CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761434Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 158899

MEETING REQUEST-
WRITTEN RESPONSES

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Argie Zoubroulis, MS
Associate Director, Global Regulatory Affairs
508 Carnegie Center Drive
Princeton, NJ 08540

Dear Argie Zoubroulis:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sibeprenlimab (VIS649).

We also refer to your submission dated November 22, 2024, containing a meeting request. The purpose of the requested meeting was to discuss Agency feedback and obtain agreement on the chemistry, manufacturing, and controls (CMC) of sibeprenlimab for inclusion in the BLA filing, as follows:

- Provision of data for (b) (4) hold time studies
- Provision of comparability data for clinical and process performance qualification (PPQ) manufacturing batches
- Provision of Drug Product (DP) transportation study reports
- Provision of stability data
- Structure and content of Module 3 of the BLA.

Further reference is made to our Meeting Granted letter dated December 05, 2024, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 19, 2024, background package.

[1] We update guidance's periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, please contact Shazma Aftab, PharmD, Regulatory Business Process Manager, at shazma.aftab@fda.hhs.gov or (301) 796 – 3138.

Sincerely,

{See appended electronic signature page}

Maria-Teresa Gutierrez-Lugo, PhD
Supervisory Chemist
Division of Product Quality Assessment XV
Office of Product Quality Assessment III
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-BLA (CMC)

Application Number: IND 158899

Product Name: sibeprenlimab (VIS649).
Indication: treatment of primary immunoglobulin A nephropathy (IgAN) in adults
Sponsor Name: Otsuka Pharmaceutical Development & Commercialization, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

1.0 BACKGROUND

Sibeprenlimab is under development for the treatment of IgAN, an autoimmune glomerulonephritis characterized by the deposition of immunoglobulin (Ig) A (IgA) containing immune complexes in the kidney glomeruli. Otsuka Pharmaceutical Development & Commercialization, Inc. intends to submit a BLA for sibeprenlimab for the treatment of IgAN in March 2025. FDA granted the waiver request to provide the requirements for providing information from a human factors summative study in the BLA on October 12, 2023. Breakthrough Therapy Designation (BTD) was granted for sibeprenlimab in the treatment of adults with primary IgAN on February 8, 2024. Otsuka intends to request priority review of the BLA. The purpose of this meeting request is for Otsuka to obtain Agency feedback and agreement specifically on the chemistry, manufacturing, and controls (CMC) of the sibeprenlimab for inclusion in the BLA filing, as follows:

- Provision of data for (b) (4) hold time studies
- Provision of comparability data to support decoupling approach to process performance qualification (PPQ)
- Provision of Drug Product (DP) transportation study reports
- Provision of DP stability data
- Structure and content of Module 3 of the BLA.

2.0 QUESTIONS AND RESPONSES

Question 1: *Does the Agency agree with the proposed submission timeline for* (b) (4) (b) (4) *hold time validation data and the final report?*

FDA Response to Question 1:

The overall proposed microbial hold time control approach described in this meeting package section 10.1 appears reasonable and we agree with the sponsor's proposal to provide the (b) (4) hold time data and report within 60 days of the initial BLA submission. However, a final decision on the adequacy of your approach will be made

during review of your BLA submission. The maximum hold times should be validated by three runs in each vessel and should be shortest of three holds. Also refer to the additional microbiology comments provided in the written responses provided on January 16, 2024.

Question 2: *Does the Agency agree with the proposed comparability submission strategy and the expected timeline for data availability?*

FDA Response to Question 2:
You provide the comparability plans for drug substance (DS) and drug product (DP) in Section 11.1 of the meeting package. You also propose to include DS comparability assessment data in the initial BLA submission, and to submit the DP comparability assessment data within 90 days after initial BLA submission. The overall proposed comparability submission strategy appears reasonable; however, we request that you submit the DP comparability assessment data within 60 days after initial BLA to allow sufficient time to review. We also have the following additional comments:

a. The proposed scales for three DP post-PPQ batches are (b) (4) in the current meeting package. To support a maximum DP scale (b) (4) we recommend that you manufacture at least one DP post-PPQ batch at the maximum (b) (4) scale, as proposed in your previous meeting package (Figure 11.2-2) submitted on June 14, 2024 (SN0066).

b. DS and DP comparative stability should include comparison of stability profiles under both long-term and accelerated/stressed conditions, as indicated in your previous meeting package (e.g., Tables 11.2-4 and 11.2-6) submitted on June 14, 2024 (SN0066).

