U.S. FOOD & DRUG ADMINISTRATION

Our Reference: PS# 010343
Meeting ID# 21721

MEETING SUMMARY
October 7, 2025

The Children's Hospital of Philadelphia
Attention: Rebecca Ahrens-Nicklas, MD, PhD
3401 Civic Center Blvd.
Philadelphia, PA 19104

Dear Dr. Ahrens-Nicklas:

Attached is a copy of the memorandum summarizing your September 19, 2025, Type B, Pre-IND meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differ from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to Meeting ID# 21721 and/or PTS# PS010343 in your future submissions related to this product.

If you have any questions, please contact [redacted].

Sincerely,

[redacted]

Division of Review Management & Regulatory Review 2
Office of Review Management & Regulatory Review
Office of Therapeutic Products
Center for Biologics Evaluation and Research

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Meeting Summary
(Includes Preliminary Meeting Responses)

Meeting ID #:	21721
Submission Type & #:	PTS# PS010343
Product Name:	Lipid nanoparticle containing mRNA encoding an adenine base editor 8e (ABE8e) protein with a V106W variant in the TadA adenosine deaminase domain and with a S. pyogenes Cas9 (SpCas9) D10A nickase, as well as a gRNA matched to a target pathogenic variant in one of six urea cycle genes: NAGS, CPS1, OTC, ASS1, ASL, or ARG/ Product Name: CHOP- LNP1.UCD.ABE
Proposed indication:	Treatment of hyperammonemia in patients [redacted] with deficiencies in enzymes or a related transporter of the urea cycle who are homozygous or compound heterozygous for a pathogenic variant in any urea cycle disorder gene, including *CPS1*, *OTC*, *ASS1*, *ASL*, *ARG*, *NAGS*, and *SLC25A15*, that can be efficiently corrected by an adenine base editor (ABE) with a *Streptococcus pyogenes* Cas9 (SpCas9) nickase and an ABE8e TadA deaminase domain with a V106W variant.
Sponsor:	The Children's Hospital of Philadelphia
Meeting Type:	Type B
Meeting Category:	Pre-IND
Meeting Date & Time:	September 19, 2025, 3:00pm – 4:00pm, ET
Meeting Format:	Virtual Face-to-Face
RPM:	[redacted]
Preliminary Meeting Responses:	September 17, 2025

FDA Attendees:

[redacted]

[redacted]

Sponsor Attendees:

[redacted]

Background and Objectives:

Sponsor submitted a meeting request on July 24, 2025, to seek input on the summarized nonclinical proof-of-concept and efficacy data; the proposed definitive animal study; the proposed assessment of potential off-target editing; the proposed chemistry, manufacturing, and controls; and the proposed clinical study. The objectives

of the meeting are to receive advice from the Agency as summarized in the enclosed questions. The pre-meeting materials were submitted on August 20, 2025.

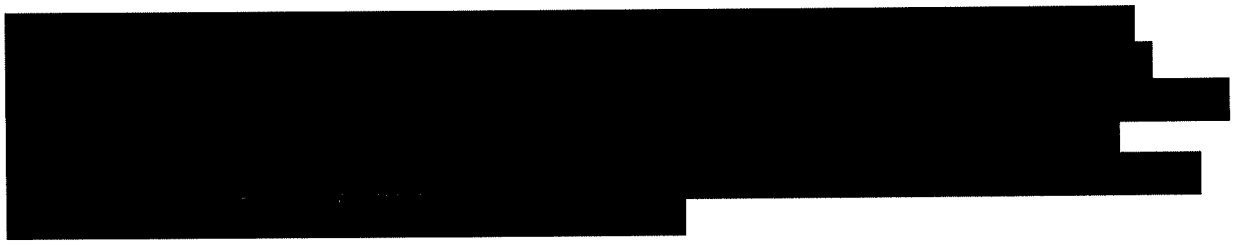
FDA provided its preliminary meeting responses to The Children's Hospital of Philadelphia's questions on September 17, 2025. After reviewing the preliminary meeting responses, The Children's Hospital of Philadelphia notified FDA on September 17, 2025, of its decision to limit the meeting to discuss questions and FDA comment numbers including Preamble, 2, 3, 9, 10, 6 and 7 in this order.

