



Our Reference: PS009720/3
Meeting ID 22692

MEETING SUMMARY

Date: July 14, 2026

Sonia Vallabh, PhD
75 Ames Street
Cambridge, MA 02142

Dear Dr. Vallabh:

Attached is a copy of the memorandum summarizing your July 07, 2026, Pre-IND meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible. Further, if you require a clarification to a single meeting response limited to a single discipline, you can submit a question via email to the Regulatory Project Manager and we will strive to respond to your inquiry within 3 business days by email.

Please include a reference to Meeting ID 22692 and/or PS009720/3 in your future submissions related to this product.

If you have any questions, please contact Julia Russell at [REDACTED] or by email at [REDACTED]

[REDACTED]

Nadia Whitt, MS
Branch Chief
Division of Review Management and Regulatory Review 1
Office of Review Management and Regulatory Review
Office of Therapeutic Products
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Meeting Summary
(Includes Preliminary Meeting Responses)

Meeting ID #:	22692
Submission Type & #:	PS009720/3
Product Name:	Recombinant Adeno-Associated Viral Vector-9 containing a single-stranded AAV2 genome encoding an epigenetic editor targeted to the <i>PRNP</i> promoter by a zinc finger (ZF) binding domain and an engineered AAV9-derived capsid BI-hTFR1v2, that has been designed to enter the human CNS via its ability to bind to human Transferrin receptor (TfR1)./Product Name: PRNP-CHARM-001
Proposed indication:	Treatment of Prion disease, including symptomatic patients and pre-symptomatic individuals at known risk of genetic prion disease.
Sponsor:	Sonia Vallabh, PhD
Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date & Time:	July 7, 2026 12:00 PM-1:00 PM, US EST
Meeting Format:	Face-to-face (Virtual)
RPM:	Julia Russell, MS
Preliminary Meeting Responses:	July 2, 2026

Virtual FDA Attendees:

Danielle Brooks, PhD, CBER/OTP/OPT
David Cantu, PhD, CBER/OTP/OPT
Andrew Harmon, PhD, CBER/OTP/OGT
Anna Kwilas, PhD, CBER/OTP/OGT
Bo Liang, PhD, CBER/OTP/OGT
Gumei Liu, MD, PhD, CBER/OTP/DCEGM
Mondona McCann, PhD, CBER/OTP/OPT
Anandan Paldurai, PhD, CBER/OTP/OGT
Cara Pardon, MS, CBER/OTP/ORMRR
Daekwan Seo, PhD, MS, CBER/OTP/OCTHT
Anurag Sharma, PhD, CBER/OTP/OGT
Mike Singer, MD, PhD, CBER/OTP/OCE/DCEGM
Prateek Shukla, MD, CBER/OTP/OCE/DCEGM
María Luisa Torruella Suárez, PhD, CBER/OTP/OPT
Ramjay Vatsan, PhD, CBER/OTP/OGT

Virtual Sponsor Attendees:

Sonia Vallabh, PhD, Director, Prion Therapeutic Science, Broad Institute
Benjamin Deverman, PhD, Senior Director, Vector Engineering, Broad Institute

Eric Minikel, PhD, Director, Prion Therapeutic Science, Broad Institute
Andrew Steinsapir, MBA, Nonclinical consultant; Director, Gene Therapy Program Lead, Deerfield Discovery and Development; Acting CTO, Apertura Gene Therapy
Christopher Davis, PhD, Nonclinical consultant; Director, Nonclinical and Translational Research, Apertura Gene Therapy
Stephen Sofen, PhD, CMC consultant
Monika Chabiovsky, PhD
Timothy Lavaute, NIH Program Officer
Pj Brooks, NIH Program Officer
Chris Boshoff, PhD, NIH Program Officer
Daniel A. Sprague, PhD, Computational Scientist, Broad Institute
Alissa Coffey, PhD, Project Manager, Broad Institute
Fiona Serack, PhD, Research Scientist, Broad Institute
Jessie Davis, PhD, Research Scientist, Broad Institute
Felicia Qashu, PhD, NIH Program Officer

Dr. Sonia Vallabh submitted a meeting request on May 11, 2026, to discuss obtain the Agency's feedback on questions that are critical to the development of the PRNP-CHARM-001 product. The Sponsor seeks feedback on the set of questions listed in Section 14, which concern non-clinical, CMC, and clinical aspects of the PRNP-CHARM-001 gene therapy program. The pre-meeting materials were submitted on June 5, 2026.