Question 3a: *Does the Agency agree with the proposed DP Transportation Study submission strategy and timeline?*

FDA Response to Question 3a:
You propose to provide commercial DP bulk and finished shipping qualification study protocols at the time of BLA filing, submit the report for commercial DP finished shipping qualification study within 60 days of the initial BLA submission and provide the report for commercial DP bulk shipping qualification study as an annual reportable change post-approval when the data and report become available. The overall submission strategy and timeline appear reasonable. We recommend that data from DP simulated transportation studies, as proposed in your previous meeting package submitted on June 14, 2024 (SN0066) be included in the initial BLA submission to further support DP commercial shipping. Acceptability of the data will be a review issue of the BLA.

Question 3b: *Does the Agency agree with the proposed* (b) (4) *study clarification and strategy?*

FDA Response to Question 3b:

(b) (4) process should be described in P.3.3 of the BLA and (b) (4) should be monitored as (b) (4) controlled. The acceptable range (b) (4) (b) (4) is not clearly described. You indicate (b) (4) concerns.

Question 4: *Does the Agency agree with the proposed drug product stability data submission strategy and timeline to support a proposed 24-month SL at the time of BLA approval?*

FDA Response to Question 4:

The proposed DP stability data submission strategy and timeline in Table 11.2-1 of the meeting package appears reasonable. In order to support your proposed dating period for drug product, you may wish to provide a "simple stability update" which is defined as follows: Stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA. The final DP shelf life will be determined after reviewing all available data during the BLA review cycle.

Question 5: *Does the Agency agree that the proposed structure and content of Module 3 (Quality) of the BLA is acceptable for filing a marketing application to support approval of sibeprenlimab for the treatment of primary IgAN?*

FDA Response to Question 5:

The proposed structure and content of Module 3 (Quality) of the BLA in Table 10.5-1 of the meeting package appears acceptable. See “Additional Product Quality Comments” below. Also refer to the additional microbiology comments provided in the written response dated January 16, 2024, and the additional comments on device constituent parts in the meeting preliminary comments dated June 14, 2024.

Additional Product Quality Comments:
To facilitate the Agency's assessment of the BLA submission, provide the information in tables as requested below. The requested tables should summarize information from Module 3 and be submitted in Module 3.2.R. These tables do not replace other sections of Module 3 or impact the nature or amount of information included in those sections of Module 3.

1. Provide the following information in a completed table like the one below for all drug master files (DMFs) referenced in the BLA:

DMF #	DMF Type	DMF Holder	Item referenced	Link to Letter of Authorization	Comments (if needed)

2. To facilitate the Agency's assessment of the drug substance (DS) and drug product (DP) manufacturing process, provide the information for each process parameter and in-process control, as applicable, in the tabular format provided below. Provide a separate table for each unit operation of the DS and DP manufacturing process, as described below.

Title: Unit Operation for DS Manufacturing Process

Process parameter/ In-process control (IPC)[1]	Proposed range for commercial manufacturing process[2]	Criticality classification [3]	Characterized range from process development[2]	Historical range from clinical DS batches[2] (mix-max[4]), n=?[5]	Process validation range from DS PPQ batches[2] (min-max[4]), n=?[5]	Justification of the proposed commercial acceptable range[6] (or link to eCTD)

1. Terminology should be adapted to the one used by the manufacturing site(s).
2. As applicable.
3. For example, critical process parameter, key process parameter, non-critical process parameter, IPC, as described in Module 3.
4. Provide mean ± 2 (or 3) SD as optional.
5. Indicate the total number of batches used for calculating minimum-maximum range for each unit operation and list the batch numbers in the footnote if applicable. If not all batches indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.
6. This could be a brief description (e.g., "development range", "validation range", or "platform experience").