Sponsor Questions:

Preamble
In the meeting package, you propose a master clinical protocol and an IND submission strategy involving a "leader IND" with DP LNP1.UCD.ABE2 and a "follower IND" with DP LNP1.UCD.ABE1, with each IND including patients with loss of function mutations in the *CPS1*, *OTC*, *ASS1*, *ASL*, *ARG*, *NAGS*, and *SLC25A15* genes, which is intriguing. We agree that this study can be conducted under a master clinical protocol, but we recommend a different IND submission strategy. We look forward to additional discussion during the tele-conference before we can provide more tailored feedback on your product development plan. In the interim, we have the following comments.

The loss of function in each gene results in a deficiency of a specific enzyme and may present with different clinical manifestations and require unique safety and efficacy considerations for product development. Therefore, as a generality, we expect a separate IND for each gene targeted by a different gene-specific product, with mutations in the gene being edited by unique variants of that gene-specific product.

For each of the seven target genes in your proposal, drug product (DP) variants will include mutation-specific gRNAs and an mRNA encoding one of two ABEs. Based on the information provided in the meeting package, it will be acceptable to include all the DP variants described in the meeting package for a single target gene under the same IND. You may be able to leverage some of the non-clinical, CMC, or clinical information submitted in the first IND to support subsequent IND submissions, as applicable.



Meeting Discussion for Preamble:
The Sponsor asked for clarification on the IND submission strategy recommended by FDA in the preamble. FDA confirmed the recommendation was for the Sponsor to submit 7 distinct gene-specific IND applications, with one for each UCD gene and the first IND incorporating the master clinical protocol. It is

acceptable to include the use of any of the 7 mRNAs described in the meeting package for manufacture of a DP variant in each gene specific IND. If mRNAs not described in the meeting package are added, please describe the complete mRNA and amino acid sequence, include an annotation of any changes in the sequence, and describe the effect of these changes have on the enzyme function and safety. FDA clarified that each gene-specific IND can be amended to include information to support an additional DP variant for a mutation in that gene. The Sponsor asked about the IND submission strategy and the Agency recommended submitting gene specific INDs when there is a patient available to treat.

For submission of CMC information, FDA recommended that information for all seven mRNAs be included in one IND, and subsequent INDs cross-reference that information.

Post Meeting Comment:
After further discussion, we recommend it may be best for the Sponsor to provide the manufacturing information for the mRNAs encoding the adenine base editor in a Type 2 Master File (MF). We think this may be the best and most efficient way to facilitate submission of the initial information for the mRNAs. The MF can be submitted prior to submission of any of the gene-specific INDs. When you cross-reference the information from the MF, please clearly indicate which mRNA is being used for each DP variant.

Nonclinical discussion:

In response to the Sponsor's request for clarification on the in vitro proof-of-concept (POC)/safety information needed for each DP variant. FDA confirmed that in vitro POC/safety data (e.g. on-target editing should be provided for each DP variant. Thus, cross-referencing on-target, off-target, and bystander editing data pertaining to a particular DP would not be adequate to support a different DP variant and target mutation between INDs. In addition, due to the large number of possible UCD mutations possible, FDA recommended that the sponsor submit their IND for a target mutation once a specific candidate subject with a specific target mutation has been identified and POC/safety studies for that DP variant have been completed.

Sponsor Question 1: *Does the Agency agree that cellular studies, rather than humanized mouse studies, will provide sufficient proof-of-concept (POC) data to support the administration of the LNP1.UCD.ABE2 DP to infantile-onset urea cycle disorder (UCD) patients?*

FDA Preliminary Meeting Response to Sponsor Question 1:
Based on the information provided in Sections 6 and 10 (pages 37-70) and Appendix 1 (pages 106-108), we agree that the biological activity of each DP can be predominantly established via in vitro cellular studies. Please refer to our

Comment No. 1 in response to your Question No. 6 regarding DP dose level extrapolation from nonclinical in vitro studies to the proposed clinical trial. If dose levels for each DP variant can be established from in vitro data collected with that variant and existing in vivo data, additional in vivo studies conducted in humanized mice are not necessary.

Meeting Discussion for Sponsor Question 1:
There was no discussion of this question during the meeting.