FDA provided its preliminary meeting responses to Dr. Sonia Vallabh's questions on July 2, 2026. After reviewing the preliminary meeting responses, Dr. Sonia Vallabh notified FDA on July 6, 2026, of their decision to limit the meeting to discuss only questions 1 and 3.

Sponsor Questions:

Sponsor Question 1: *Does the Agency agree with the Sponsor's position that the proposed in silico, in vitro, and in vivo study designs to assess PRNP-CHARM-001 off-target activity are sufficient to proceed with an IND submission and subsequent clinical administration of the PRNP-CHARM-001 drug product?*

FDA Preliminary Meeting Response to Sponsor Question 1:

We cannot yet agree that your off-target assessment strategy is sufficient to support the safety of your product for first-in-human use. The information provided in your briefing package is insufficient for a comprehensive evaluation. Based on the information provided in your package, we cannot determine whether the observed downregulation of certain genes represents a true off-target effect. To allow for a complete safety review, please provide the following information in your IND submission:

1. You performed RNA-sequencing (RNA-seq) using a panel of five immortalized human cell lines. However, a scientific justification for the selection of this

specific panel was not provided, and it notably lacks the primary therapeutic target cell or cell line. This information is necessary to evaluate whether the scope of your in vitro off-target assessment is adequate. We have the following comments:

- a. We are concerned that the methylation profile of immortalized human cell lines may not recapitulate the methylation profile of primary human cells (PMID: 24371281). Please conduct additional off-target analysis in relevant primary human cells to characterize the off-target profile of PRNP-CHARM-001. If off-target analysis in relevant primary human cells is not feasible, please provide justification.
 - b. Please incorporate additional cell types in your off-target assessment based on observed transgene expression following your planned comprehensive BD evaluation of PRNP-CHARM-001 (Appendix XI).
2. In Table 6 of Appendix XII (page 274), you provided a list of genes with statistically significant, cell-line-specific expression changes. However, you did not provide a risk assessment for these findings in each cell line. Genes with similar patterns to the expression level of PRNP are considered potential off-target genes. Please provide a risk assessment for these genes and the potential safety implications of their unintended downregulation within each specific cell line.
3. In Table 6 of Appendix XII (Page 274), you provided inconsistent on-target efficacy results across different cell lines. A clear understanding of these inconsistencies is important for evaluating the predictability of your product's mechanism of action. Please provide a discussion that addresses both: 1) why the downregulation of *PRNP* was not statistically significant in the hCMEC/D3 cell line, and 2) why *PRNP* downregulation was statistically significant in the THLE-2 liver cell line, despite the inclusion of 3x miR-122 target sites intended for liver de-targeting.
4. You provided the list of candidate off-target genes (Table 6 of Appendix XII, Page 274), identified from your RNA-seq analysis. However, this list does not represent the complete dataset of off-target genes. To complete our review of your off-target assessment, please provide the RNA-seq results in a Microsoft Excel file format, including raw and normalized counts, the complete list of differentially expressed genes for each cell line, and both raw p-value and adjusted p-values at the gene level from your Bayesian mixture model.

Meeting Discussion for Sponsor Question 1:

The Sponsor indicated that preliminary CapX biodistribution transgene expression data supports evaluation of off-targets in the CNS, liver, adrenal gland, and heart. The Sponsor indicated that they would evaluate off-targets in immortalized human heart and adrenal cell lines, iPSC-derived induced neurons,

and primary hepatocytes in addition to existing data. The Sponsor indicated that additional cell lines would be nominated if warranted by the GLP study in hTFR1 mice. FDA agreed with the Sponsor's proposal.

The Sponsor provided data indicating that differences in PRNP knockdown in cell lines is likely due to differences in permissiveness to transduction by the CapX capsid. FDA agreed that this conclusion was reasonable. FDA referred the Sponsor to Comment 4, which requests differentially expressed gene data, and reminded the Sponsor to include this information in the IND submission.

The Sponsor provided their reasoning that the PRNP knockdown observed in liver cells was due to the high capsid concentration evaluated in the cell lines masking the effect of the miR-122 binding sites. To support this hypothesis, the Sponsor provided evidence that the inclusion of miR-122 binding sites decreased the extent of PRNP mRNA knockdown in mouse livers. FDA agreed that this conclusion was reasonable.

