lead to differences in performance in an open-label interventional study versus

in a natural history study. FDA strongly encourages randomized, blinded, concurrent-control study designs with enough patients in the treatment and the control arms. The general recommendation is to obtain data from randomized, blinded, concurrent-controlled trials to demonstrate safety and efficacy.

Meeting Discussion:
FARA proposes not to replace a concurrent control arm. Given the prevalence of the disease, FDA is open to discuss the possibility of using an external control to "augment" the concurrent control arm, provided that a sponsor provides sufficient data to justify such an approach. FDA believes that a randomized, concurrent-controlled design with sufficient numbers of subjects in both the treatment and concurrent control arms would likely result in only a modest increase in the number of subjects but would substantially improve the interpretability of the clinical data and is the most efficient way to demonstrate the safety and effectiveness of a product to treat Friedreich's ataxia.

Question 3.5
Can FDA comment on FARA's request that FDA not recommend unilateral administration, especially in the case of intraparenchymal administration to the dentate nucleus in FA?

Alex Fielding shared the community view on the FDA recommendation. Overall, the community accepts invasive procedures, especially to reach brain structures, if potential benefits outweigh the risks. The community understands the need for placebo/control groups in gene therapy trials. However, the community is not willing to accept unilateral injections in specific nuclei of the cerebellum because of the potential of making the disease worse if the treated area of the cerebellum either does better or worse than the untreated side. Adding a new variable due to unilateral treatment adds an unnecessary challenge that will frustrate, fatigue, and depress the FA psyche. Patients are willing to accept the risk of worsening of the entire system caused by a bilateral treatment, rather than a potential imbalance caused by a unilateral injection that does not achieve the intended de-risking.

FDA Response to Question 3.5
Although animal studies may indicate a potential for benefit, animal models are limited regarding prediction of clinical benefit. FDA favors a stepwise approach when a product is intended to be delivered to a critical anatomical structure, such as the brain parenchyma. FDA recommended that the first several subjects in an FIH study receive the product unilaterally. Those subjects should be followed for a reasonable amount of time to monitor for procedure-related adverse events before investigators move on to bilateral administrations for the rest of subjects in the FIH study. FDA would be willing to consider bilateral administration for all subjects in a FIH study, on a case-by-case basis taking into consideration the experience of the surgical team, among other factors.

Meeting Discussion:
The neurologists attending the meeting reviewed the anatomy of the cerebellum for the attendees. A unique feature of cerebellar anatomy and neurophysiology is that it is a strictly

double-crossed pathway. Therefore, they concluded that unlike intraparenchymal injections to other areas of the brain, it is likely that the risk of injecting both cerebellar hemispheres is not much more than the risk of injecting one, yet without gene therapy/gene editing on both sides of the cerebellar nuclei, functional benefit on gait or speech will not be achieved, due to the bilateral nature of the cerebellar circuits controlling these functions. FDA reiterated that it is unknown whether an investigational product at the starting dose would provide any clinical benefit, while the potential risk associated with an invasive delivery procedure to a vital anatomic structure has to be closely assessed.

4. Vision system focused therapies

Question 4.1

FARA would like to provide additional information on the impact of vision on quality of life for individuals with FA, and the patient perspective on benefit/risk of treating vision loss.

Jack DeWitt shared the FA community perspective on vision loss. Vision has a huge impact on later stage FA patients. The community has a high tolerance for risk when it comes to gene therapies/gene editing for FA vision, even if there is not yet human data to support these procedures. Before enrolling in a trial, the community would like to know how well the therapy worked in animal models, and that there was a realistic chance that even the lowest dose would provide benefit.

FDA Response to Question 4.1

FDA thanked Mr. DeWitt for providing perspective. FDA had no further comments.

Question 4.2

Can FDA comment on proposed plan to use a weight of evidence approach using multiple available models to evaluate proof of concept and extrapolate doses?

FDA Response to Question 4.2

FDA agrees with the proposed approach.

Question 4.3

Would FDA consider RNFL loss to be an acceptable endpoint in FA?

FDA Response to Question 4.3

It is premature to answer the question regarding acceptability of using retinal nerve fiber layer (RNFL) loss as a primary efficacy endpoint. FDA would be willing to look at a proposal that defined the specific locations and the amount and time course of change in RNFL, which are critical to determine whether such a change would be clinically meaningful to patients with FA.

Meeting Discussion:

The FA Natural History study has accumulated data on the loss of low contrast and high contrast visual acuity, progressing to no light perception in some individuals, over the course of

20 years. Long-term optical coherence tomography (OCT) data show a rate of RNFL loss of about one micron per year, with a reproducibility between subjects of about one micron.

FDA clarified that low contrast visual acuity is an acceptable endpoint. Change in low contrast visual acuity resulting in doubling or halving of the visual angle (3 lines or 15 letters) when compared to an appropriate control group is considered clinically meaningful.

Question 4.4

FACOMS has collected data on annual visual assessments. These data inform trial design, patient selection, outcome measures and can also supplement the placebo group data to reduce number of participants in placebo arm. **Does FDA have a comment on the use of natural history data?**

FDA Response to Question 4.4

Natural history data are very helpful in helping design the clinical program. FDA does not agree that the natural history data can be used as the control arm to replace a concurrent control group, or to reduce the number of subjects in a concurrent control group. This concern applies to functional outcome measures, including the visual function assessment, because these outcome measures are effort-driven. In situations where assessments are effort-driven, measurement and performance can differ in clinical trials, compared to when the same assessments are made as part of a natural history study.

Closing Comments

Dr. Bryan provided closing comments, expressing gratitude to everyone for this meeting, and particularly for the patient perspective. He stated that the natural history study conducted by FARA is quite valuable.

Ron Bartek provided additional closing remarks of many thanks to FDA and to the industry sponsors. He noted the importance of having on the call sponsors, the FA community, the GT community, and FDA, and expressed hope that the meeting was helpful for all.

The meeting was adjourned at 11am ET.