Sponsor Question 2: *Does the Agency agree that the proposed definitive biodistribution/toxicology study of one version of the LNP1.UCD.ABE2 DP in wild-type rats will provide sufficient data to support an IND application for all versions of the LNP1.UCD.ABE2 DP?*

FDA Preliminary Meeting Response to Sponsor Question 2:
We agree that the proposed, definitive, Good Laboratory Practice (GLP)-like biodistribution (BD)/toxicology study to be conducted in Sprague-Dawley (SD) rats is sufficient to support INDs submitted for multiple DPs that differ with respect to the target gene and target mutation, gRNAs, and ABEs. Please address the following comments in your IND:

1. Ideally all safety studies should be carried out in compliance with GLP as per 21 CFR Part 58. However, if technical limitations do not allow for this, it is acceptable to perform the study in a non-GLP testing facility. The study should: a) be conducted according to a prospectively written protocol, b) be performed in as nonbiased a manner as possible, c) have appropriate record keeping and documentation of all data, and d) include Quality Assurance measures such that we can be confident that the resulting data are of sufficient quality and integrity to support the proposed clinical trial. In addition, as directed by 21 CFR Part 312.23(a)(8)(iii), the final study report should state why the study was not conducted in compliance with GLP and specify any areas that deviate from the prospectively written protocol and the potential impact of these deviations on study integrity.

2. Regarding BD:

   a. Discuss, with supporting data, the impact of LNP cargo (e.g. gRNA and ABE) on stoichiometry of each DP variant. For any stoichiometric differences identified between the DP variant planned for administration in the proposed GLP-like rat BD/toxicology study [redacted] and all other DP variants discussed in your pre-IND meeting package, please discuss their impact on translatability of the nonclinical BD data to the clinical trial.

   b. Regarding BD assessment for gene therapy products, please refer to the document titled, S12 Nonclinical Biodistribution Considerations for Gene

Therapy Products: Guidance for Industry (May 2023), available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s12-nonclinical-biodistribution-considerations-gene-therapy-products.

3. Incorporate the following elements into your proposed study design:

   a. Assessment of safety endpoints to include daily clinical observations, body weights, clinical pathology parameters (hematology, serum chemistry, and coagulation), immunogenicity (anti-PEG and anti-ABE antibodies), complete macroscopic exams, organ weights (brain, heart, lungs, spleen, liver, adrenal glands, kidneys, and gonads), and histopathology of a comprehensive set of tissues. All in-life parameters should be evaluated at baseline and at several time points post-dose for all surviving animals at the specified time points. Interim and terminal sacrifice time points should reflect peak of product activity/expression and plateau of the DP variant activity. Please provide your rationale for all selected sacrifice timepoints.

   b. Evaluate the BD of the DP variant administered (lipid excipients) and ABE expression in a comprehensive panel of tissues (including blood) at sacrifice. For all samples that are positive for lipids, ABE expression should also be measured. If a particular tissue is negative for lipids at a specific time point, then that respective tissue does not need to be analyzed at later time points. If a particular tissue is determined to be negative for lipids, then that respective tissue does not need to be analyzed for ABE expression. However, all tissues, whether analyzed or not, should be archived for possible future analysis.

   c. We recommend that you incorporate central nervous system (CNS), respiratory, and cardiovascular (CV) safety pharmacology endpoints into your study. If BD to the heart, lung, and brain are not observed in animals sacrificed at 2-weeks post-dose, CNS, respiratory, and CV safety pharmacology assessments need not be assessed at 19-weeks post-(first) dose.

   d. For all unscheduled deaths, please perform comprehensive clinical pathology, gross pathology, and histopathology on a complete panel of tissues, and other assessments, as appropriate, to determine the potential cause of death.

Meeting Discussion for Sponsor Question 2.2.a:
In response to the Sponsor's request for clarification on their BD/toxicology plan, FDA confirmed that their proposed 'GLP-like' wild-type rat BD/toxicology study can be completed for a single DP variant/target mutation [redacted] and cross-referenced across INDs provided that the Sponsor addresses FDA's

concerns regarding the impact of RNA cargo on LNP physiochemical properties. FDA clarified that it is acceptable for the sponsor to model the potential changes in the LNP properties due to the different modified RNA cargo for each DP. FDA requested that the modelling data be provided in each IND. The Sponsor should also provide their rationale for the modeling method used.