Sponsor Question 2: *Does the Agency concur with the Sponsor's proposed plan for translating dosing based on IV administration of the PRNP-CHARM-001 product in hTFR1 KI mice, where safety and toxicology assessments, together with vector biodistribution data, will be used to establish dose range selection for the clinical program?*

FDA Preliminary Meeting Response to Sponsor Question 2:

Your proposed plan appears reasonable to establish a selected dose range for your clinical program. However, this is also contingent on additional nonclinical data (including NOAEL determination) requested as detailed in our response to your question #3. We have the following comment to address in your IND submission:

We agree with your strategy for dose translation using vg/kg from mouse to human. Please ensure that your IND submission contains a comprehensive discussion of your rationale for targeting 30% PRNP knockdown with your starting clinical dose level. This rationale should include: 1) a discussion of the data used to support this target level (i.e., anti-sense oligo, heterozygous PRNP knockout animals), 2) an outline of relevant differences between these data and your intended clinical drug product (i.e., biodistribution, endpoints relative to drug product administration, endpoints relative to disease model induction, etc.), and 3) a discussion of how any of these differences impact the relevance of these data to PRNP-CHARM-001 administration.

Meeting Discussion for Sponsor Question 2:

There was no discussion of this question during the meeting.

Sponsor Question 3: *Does the Agency agree with the Sponsor's position that the proposed design of the GLP PRNP-CHARM-001 safety and biodistribution study is*

sufficient to generate the necessary data to proceed with an IND submission and initial clinical administration of the PRNP-CHARM-001 product?

FDA Preliminary Meeting Response to Sponsor Question 3:

Based on the information provided in Sections 10 and 14.1 (pages 31-42, 77-81) of your pre-IND meeting package, we do not agree that the hTFRC KI mouse alone is sufficient for GLP toxicology and biodistribution (BD) studies to support an IND for PRNP-CHARM-001. We acknowledge that this advice differs from our INTERACT feedback in February 2025. However, new developments in the field have changed our understanding of the possible risks of capsids designed to cross the blood brain barrier (BBB). Specifically, we have safety concerns regarding the novel BBB targeting TfR1 CapX capsid including potential for off-target toxicity (independent of TfR1-mediated binding) following systemic intravenous (IV) administration. Additionally, a safety study in rodents may not be adequate to address potential toxicities due to differences in the BBB structure and function between rodents and humans, or safety signal detection related to neurotoxicity, immunotoxicity (e.g., coagulation, complement, cytokines, etc.), or hepatotoxicity. We have the following comments regarding your safety and biodistribution evaluation of PRNP-CHARM-001:

1. We recommend that you conduct the proposed GLP study in hTFRC KI mice as well as a supplemental safety study in a limited number of large animals to adequately characterize the toxicities associated with IV administration of PRNP-CHARM-001. Alternatively, it may be acceptable to provide nonclinical data from an adequate large animal safety study evaluating a drug product using the same TfR1 CapX capsid at relevant dose levels to support the safety of IV administration of PRNP-CHARM-001. We note that you submitted a study report for study AS-1801 (Appendix IV, pages 109-122), which we do not consider adequate because it: a) did not evaluate the intended capsid; b) was of limited study duration (i.e., 28 days); and c) did not include comprehensive safety evaluation.
2. Considering our recommended change to your nonclinical approach, we are willing to review a nonclinical protocol, or comment on the adequacy of a completed nonclinical study, as a pre-IND follow-up interaction or a Type D meeting.
3. We have the following comments regarding the conduct of your proposed GLP study in hTRFC KI mice:
 - a. The study should be of sufficient duration to evaluate potential acute and long-term toxicities, as well as the potential for resolution or worsening of any findings. Longer timepoints may be required: i) in the absence of resolution of any observed toxicities or ii) in the absence of data supporting plateauing expression of your epigenetic editor.