Title: Unit Operation for DP Manufacturing Process

Process parameter/ In-process control (IPC)[1]	Proposed range for commercial manufacturing process[2]	Criticality classification [3]	Characterized range from process development[2]	Historical range from clinical DP lots[2] (mix-max[4]), n=?[5]	Process validation range from DP PPQ lots[2] (min-max[4]), n=?[5]	Justification of the proposed commercial acceptable range[6] (or link to eCTD)

1. Terminology should be adapted to the one used by the manufacturing site(s).
2. As applicable.
3. For example, critical process parameter, key process parameter, non-critical process parameter, IPC, as described in Module 3.
4. Provide mean ± 2 (or 3) SD as optional.
5. Indicate the total number of lots used for calculating minimum-maximum range for each unit operation and list the lot numbers in the footnote if applicable. If not all lots indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.
6. This could be a brief description (e.g., “development range”, “validation range”, or “platform experience”).

3. To facilitate the Agency’s assessment of the control strategy for the product, provide information for quality attributes and process and product related impurities for DS and DP in the following tabular format. Provide a separate table for the DS and DP.

Quality Attributes (including process and product related impurities for DS and DP)	Criticality classification[1]	Impact[2]	Source[3]	Analytical method[4]	Proposed control strategy[5]	Justification of the proposed control strategy[6]

1. Indicate if it is a CQA or not.
2. What is the impact of the attribute (e.g., contributes to potency, immunogenicity, safety, efficacy, etc.)?
3. What is the source of the attribute or impurity (e.g., intrinsic to the molecule, fermentation, purification column, etc.)?
4. List all methods used to test an attribute in-process, at release, and/or on stability. For example, if two methods are used to test identity, list both methods for that attribute.
5. List all strategies by which the attribute is controlled (e.g., in-process testing, validated removal, release testing, stability testing, etc.).
6. This could be a brief description or links to the appropriate section of the eCTD.

4. To facilitate the Agency’s assessment of the adequacy of the proposed commercial DS and DP release specifications, provide information for each release specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. Use footnotes for each column of grouped results to indicate the lots used for each calculation of the minimum-maximum range and provide the number of lots (n=?) in the table.

Release Specification for Drug Substance							
Attribute	Analytical Method	Proposed commercial release acceptance criteria	Release results from developmental and nonclinical	Release results from clinical DS	Release results from DS PPQ	Release results from all DS batches[a] manufactured using the	Justification of specification (e.g., clinical experience,

			batches (n=?) (min-max)	batches (n=?) (min-max)	batches (n=?) (min-max)	commercial process (n=?) (min-max)	manufacturing capability, etc.)

a. Include all batches with available release data that were manufactured following the proposed commercial process, including those prior to PPQ campaign. Provide a list of batches included in the analysis as a footnote in the table.

Release Specification for Drug Product

Attribute	Analytical Method	Proposed Commercial Release acceptance criteria	Release results from developmental and nonclinical DP lots (n=?) (min-max)	Release results from clinical DP lots[a] (n=?) (min-max)	Release results from DP PPQ lots (n=?) (min-max)	Release results from all DP lots[b] manufactured using the commercial process (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

a. Include all lots used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List all lots as a footnote in the table.
b. Include all lots with available release data that were manufactured following the proposed commercial process. Provide a list of lots included in analysis as a footnote in the table.

5. To facilitate the Agency's assessment of the adequacy of the stability specifications of DS and DP, provide stability information for storage at recommended condition for each stability specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. If any stability acceptance criteria are different from the corresponding release acceptance criteria for which the same analytical method is used, provide justification as to why different acceptance criteria are proposed for release and stability. Include footnotes in the tables to list all batches that were used in each assessment. The assessment should consider data from all stability time points, not limited to the release and end of proposed shelf-life time points. If a lot has not completed stability testing to the end of proposed shelf-life, include data from all time points that are currently available.

