U.S. FOOD & DRUG ADMINISTRATION

Preliminary Meeting Responses

Our Reference: [redacted]

DATE: February 14, 2025 **PAGES:** 8

TO: [redacted]

FROM: [redacted]

SUBJECT: INTERACT meeting to obtain Agency reviewer guidance and feedback on early development CMC, nonclinical and clinical plans in preparation for a Pre-IND and eventual IND application. Specifically, the investigators wish to seek agreement and input from the Agency for specific questions listed in this meeting request.

PRODUCT: Recombinant Adeno-Associated Virus 8 Human Solute Carrier Family 4 Member 11 (rAAV8-hSLC4A11)

PROPOSED INDICATION: Congenital hereditary endothelial dystrophy (CHED).

FDA Participants:

[redacted]

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[redacted]

This material consists of our preliminary meeting responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 19, 2024. We are sharing this material to promote a collaborative and successful discussion at the meeting.

Although we continue to reserve February 19, 2024 from 9:00AM – 10:00AM EST, with you regarding this product, if you find that our attached responses and advice are sufficiently clear and complete to obviate the need for further discussion, please inform us in writing as soon as possible, and 3 calendar days from the date of receipt of FDA's Preliminary Responses, so that we may clear the meeting time. These responses would then become the official FDA responses to your questions.

If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. If you have questions regarding specific responses or advice included in this preliminary response, please inform the RPM so that the appropriate members of the Review Committee can provide clarification during the reserved meeting time. Please refer to the *Respond to Meeting Request-Granted* communication you received for details about your scheduled meeting.

Please be aware that your future submission should include all components for a complete submission and should be in compliance with all appropriate statutes and regulations. For input on additional issues that were not posed in your meeting package or addressed in our preliminary meeting responses, you may submit a new meeting or a WRO request, as we may not be prepared to discuss or reach agreement on new topics at the meeting.

Please include a reference to PTS #PS009683 and/or Meeting ID #20980 in your future submissions related to this product.

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Annotated Preliminary Meeting Responses

Chemistry, Manufacturing, and Controls

Question 1:
Does the Agency agree that measurement of hSLC4A11 mRNA expression in a serotypesusceptible (AAV8) cell line, coupled with Sanger sequencing, is an appropriate measure of potency for release of Phase 1 clinical drug product?

FDA Response to Question 1:
Yes. We agree that the proposed potency assurance strategy is an acceptable approach for potency release during Phase 1 clinical trials.

Question 2:
Once validated, the investigator/BGTC believe that these same mRNA quantification and Sanger assays described in Question 1 would be an adequate and reproducible measure of potency for release of Phase 3 and commercial product. The investigator/BGTC request Agency feedback on the plan for potency testing including any guidance on the use of these assays for commercial release of drug product.

FDA Response to Question 2:
We do not agree with your proposal to use Sanger sequencing and mRNA expression for potency assurance of product released for Phase 3 trials and commercialization.

1. We recommend continuing efforts to develop a bioactivity assay that represents the mechanism of action for hSLC4A11.

2. If you choose to pursue a potency assurance strategy combining a validated and precise transgene expression assay and sequencing, you will need to implement a sensitive NGS method for DP release testing that can detect low levels of sequence variants. The use of Sanger sequencing is not sufficient.

3. For transgene expression and bioactivity assays, we recommend that you report the potency of each product lot relative to a thoroughly characterized product-specific reference vector lot that will be included in each assay run. In our experience, assessing relative potency helps to improve assay control and reduces inter-assay variability of cell-based assays.

4. We recommend that you engage with FDA early on in clinical development on development of a late-phase appropriate potency assurance strategy. Additionally, please refer to “Guidance Document: Potency Assurance for Cellular and Gene Therapy Products,” from December 2023 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/potency-assurance-cellular-and-gene-therapy-products).

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Question 3:
Does the Agency agree with the proposed time points and proposed source of stability test samples, with the condition that specifications and methods for these tests will be provided at Pre-IND? The investigator/BGTC wish to obtain agreement with the Agency on these specific points prior to Pre-IND as there is a need to plan for production quantities at this time.