Sponsor Question 3: *Does the Agency agree that the proposed definitive biodistribution/toxicology study of one version of the LNP1.UCD.ABE2 DP in wild-type rats will provide sufficient data to support re-dosing of patients with the LNP1.UCD.ABE2 DP?*

FDA Preliminary Meeting Response to Sponsor Question 3:
We agree that complete data following repeat administration of this DP variant [redacted] to SD rats in the proposed GLP-like BD/toxicology study will be adequate to support repeat dosing [redacted] of this DP variant in the proposed clinical trial.

Meeting Discussion for Sponsor Question 3:
There was no discussion of this question during the meeting.

[redacted]

Sponsor Question 5: *Does the Agency agree that the proposed off-target editing studies of a given version of the LNP1.UCD.ABE2 DP will provide sufficient data to support the administration of that version of the LNP1.UCD.ABE2 DP to infantile-onset UCD patients?*

FDA Preliminary Meeting Response to Sponsor Question 5:
Your proposed on-target edit analysis, bystander edit analysis, off-target nomination, and confirmatory testing methods are acceptable. Please submit your study reports for each of the gRNAs you propose to use in your IND. In addition, please address the following comments in your IND submission:

1. When using engineered cells for on and off-target editing studies, please specify whether the engineered cells harbor the target mutation at the native genomic location or in the integrated LVV cassette. When reporting on-target editing rates from LVV transduced cells, please measure and report on-target editing rates at LVV integration site and the respective native genic site. Please use appropriate primers to enable independent measurements at the two distinct genomic locations.

2. For each proposed gRNA, ABE editor, and Cas9 combination, please clarify whether you plan to use standard [redacted] gRNA. Please perform off-target nomination and confirmatory testing studies using the gRNA with the ABE and Cas9 combination that you intend to use in your final drug product.

3. In Figures 15 and 16 on page 50 of the briefing document, you showed on-target editing data using multiple candidate gRNAs in two independent HuH7 engineered cell lines that were either generated with a prime editor or were transduced using LVV. [redacted]

   b. Additionally, please discuss whether the on-target edit rate and outcome are likely impacted by whether the editing is occurring at the native genic site or at the LVV cassette integration site and whether this factor impacts the edit outcomes/editing rates in vivo.

   c. Please use this information to justify your use of LVV transduced cells as a cell model to perform on-target edit site analysis for different gRNAs.

4. While your proposal to use targeted sequencing for confirmatory testing is acceptable, we do not agree with your proposal to use 20 times the effective concentration EC90 for this analysis. Based on the data published in a recent publication [PMID: 39631713], we are concerned that the use of high concentration of LNPs can be detrimental to adequate uptake and trafficking of your drug product to the nucleus of cells. This may potentially impede the genome editor activity and off-target editing rate outcome.

a. Please use appropriate concentrations of your drug product that facilitates efficient on-target editing without impacting the cellular trafficking machinery.

b. Please provide justification to support your updated confirmatory testing strategy performed with lower concentrations of the LNP.

Meeting Discussion for Sponsor Question 5:
There was no discussion of this question during the meeting.

Sponsor Question 6: *Does the Agency agree that the overall nonclinical development plan is sufficient to support an IND application for all versions of the LNP1.UCD.ABE2 DP, as well as a separate IND application for all versions of the follower LNP1.UCD.ABE1 DP?*

FDA Preliminary Meeting Response to Sponsor Question 6:
We cannot yet agree that the nonclinical data provided to date in your pre-IND meeting package are sufficient to support administration of all DP variants in a first-in-human (FIH) clinical trial. Please address the following comments in your IND:

1. For each DP variant, please provide the following information:

   a. Dose level extrapolation from in vitro data demonstrating product activity (e.g. percent editing of target mutation collected in HuH-7 cells transduced with a lentiviral vector carrying the target mutation incubated with the DP variant) to safe and potentially biologically active dose levels proposed for the FIH clinical trial. Discuss your method of extrapolation and provide a sample calculation, as applicable.

   b. Percentage on-target, off-target, and bystander edits in a relevant in vitro test system.