- b. For all unscheduled deaths, please perform comprehensive clinical pathology, gross pathology, and histopathology on a complete panel of tissues, and other analyses, as appropriate, to determine the potential cause of death.
- c. We note that you intend to evaluate dorsal root ganglia (DRG) histopathology. Please evaluate DRGs at multiple levels, as well as select peripheral nerves (sciatic), as feasible.
- d. Regarding your BD assessments:
 - i. It is not clear whether you intend to evaluate BD in all of your study groups. Assessment of BD in control animals and in a group of animals that receives either the maximum dose level or a clinically relevant dose level is adequate.
 - ii. You have designated adrenal gland, kidney, lung, and gonads as optional for BD evaluation. Please evaluate BD in these tissues.
 - iii. Please measure transgene expression levels in all tissues which test positive for the presence of your vector.
- 4. Please provide pharmacokinetic (PK) data that supports waning or plateauing CHARM protein expression over time following PRNP-CHARM-001 administration. You may be able to incorporate this assessment into your long-term study “PRNP-CHARM-001 LOTAS: Long-term in vivo Off-Target Accumulation Study” (pages 44-45). Brain (on-target) and liver (off-target) tissues would be sufficient for your PK evaluation.
- 5. Please include a risk assessment with supporting RNA-Seq data that addresses whether the miR-122-5p binding sites present in the PRNP-CHARM-001 drug product may have an adverse saturating effect on endogenous miR-122 function given its role in liver homeostasis, metabolism, liver size, and as a tumor suppressor (PMID: 22820290). Additionally, please provide data supporting the specificity of your miR-122 target sequences for miR-122 binding and lack of binding to other unintended endogenous miRNAs.

Meeting Discussion for Sponsor Question 3:

The Sponsor proposed a 2-month safety study in minipigs or non-human primates. FDA stated either species was acceptable and agreed that the study design was generally acceptable. The Sponsor indicated their intention to submit a nonclinical study protocol for review by FDA. FDA agreed and recommended that the Sponsor submit a type D meeting request.

The Sponsor inquired if the IND could be submitted with a complete study report for the proposed GLP study in hTFRC KI mice and 1 month of in-life data from

the large animal study. FDA agreed with the strategy for the proposed GLP study in hTFRC KI mice, but requested that complete in-life data from the large animal study be submitted at the time of IND submission.

The Sponsor proposed to only evaluate histopathology in tissues nominated by in-life findings. FDA did not agree with this proposal and requested evaluation of all tissues where AAV9 biodistribution is expected based on existing literature.

The Sponsor noted that the peripheral biodistribution of PRNP-CHARM-001 is expected to be higher in either of the proposed large animal species compared to humans or hTFRC KI mice due to lack of TFR1 binding in non-human primates and minipigs. The Sponsor requested clarification on how the results of this study would be interpreted given the expected species differences. FDA acknowledged that the large animal study would likely be an example of exaggerated pharmacology in peripheral tissues and was intended to characterize potential peripheral toxicities that may not be recapitulated in mice. FDA stated that these data would be reviewed in the context of increased peripheral distribution. FDA stated that the rationale for dose level selection in the large animal study should be provided along with the nonclinical protocol to assist in FDA's review.

The Sponsor proposed an end-of-life human study that would substitute for or supplement the proposed large animal study. FDA responded that this topic was beyond the scope of the meeting, but stated that this end-of-life study would not obviate the need to conduct a large animal study. FDA offered that the Sponsor may submit information regarding clinical monitoring as part of a type D meeting for review and advised the Sponsor to provide as much context from prior relevant clinical experience to inform the review of the future clinical protocol. The Sponsor acknowledged this advice.

The Sponsor proposed to lengthen the proposed GLP toxicology study to 6 months if pilot data suggested a lack of resolution of adverse findings at 3 months. FDA agreed with this reasoning.

The Sponsor presented data from the H3X study showing that transgene mRNA expression in the brain decreased from 6 to 12 weeks. The Sponsor indicated that liver mRNA expression levels from the same study would also be provided in the IND. The Sponsor indicated that detection of CHARM protein would likely be infeasible, as all major CHARM domains mimic endogenous proteins. FDA agreed that data indicating plateauing levels of CHARM mRNA expression in brain and liver would be sufficient.

The Sponsor proposed to evaluate transgene mRNA as part of the 'Long-term off-target accumulation study' in lieu of the GLP toxicology study. FDA agreed with this strategy.

The Sponsor proposed to evaluate biodistribution of PRNP-CHARM-001 DNA and mRNA in oocytes and sperm cells using in situ methodology, in lieu of biodistribution evaluation in whole gonadal tissue in the GLP study. FDA agreed that this was acceptable. FDA also noted that the rationale provided in the point-by-point response document that this data would not be required prior to administration of PRNP-CHARM-001 in symptomatic patients is acceptable.