FDA Response to Question 3:
Yes, we agree with the proposal to use toxicology lots for stability studies and confirm that six months of data is sufficient for initiation of your clinical studies. Please note that testing stability samples for subvisible particles is not required. For more information, see Guidance Document: "Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products" from July 1996 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q5c-quality-biotechnological-products-stability-testing-biotechnologicalbiological-products).

Nonclinical

Question 4:
Does the Agency agree with the design of the non-GLP pilot toxicology and biodistribution studies, including the selection of Gottingen mini pigs as an appropriate large animal model, the dose translation strategy, in vivo safety parameters, biodistribution analysis and study duration?

FDA Response to Question 4:
Based on the information provided in Section 8.2.1 (pages 16-22), we agree with the overall design of your planned pilot non-GLP toxicology and biodistribution (BD) study in Gottingen mini pigs; however, we question the need for this pilot study in addition to a definitive GLP toxicology and BD study to support your proposed first-in-human clinical trial. If you elect to conduct the pilot non-GLP toxicology and BD study, we recommend reducing the number of animals included in each group to 2/sex/group for animals receiving AAV8-hSLC4A11 and 1/sex/group for animals receiving the vehicle. We have the following comments regarding your overall nonclinical program that you should address in a future pre-IND submission:

1. We recommend a stepwise approach to your nonclinical program, conducting the definitive IND enabling proof of concept (POC) studies as described in Section 12.3.1 (AAV8-hSLC4A11 dose optimization in *Slc4a11*$^{-/-}$ mouse model of congenital hereditary endothelial dystrophy [CHED]) to determine a minimal effective dose level (MED) of AAV8-hSLC4A11. The information gathered from the planned POC studies should inform the design of the definitive GLP toxicology and biodistribution study.

2. Please provide a comprehensive discussion, with accompanying data, about the biological relevancy of each animal model of CHED used in your proof of concept (POC) studies to the proposed patient population. The discussion should include the severity of the animal model (i.e., *Slc4a11*$^{-/-}$ mouse), how the

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model/mutation was generated (i.e., CRISPR), the acute and/or chronic nature of the corneal manifestations at the time of product administration, functional changes in the cornea, and/or any other applicable factors.

3. You observed corneal opacification and vascularization in *Slc4a11* $^{-/-}$ mice administered the unpurified AAV8-hSLC4A11 and attributed these findings to impurities in this vector batch. Please provide a tabulated summary showing the similarities and differences between all nonclinical products compared to the intended clinical product. This should include the AAV serotype, transgene, promoter, formulation buffer, major differences in the manufacturing process, vector genome titer, infectivity, and full:empty particle ratio for the original 'unpurified' nonclinical product (VectorBuilder) used in the completed nonclinical studies summarized in Section 12.2, and the "research grade" and "toxicology grade" (GMP quality from Andelyn) rAAV8-hSLC4A11 products, as feasible. For any differences, please provide a discussion on the potential impact this may have on the translation of the nonclinical dose levels and resulting data, to the proposed clinical scenario.

4. Your rationale for dose level extrapolation from animals to human described in Section 8.3.2 (Table 3; page 25) is adequate. Please provide the parameters (cornea volume, surface area, etc.) and methods used to calculate dose level extrapolation from each species (mouse, Gottingen mini pigs) in your nonclinical studies and provide a summary of your justification with supporting data from the cited publications.

5. Please provide a comparison of the delivery device and administration procedure(s) used/planned in each nonclinical study to the planned intrastromal clinical delivery device and procedures (e.g., syringe, injection rate, injection volume, injection depth, anatomic location, etc.). This comparison should include any modifications that were made or are planned to accommodate anatomic differences.

Question 5:
The investigator will be submitting a noncommercial IND for rAAV8-SLC4A11 (i.e., the product is not intended for commercial distribution). Does the Agency agree that the preclinical safety studies contained in the IND would be exempt from standardized study data requirements (i.e. SEND) as provided by FDA Guidance for Industry, Providing Regulatory Submissions In Electronic Format – Standardized Study Data and Section 745A(a) of the FD&C Act?