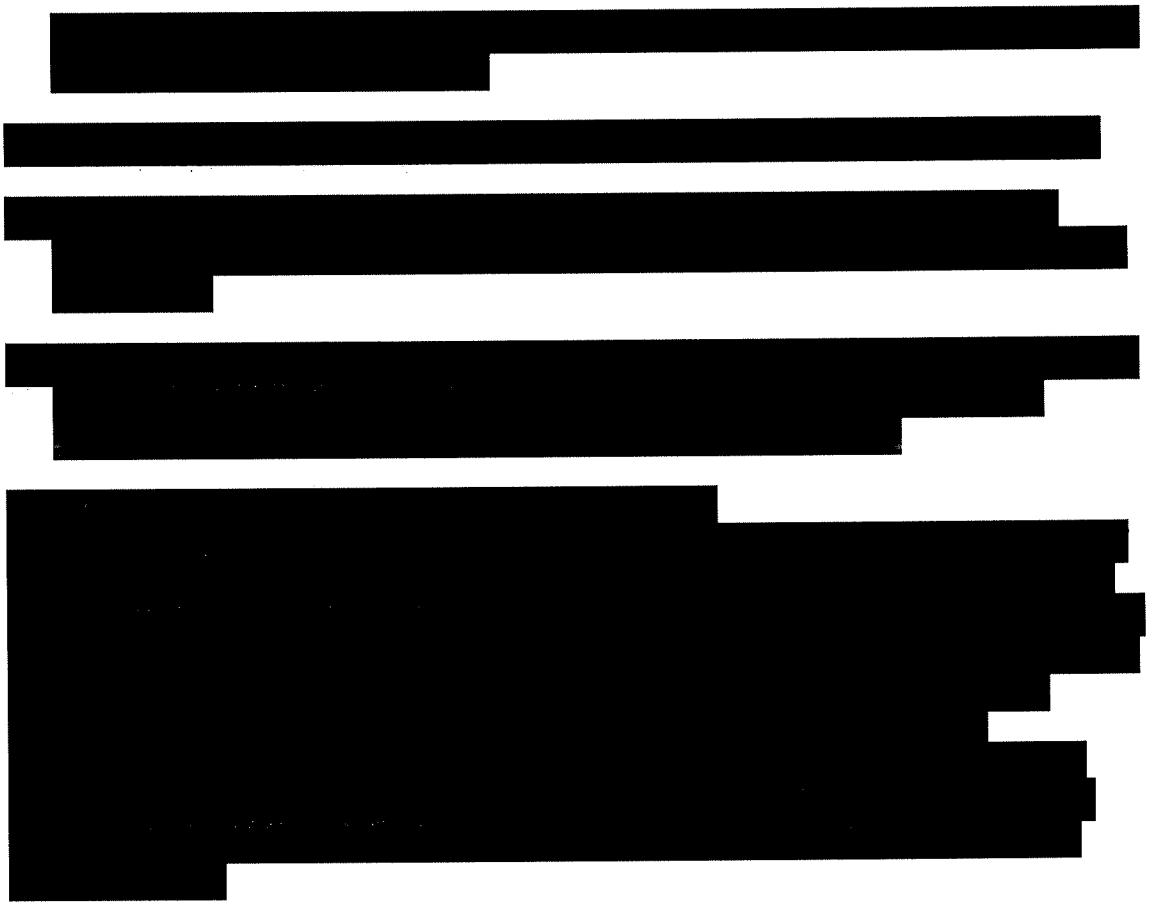
   c. A discussion, with supporting data, on the impact of repeat DP variant administration on the percentage of bystander and off-target editing, and how an increase in either parameter may impact activity and safety of the DP variant, respectively.

   d. Provide data from bench testing that confirm the compatibility of nonclinical DP lots with the needle/syringe system used in each in vivo nonclinical study. Your evaluation should include the ability to consistently deliver accurate pre-specified dose levels of the DP (e.g., assessment of LNP concentration after passage of each nonclinical lot through the syringe/needle system used). If LNP loss is observed, in the study report and data tables, please provide the actual DP variant dose level administered.