Stability Specification for Drug Substance

Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at recommended long-term storage condition (n=?) Min – Max (Range for all data from time 0 to proposed end of shelf life or currently available time points)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

Stability Specification for Drug Product				
Attribute	Analytical Method	Stability acceptance criteria	Stability results for batches stored at recommended long-term storage condition (n=?) Min – Max (Range for all data from time 0 to the proposed end of shelf life or currently available time points)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

6. To facilitate the Agency's assessment of the suitability of the analytical methods for DS and DP release and stability testing and for in-process test methods, provide summarized results of method validation in the tabular format provided below. Provide a separate table for each analytical method. Each parameter (e.g., specificity, precision, accuracy, etc.) should be described in a separate row. Add additional rows for additional parameters as needed. Study design should include a brief description of the testing material (such as batch information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used (e.g., DS release/stability, DP release/stability, and in-process testing).

Summary of Validation Results for XXX (Method) (Used for DS/DP release/stability, in-process testing, etc.)			
Location of testing site:		**Location where method was validated:**	
System Suitability Acceptance Criteria:			
Parameter	Study Design	Acceptance Criteria	Validation Results

7. Regarding the immunogenicity testing in the BLA submission, we recommend you provide an Integrated Summary of Immunogenicity (ISI) in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This ISI should include: (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, and (4) Clinical Immunogenicity Data Analysis. For more information, refer to 2019 FDA Guidance for Industry: "*Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection*".

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARIA T GUTIERREZ LUGO
01/21/2025 01:44:48 PM

IND 135282

MEETING MINUTES

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Catherine Sheppard, PhD
Senior Director, Global Regulatory Affairs Strategy
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Sheppard:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sibeprenlimab (VIS649).

We also refer to the teleconference between representatives of your firm and the FDA on November 17, 2021. The purpose of the meeting was to discuss your development program.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301)796-1129.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology & Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: November 17, 2021 from 12-1 PM, ET
Meeting Location: Teleconference

Application Number: 135282
Product Name: Sibeprenlimab (VIS649)
Indication: Treatment of IgA Nephropathy (IgAN)
Sponsor Name: Visterra, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Aliza Thompson, MD, MS
Meeting Recorder: Anna Park, MS, RPh, RAC

FDA ATTENDEES

OND Immediate Office

Mary Thanh Hai, MD	Deputy Director

Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

Lisa Yanoff, MD	Deputy Director

Division of Cardiology and Nephrology (DCN)

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD, MS	Deputy Director
Kirtida Mistry, MBBCh, DCH, MRCPCH	Clinical Reviewer
Michael Monteleone, MS., RAC	Associate Director for Labeling

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)

Jean Wu, PhD	Pharmacology Team Leader
James Willard, PhD	Pharmacology Reviewer

Division of Regulatory Ops for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Edward Fromm, RPh, RAC	Chief, Project Management Staff
Anna Park, MS, RPh, RAC	Regulatory Project Manager

Office of Clinical Pharmacology

Li Wang, PhD	Reviewer

Office of Biostatistics	
Jialu Zhang, PhD	Team Leader
William Koh, PhD	Reviewer
Division of Biotechnology Review and Research (DBRR)	
Jun Liu, PhD	Reviewer

SPONSOR ATTENDEES

Charlotte Jones-Burton, MD, MS	Vice President, Global Clinical Development, Nephrology, Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)
Jeffrey Hafkin, MD, MSCE	Senior Director, Global Clinical Development, OPDC
Pralay Mukhopadhyay, PhD	Vice President, Head of Clinical Analytics, OPDC
Jingli Song, PhD	Senior Director, Biostatistics, OPDC
Mary Hobart, PhD	Vice President, Global Head, Global Regulatory Affairs, OPDC
Catherine Sheppard, PhD	Director, Global Regulatory Affairs, OPDC
David Oldach, MD	Chief Medical Officer, Visterra, Inc.
Asher Schachter, MD	Vice President, Translational Medicine, Visterra, Inc.
Mohit Mathur, MD	Director, Clinical Development, Visterra, Inc.
William Tubbs	Executive Director, Regulatory Affairs, Visterra, Inc.