Sponsor Question 4: *Does the Agency agree that the proposed drug product manufacturing plan, stability testing plan, and draft release testing plan are appropriate for the PRNP-CHARM-001 product to be used in the program's initial Phase I/II clinical trial?*

FDA Preliminary Meeting Response to Sponsor Question 4:

In general, your proposed drug product (DP) manufacturing plan, stability testing plan, and draft lot release testing plan are appropriate for the PRNP-CHARM-001 DP to be used in the program's initial Phase I/II clinical trial. Please address the following comments:

1. DP manufacturing plan:

- a. Please provide comprehensive information on the manufacture and qualification of the HEK293 cell line Pro10™ cells Master Cell Bank (MCB) in your IND submission. Alternatively, you may provide a Letter of Authorization (LOA) to cross-reference the MCB information to another IND or a Master File (MF).
- b. As the IND Sponsor, you bear full responsibility for ensuring that all Chemistry, Manufacturing, and Controls (CMC) information necessary to support an adequate assessment of product safety for the planned clinical study is included in the IND submission. This information should be provided either directly within the IND submission or through the submission of an appropriate Letter of Authorization (LOA) granting the FDA permission to reference relevant CMC information contained in an existing IND or MF. For guidance on the preparation of the CMC section of your IND submission, please refer to the January 2020 Guidance for Industry: *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)*, available at: <https://www.fda.gov/media/113760/download>.

2. Drug substance (DS) and DP release testing plans:

- a. Given the rare disease designation of the prion disease indication and your intention to leverage the Phase 1/2 clinical study to support future licensure application, we recommend that the DS lot release specification and stability plan include tests for potency and/or infectious titer to collect

meaningful stability data that can be used to set a commercial DS shelf life. Inclusion of these tests will also help ensure adequate control of potency during DS storage. We recommend that you propose acceptance criteria for these tests and incorporate them into the DS stability protocol at the earliest stage of development to help align with potentially expedited clinical development.

- b. We note that the proposed DP lot release testing does not include a test for transgene sequence identity. The identity testing panel should include sequence confirmation of the complete transgene payload, including confirmation of all three miR-122-5p target sites (3x miR-122-5p), for each manufactured lot. We recommend incorporating a sequencing-based method (e.g., next-generation sequencing or Sanger sequencing) capable of confirming the integrity and identity of the full transgene cassette as part of the DP lot release specification.
- c. We note that the proposed capsid identity testing strategy relies on detection of VP1, VP2, and VP3 capsid proteins. As TfR1 CapX is a novel capsid, detection of VP1, VP2, and VP3 alone may not be sufficient to confirm the identity of this specific capsid. We recommend that you employ an identity testing method capable of specifically identifying the novel TfR1 CapX capsid, please provide additional scientific justification demonstrating that this method can reliably distinguish TfR1 CapX from other serotypes produced in the same manufacturing facility.
- d. We note that the proposed DP lot release specification includes two vector genome (vg) titer assays. Please clarify which assay will be designated as the primary method for dose measurement in the clinical setting. Please note that the assay selected for dose measurement should be qualified prior to initiation of the IND study. Please refer to our Additional CMC Comment #1 in the INTERACT Preliminary Meeting Responses dated February 5, 2025, for additional comments on qualification of this assay.
- e. Please provide detailed descriptions of all DS and DP lot release assays in your IND submission, including the methodology, acceptance criteria (AC), and the rationale for assay selection for each release test.
- f. Please provide adequate justification for the proposed specifications for DS and DP lot release testing in your IND submission. Justification should be supported by relevant development data, compendial standards, and/or risk-based rationale, as applicable.

3. Stability testing plan:

- a. We note that your proposed stability testing plan for the PRNP-CHARM-001 DP does not include testing at 9-month timepoint. We recommend

that your IND submission include stability data (if available) or a stability testing plan for the PRNP-CHARM-001 DP that incorporates timepoint at 9 months, in addition to any later timepoints already proposed, in accordance with the draft ICH Q1 guidance. An additional timepoint early in the stability plan may be helpful in the robust regression analysis for determining commercial shelf life at the time of BLA submission. The stability testing plan should include proposed stability AC appropriate for the DP.

Meeting Discussion for Sponsor Question 4:

There was no discussion of this question during the meeting.