Meeting Discussion for Sponsor Question 6.1.a:
The sponsor proposed to standardize clinical dose levels [redacted] based on DP variant bioactivity (on-target editing) calculated in reference to their proposed potency assay (e.g., on-target editing of one DP variant in Huh-7 cells transduced with a lentiviral vector containing the target mutation for that variant). FDA agreed that this approach appeared reasonable. FDA added that the sponsor should extrapolate dose levels using both the in vitro and in vivo nonclinical data to the proposed clinical dose level(s) for the DP variant selected for the potency assay and provide these calculations in their IND. FDA confirmed that in vivo data collected with LNP.CPS1. Q335X (e.g. *Rosa26* insertion) can be used for these purposes.

FDA stated that the sponsor should provide their rationale for selection of a threshold editing efficiency used for dose extrapolation. In addition, a rationale, with supporting calculations, should be provided for clinical dose level(s) extrapolation for any DP variant demonstrating on-target editing efficiency below this threshold.

[redacted]



Sponsor Question 8: *Does the Agency agree that the proposed potency assay for the LNP1.UCD.ABE2 DP is acceptable to support an IND application for all variant-specific versions of the LNP1.UCD.ABE2 DP?*

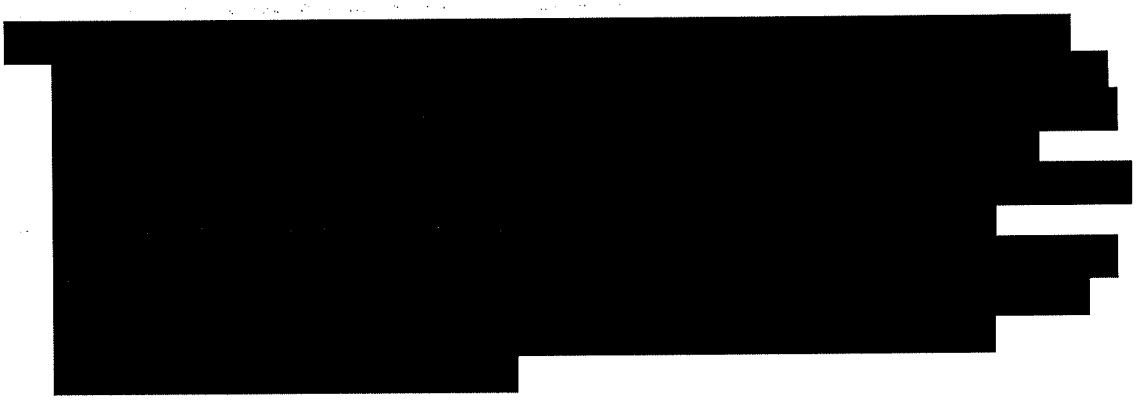
FDA Preliminary Meeting Response to Sponsor Question 8:
We agree the proposed potency assay for the LNP1.UCP.ABE2 DP using a lentivirus transduced Huh7 cell line harboring the target mutation and positive reference control mutations is acceptable to support IND applications for all LNP.UCD DP variants. Your IND submission should include a justification for your selection of the reference control, as well as an explanation of how your proposed editing efficiency threshold is appropriate to ensure potency of the DP.

We are concerned that a long-term plan to use a single reference standard to measure the relative potency for all DP variants discussed in the meeting package may lead to an excessively wide acceptance criterion for potency. We recommend during continued product development that you address potential variation in the relative potency between DP variants designed to correct different mutations in your overall potency assurance strategy. For example, how will you address whether a particular variant of the DP has degraded potency with storage?

Meeting Discussion for Sponsor Question 8:
There was no discussion of this question during the meeting.

Sponsor Question 9: *Does the Agency agree that the general design, including the proposed safety and exploratory efficacy outcome measures, enrollment criteria, and long-term follow-up plan are appropriate for the Phase I/II umbrella trial protocol outlined in the protocol synopsis?*

FDA Preliminary Meeting Response to Sponsor Question 9:
We agree with your plan for a master clinical protocol to evaluate safety and exploratory efficacy of the similar drug products across the various urea cycle disorders. We have the following specific comments related to your study design and eligibility criteria:



b. We recommend you initially tailor your enrollment criteria to the specific genes / Urea Cycle (UC) disorders targeted in your initial INDs, and the master clinical protocol can then be revised and cross-referenced as each new IND is initiated for additional gene targets/UC disorders. Please also explore if each new gene target /disorder can be added as a separate treatment arm in the master clinical protocol.