FDA Response to Question 5:
We agree that the nonclinical safety studies are exempt from SEND based on your plan to submit a noncommercial IND. Please note that, per the guidance Section 745A(a), the term noncommercial IND refers to an IND for a product that is not intended for commercial distribution and includes investigator-sponsored INDs. Further details on this requirement, including the types of nonclinical studies and exceptions from this requirement can be found at https://www.fda.gov/industry/study-data-standards-

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resources/study-data-submission-cder-and-cber and in the "Study Data Technical Conformance Guide" at https://www.fda.gov/industry/fda-data-standards-advisory-board/study-data-standards-resources. Questions regarding SEND should be directed to CBER-edata@fda.hhs.gov.

Clinical

Question 6:
Does the Agency agree with the investigator's proposal to include pediatric subjects in the first-in-human trial, in compliance with 21 CFR Part 50, Subpart D, given evidence of a direct benefit for the pediatric population based on the natural history of the disease and efficacy data from the only disease model available?

FDA Response to Question 6:
Yes, your plan to treat pediatric patients is reasonable. In your pre-IND, please discuss the results of the planned toxicology study to further characterize the potential risk of neovascularization and subepithelial opacification development in the clinical trials. Please refer to FDA response to Question 4.

Question 7:
Does the Agency agree with the dose translation strategy from the planned minipig toxicology study to first-in-human clinical trial?

FDA Response to Question 7:
We agree with the rationale for dose level extrapolation from the minipig to humans.

Additional FDA Questions/Comments:

General Considerations

1. We recommend that you request a pre-IND meeting with CBER/OTP when ready, to obtain feedback regarding your product development plan from the three CBER/OTP review disciplines, consisting of product manufacturing (CMC), pharmacology/toxicology (P/T), and clinical. Please be advised that you should consider and address all recommendations provided in these INTERACT comments when you submit a pre-IND meeting package.

2. We refer you to OTP Learn, a series of online presentations provided by the Office of Therapeutic Products (OTP) which address important topics in the development of products regulated by OTP. You may find some of these presentations useful in your preparation of regulatory submissions and briefing materials for meetings with FDA. OTP Learn is available at: https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/otp-learn.

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Chemistry, Manufacturing, and Controls

3. Please note that DNA plasmids used for transfection in AAV product manufacturing are considered critical starting materials, and do not need to meet the same requirements as drug substance (DS). You should provide the following information in your IND:

    a. Annotated maps for all plasmids used in manufacturing, identifying all open reading frames, genetic components (promoters, introns, known coding sequences, polyadenylation signals, and untranslated regions). If using a bacterial master cell bank approach, we recommend sequencing each plasmid master cell bank to verify the correct sequence and detect any unexpected elements.

    b. Certificates of analysis (COAs) for all plasmids used in product manufacturing. COAs should indicate the grade of plasmid.

    c. A narrative description and flow diagram of the plasmid manufacturing process.

    d. A description of the Quality Unit and procedures at the plasmid manufacturer that prevent cross-contamination between plasmid DNA lots, including segregation, tracking, and changeover systems for manufacturing.

    e. An identity release test that can distinguish your plasmid from other plasmids manufactured at the facility.

    f. Provide a complete list of raw materials and manufacturing equipment used in plasmid production. Indicate which materials are single-use versus reusable. For reusable product-contact materials, describe the established cleaning procedures for preventing contamination and summarize validation studies that prove these cleaning procedures effectively and consistently remove plasmid DNA.

    g. A complete list of animal-derived materials (if any) used to make the plasmids.

    h. A description of the acceptance testing that will occur after receipt of each plasmid at the AAV DS manufacturing facility. At a minimum, each lot of plasmid should be tested for identity.

4. In Section 4.3. Manufacturer, Manufacturing Process and Schematic you describe the pTR-EF1-SLC4A11_Kan and AAV8 helper plasmids but provide no information on the Rep/Cap plasmid. Please clarify how many plasmids are used in your manufacturing process.

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5. For more information, please see FDA Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (January 2020).

Nonclinical

6. We recommend that you refrain from initiating a definitive Good Laboratory Practice (GLP) safety study until receipt of detailed feedback from us at the time of your pre-IND. You should submit detailed protocols for all planned safety assessments in your future pre-IND, at which time we will provide more substantive commentary regarding the designs of your proposed studies.

7. For a comprehensive summary regarding the nonclinical assessment of cell and gene therapy products, please refer to the document titled, Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013), available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products.

END

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