Sponsor Question 5: *Does the Agency agree that the proposed delivery-device compatibility and in-use stability study is appropriate for initial clinical administration of the PRNP-CHARM-001 product?*

FDA Preliminary Meeting Response to Sponsor Question 5:

In general, the proposed delivery-device compatibility and in-use stability study are appropriate for initial clinical administration of the PRNP-CHARM-001 product. Please address the following comments:

1. We note that you proposed using a TCID₅₀ assay as the potency measure within the device compatibility testing plan. We are concerned that the TCID₅₀ assay may exhibit high variability, and reliance on this assay alone may not provide adequate sensitivity to detect potency changes attributable to device interaction. We recommend that you include a more precise and product-relevant potency assay in the device compatibility testing plan to ensure that any impact of the delivery device on biological activity of the product can be reliably detected and assessed.
2. In your briefing document, you have not provided the acceptance criteria for device compatibility testing. We recommend that you establish and document pre-defined acceptance criteria for all assays included in the device compatibility testing protocol prior to study initiation. Acceptance criteria should be scientifically justified and based on relevant product quality attributes.

Meeting Discussion for Sponsor Question 5:

There was no discussion of this question during the meeting.

Sponsor Question 6: *We propose to use RT-qPCR-based quantification of PRNP RNA lowering in human HEK293T cells as a potency assay for release criteria. Does the Agency agree that the proposed potency assay will be adequate to support licensure-enabling studies?*

FDA Preliminary Meeting Response to Sponsor Question 6:

Your proposed RT-qPCR-based quantification of PRNP RNA lowering in human HEK293T cells as a potency assay may be adequate to support licensure-enabling studies if it is qualified appropriately and deemed suitable for the intended purpose. As noted in our previous recommendation (Response to CMC Question 5, Comment 3, in the INTERACT Preliminary Meeting Responses dated February 5, 2025), we reiterate that potency assay(s) should be qualified prior to initiation of studies designed to obtain primary efficacy data intended to support a biologics license application (BLA) and should be fully validated prior to BLA submission.

Meeting Discussion for Sponsor Question 6:

There was no discussion of this question during the meeting.

Sponsor Question 7: *Does the Agency agree with the Sponsor's position that symptomatic prion disease patients and presymptomatic individuals at risk of genetic prion disease are separate populations and can be addressed in separate first-in-human studies?*

FDA Preliminary Meeting Response to Sponsor Question 7:

We agree. Your plan to separately study your product in symptomatic prion disease patients, and in presymptomatic individuals at risk of genetic prion diseases, in the coordinated manner you have proposed is reasonable.

Meeting Discussion for Sponsor Question 7:

There was no discussion of this question during the meeting.

Sponsor Question 8: Does the Agency agree that the clinical plan overview for first-in-human studies of PRNP-CHARM-001 in symptomatic prion disease patients and individuals at risk for presymptomatic genetic prion disease is reasonable, including general trial structure, staging of trial arms, and endpoints?

FDA Preliminary Meeting Response to Sponsor Question 8:

We agree that your proposed staging of trial arms and proposed endpoints are reasonable.

We recognize the challenges of developing gene therapies for patients who are at risk of prion disease or have become symptomatic. We have the following comments regarding your proposed clinical trial design and other aspects of your clinical development plan:

1. For symptomatic patients, you propose to have a “symptomatic treatment” arm and a “symptomatic observational” arm. Patients will be enrolled in the observational arm when sentinel dosing or dose escalation criteria preclude their enrollment in the treatment arm; if the treatment arm re-opens, observational patients who still satisfy the inclusion criteria and have completed at least 4 weeks of follow-up may then receive your product as part of the treatment arm.

As you note, this design is similar to that of your PRiSM study, testing a PrP-lowering siRNA.

We suggest that you consider, if feasible, a randomized, double-blind, placebo-controlled “cross-over” design, in which after an interval of ≥ 4 -8 weeks, patients who initially received placebo are then administered your product, and vice-versa. While the proposed open-label design of your study is acceptable at this early stage of development, incorporation of randomization, blinding, and a concurrent control can be useful to facilitate interpretation both of safety data and preliminary clinical assessments of efficacy.

2. For immunosuppression, you propose to administer rituximab, sirolimus (or tacrolimus), and corticosteroid. You note that the medications, doses, and dose ranges are preliminary, and will be specified in your final clinical protocol. In your future Investigational New Drug (IND) submission, please also provide justification for the agents and doses you choose.
3. Since no well-defined, predictable disease progression timeline is known for the presymptomatic phase of genetic prion disease, consider extending the long-term follow-up component of your study beyond 5 years.

Meeting Discussion for Sponsor Question 8:

There was no discussion of this question during the meeting.