Meeting Discussion for Sponsor Question 9.a:
FDA acknowledged that re-dosing may be necessary for patients who do not achieve an adequate response with the initial dose [redacted]. In the context of the IND submission, the sponsor should clearly specify re-dosing criteria, including criteria related to safety and efficacy, and the rationale. It is difficult to provide definitive guidance on re-dosing within the Phase III study at this time, particularly if patients in the Phase I/II study receive a variable number of doses, as the Sponsor may need to treat additional patients in the Phase I/II study to determine the optimal dose(s) for the Phase III study.

Sponsor Question 10: *Does the Agency agree that a Phase III extension of the Phase I/II umbrella trial protocols in the LNP1.UCD.ABE2 DP IND application and the follower*

LNP1.UCD.ABE1 DP IND application, combining the efficacy studies of the two DPs into a single clinical trial conducted under a master protocol IND, would be appropriate?

FDA Preliminary Meeting Response to Sponsor Question 10:
Our advice regarding separate INDs for each drug product (DP) targeting a single gene (as mentioned in the Preamble) and regarding a single master clinical protocol that could be cross-referenced across INDs (as discussed in response to Question 9) also applies to your proposed Phase III extension study at this time. We recommend you request an end of Phase 2 (EOP2) meeting after completing your Phase I/II study to discuss the most appropriate approach for your Phase III extension study.

Meeting Discussion for Sponsor Question 10:
The sponsor asked if a patient with a new UCD subtype could be treated in the Phase III study if a patient with that UCD has not been treated in the Phase I/II study. FDA stated it was premature to discuss at this stage of development and could be discussed at the EOP2 meeting. If consistent results in clinical outcomes and safety are observed across the UCD subtypes in the Phase I/II study, it could be reasonable to treat new UCD subtypes in the Phase III study (with a new IND still submitted for each new gene/disorder). However, if there is significant variability in dosing and/or treatment response in the Phase I/II trial, additional patients with different UCD subtypes may need to be treated in the Phase I/II study to inform the appropriate population and dosing regimen(s) for the Phase III study.

FDA Additional Comments sent in Preliminary Meeting Response:

Chemistry, Manufacturing, and Controls

1. As product development continues, we recommend that you develop an assay to measure the activity of the mRNA DS and add the assay to the lot release specification.

2. Information for the lipid components of the DP should be provided in eCTD section 3.2.P.4 Control of Excipients. Please note that the lipid components in the LNP are an integral part of the product due to their essential role in the delivery of the RNA payload to target cells. Any changes to these components could have an effect on the quality and performance, and therefore, safety and efficacy of the product. Therefore, the lipid components of LNPs are considered critical components that should be fully characterized, and relevant CMC information should be submitted in the IND. For more common lipid excipients, such as cholesterol, vendor and grade information and a certificate of analysis are sufficient. Novel lipids generally require additional CMC information to be provided in the IND to assure quality and safety (with a similar level of detail and a similar CTD organization as for a drug substance). Complete CMC information for each novel lipid may be provided in a separate section of the appendix, 3.2.A.3 Excipients. Please provide the following information for each novel lipid.

a. The name and address of the lipid manufacturer.

b. A certificate of analysis (CoA) for the lipid. If documentation for a lipid excipient is incomplete, testing for the incomplete attribute(s) of the lipid excipient should be performed.

c. The full molecular structure of the lipid.

d. A narrative description and flow diagram of the manufacturing process, including in process tests and controls.

e. A description of all analytical methods used during lot release.

f. A justification for acceptance criteria in the lot release specification.

g. Stability study data and conclusions.

h. The container closure system.

i. A description of any reference standards used for testing.

j. Please note that some or all of this information can be provided by cross reference to a master file (MF), if applicable. Please provide a signed letter of authorization from the MF holder detailing what information can be cross referenced.

FDA Additional Comments:
There was no discussion of this FDA comment during the meeting.

END