Sponsor Question 9: *Does the Agency concur with our proposed regulatory and clinical development engagement plan and staging of application for relevant designations for the PRNP-CHARM-001 gene therapy program?*

FDA Preliminary Meeting Response to Sponsor Question 9:

Timing of requesting relevant designations will ultimately depend on availability of appropriate supporting data. Although Orphan Drug designation may be requested prior to submission of an IND, application for Fast Track designation can be made at the time of IND submission or at any time afterward, but ideally no later than the pre-BLA (Biologics License Application) meeting. At this time, FDA’s Support for Clinical Trials Advancing Rare Disease Therapeutics (START) pilot program is no longer accepting applications.

For further information about the available expedited programs, please refer to the [FDA Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics](#). For all programs, of course, the decision is based on the interpretability and persuasiveness of the data.

Meeting Discussion for Sponsor Question 9:

There was no discussion of this question during the meeting.

FDA Questions/Comments sent in Preliminary Meeting Response:

General Considerations:

Please provide an Investigator Brochure in the IND submission. For additional recommendations on the preparation and content of your IB, please refer to Section 7 of the document titled, E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) – Guidance for Industry (March 2018), available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r3-good-clinical-practice-gcp>.

Chemistry, Manufacturing, and Controls:

1. Under Section 3.2.S.1.2 (Structure) of your IND submission, please describe in detail the modifications to the AAV9 capsid and provide an amino acid sequence alignment of AAV9 and the TfR1 CapX highlighting the amino acid insertion and assignment differences.
2. In IND submission, please provide a tabular listing of the product lots, noting the intended purpose of the lots (POC/toxicology/dose-finding/clinical, etc.) and whether the same critical starting material, manufacturing process, and analytical procedures were used for manufacturing the clinical lots and the nonclinical POC/toxicology lots. If different, please describe how data generated with the product lots used in the nonclinical POC/toxicology studies will support product quality for the intended clinical study. Please consider a variety of quality attributes, including (but not limited to) vector strength, potency, and purity (e.g., endotoxin and process- and product-related residuals that may affect product safety).
3. We note that you have proposed assessing cerebrospinal fluid (CSF) prion protein (PrP) levels as a pharmacodynamic biomarker in the planned clinical study, and that you have indicated an intent to pursue CSF PrP lowering as a potential surrogate endpoint to support a future Accelerated Approval application in the presymptomatic population. Should CSF PrP lowering be found suitable as a surrogate endpoint for this purpose, we offer the following comments regarding the bioanalytical assay used to measure CSF PrP:
 - a. You have indicated (Section 12.5) that the CSF PrP quantification assay will be qualified at the time of first-in-human dosing and validated prior to BLA submission. We note that you have also referenced prior CDER engagement on this topic (Section 8.1.1), and we encourage you to ensure that any assay development and validation plans are consistent with guidance and advice previously received from CDER, to avoid conflicting regulatory expectations across review divisions.
 - b. We advise that the bioanalytical assay used to measure CSF PrP - to the extent it is intended to serve as a primary endpoint in any study whose

data will support a marketing application - should be fully validated in accordance with ICH M10 (Bioanalytical Method Validation and Study Sample Analysis) prior to the initiation of any study in which CSF PrP is intended to serve as a primary endpoint supporting that application. We note that your proposed Phase 1/2 study appears, based on the information provided (Section 12.2 and Section 12.5), to be the study from which pivotal efficacy data would be drawn for a future license application. In that context, we recommend you carefully consider the timing of full validation relative to study initiation, and engage proactively with the Agency to align on what level of assay characterization is required at each stage of development.

- c. We recognize that you have distinguished between "qualification" (prior to first-in-human dosing) and "validation" (prior to BLA submission). We encourage you to clarify, in future submissions, how your use of these terms aligns with the definitions and requirements set forth in ICH M10, and to confirm that your qualification activities will be sufficient to support the reliability and interpretability of biomarker data collected during the Phase 1/2 study.
 - d. We recommend that you establish and maintain a prospective plan for clinical sample retention (e.g., retention of CSF aliquots collected at each scheduled timepoint) to enable future retrospective testing should additional analyses be required. In accordance with ICH M10, your bioanalytical plan should also include incurred sample reanalysis (ISR) on clinical study samples to confirm the reproducibility of CSF PrP measurements in actual study samples. ISR is a regulatory expectation for validated bioanalytical methods applied to clinical samples and should be incorporated into your assay validation and study sample analysis plan.
4. In your IND submission, please provide a sample Pharmacy Manual ('Instructions to the Pharmacy' document) or provide a detailed description of how the product will be thawed and prepared for administration at the clinical site. This description should include how the product will be transported, stored, thawed, and formulated at the clinical site prior to administration. These procedures under the worst-case conditions should be supported by the device compatibility data.

Pharmacology/Toxicology:

5. We have the following response regarding your additional question received on June 30, 2026. You are proposing to conduct biodistribution assessments in DRG tissue from your proposed GLP study in hTRFC KI mice only if adverse histopathology findings are observed in the DRG tissues collected from your pilot safety study. We consider your risk-based approach for DRG biodistribution

evaluation to be acceptable.

6. Depending on the results of your biodistribution/toxicology evaluation in gonadal tissues, the potential for developmental and reproductive toxicity (DART) of PRNP-CHARM-001 following administration to women of childbearing potential may need to be addressed particularly for pre-symptomatic individuals with genetic/familial prion disease. In your IND submission, please include a comprehensive discussion of your plan for assessing reproductive safety risks, such as an evaluation of epigenetic marks in germline cells (i.e., oocytes and spermatogonia) and transgenerational epigenetic inheritance of PRNP-CHARM-001. Please also refer to the FDA guidance titled *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* “(May 2021) at: S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals | FDA.
7. Please provide data from bench testing that confirms the compatibility of the nonclinical lots of PRNP-CHARM-001 with the needle/syringe system used in each nonclinical study. This can consist of assessment of mRNA concentration before and after passage of each lot through the respective needle/syringe delivery system used in each study. If significant product loss is noted, the dose level administered in your nonclinical studies should be recalculated on this basis.
8. Please note that per 21 CFR 312.23(b) reference to nonclinical studies included in other regulatory submissions submitted to the FDA requires a letter from the holder of the regulatory file granting the FDA access to the active IND or master file in support of your eventual IND submission. The sections containing the nonclinical studies should be specified in the letter of authorization.
9. Please provide a copy of all key publications cited that were used to support the safety and rationale for administration of your product in humans. Please include a comprehensive summary for each publication that also contains the reason for including the publication, as well as a discussion regarding the similarities and differences of the product(s) used in the publication to the final clinical product, and how any differences impact the relevance of these data to the final clinical product.
10. Please provide a tabular summary of all nonclinical lots used in your nonclinical studies as well as the clinical lot comparing the capsid, the vector backbone, transgene(s), titers, and other applicable parameters. For cross-referenced and/or previously published studies, please include all relevant nomenclature (e.g. BI-93, TfR1Cap01 etc.).
11. In your IND, please provide complete study reports for all nonclinical studies used to support the safety and rationale of your proposed clinical trial. These reports should include, but should not be limited to: a) a prospectively written

protocol and all protocol amendments or a detailed methodology; b) a detailed description of the study design [e.g., description of the test system used, animal species/animal models, control and test articles administered, dose levels, detailed procedures for test article administration (including delivery device description), and collection of all study protocol parameters, etc.]; c) results for all parameters evaluated for each animal on study; and d) your analysis and interpretation of the study data.

12. Datasets for nonclinical studies that can be modeled in an FDA-supported Standard for Exchange of Nonclinical Data (SEND) Implementation Guide (SENDIG) version and were initiated after March 15, 2023, are required to be submitted in SEND format. This currently includes single dose, repeat-dose general toxicology, carcinogenicity studies, and safety pharmacology studies. The requirement for SEND is not limited to GLP studies. As both GLP and non-GLP toxicity studies may be submitted to the FDA to support clinical safety, the decision for inclusion of SEND is independent of GLP status. In cases where non-GLP toxicity studies are submitted to support a determination of safety, as outlined above, such studies must include SEND. If SEND datasets are generated for nonclinical studies that are not intended to support clinical safety, the Agency would accept these; however, submission of these datasets would not be required. For additional information, please refer to the “Study Data Technical Conformance Guide” at: <https://www.fda.gov/media/153632/download>. Questions regarding SEND should be directed to [REDACTED]

Meeting Discussion for FDA Questions/Comments:

There was no discussion of the FDA questions/comments during the meeting.

Additional FDA Comment:

During the meeting the Sponsor requested clarification regarding the requirement to submit SEND datasets. FDA would like to clarify that research INDs are exempt from the SEND requirement.