1.0 BACKGROUND

Sibeprenlimab is a humanized IgG2 monoclonal antibody (mAb) directed against A Proliferation Inducing Ligand (APRIL) that blocks the binding of soluble APRIL to its receptors, transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B-cell maturation antigen (BCMA). APRIL regulates B-cell-mediated immune responses through several mechanisms, including playing a role in class switch recombination and T-cell independent production of immunoglobulin A in mucosa. Sibeprenlimab is being studied as a potential treatment for biopsy-confirmed immunoglobulin A nephropathy (IgAN) and is intended for chronic use to prevent progression of this condition to kidney failure.

Visterra requested this meeting to obtain feedback on the design of their phase 3 trial and the clinical and nonclinical data packages proposed for licensure.

Preliminary responses to the submitted questions were provided to the Sponsor, and are copied below, followed by any additional discussions that took place during the

meeting. The Sponsor used the appended slide presentation to guide the discussion. The meeting discussion focused on questions 1, 2, 3, 4 and 7.

2.0 DISCUSSION

2.1 Clinical

Question 1:
Does the agency agree that a significant reduction in proteinuria relative to placebo at 9 months, as measured by the uPCR from 24-hour urine collection, is a clinically meaningful surrogate endpoint to support Accelerated Approval of sibeprenlimab for the treatment of IgAN?

Question 2:
Does the agency agree that for the phase 3 Trial 417-201-00007, measuring the difference in eGFR slope over approximately 24 months in the sibeprenlimab-treated group compared with the placebo-treated group is acceptable as the clinical endpoint for confirmatory approval?

Preliminary FDA Response to Questions 1 and 2:
In brief, you propose a single phase 3 randomized, double-blind, placebo-controlled trial (417-201-00007) in approximately 484 adults with biopsy-confirmed IgAN on stable, maximally tolerated renin-angiotensin-aldosterone system (RAAS) blockade for at least 3 months, urine protein-to-creatinine ratio (UPCR) ≥0.75 g/g or urine protein ≥1 g/day, and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. Patients will be randomized 1:1 to sibeprenlimab or placebo administered as a subcutaneous injection once every 4 weeks for 26 doses (until Week 100). Randomization will be stratified by screening UPCR (≤2 g/g vs >2 g/g), eGFR (30-44 vs ≥45 mL/min/1.73 m^2), and sodium-glucose cotransporter-2 inhibitor (SGLT2i) use (yes or no). The study will exclude patients with nephrotic syndrome, a serum IgG level <500 mg/dL, or a mesangial cellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy (MEST) or MEST-crescents (MEST-C) score of T2 or C2 on kidney biopsy. The proposed primary endpoint is the ratio of 24-hour UPCR at 9 months to baseline. The key secondary endpoint is eGFR slope over approximately 24 months. You plan to request accelerated approval based on the primary endpoint, and subsequent full approval based on the key secondary endpoint.

We have the following general comments on the design of a development program to support accelerated approval for the treatment of IgAN. We encourage you to consider requesting a follow-up meeting after you have given further thought to these issues, as well as our statistical comments.

a. We would accept a substantial reduction in proteinuria as a reasonably likely surrogate endpoint in IgAN and as a basis for accelerated approval. However, to support accelerated approval, the magnitude of the treatment effect on proteinuria would need to be sufficient to provide confidence that the post-marketing phase of

the trial is adequately powered to detect a treatment effect on the endpoint that will be used to verify the benefit in the post-marketing phase of the trial. This power calculation should be based on a quantitative model of the relationship between the endpoint that will be used to support accelerated approval and the endpoint that will be used to verify the benefit in patients with IgA nephropathy.

b. Your power calculations for the confirmatory phase of your trial should account for sources of uncertainty including uncertainty in the treatment effect on proteinuria and the uncertainty in the relationship between treatment effects on proteinuria at 9 months and treatment effects on eGFR. Note that an effect on proteinuria that barely excludes no effect leaves insurmountable uncertainty in the predicted effect on eGFR. For this reason, we believe it is important to power your trial to provide greater precision around the estimate for the treatment effect on proteinuria.

Sponsor Response:
See attached slides

Discussion during the meeting:
The Sponsor provided an overview of their proposed statistical approach for phase 3 (see slides 5 and 6). The Sponsor indicated that data on the relationship between proteinuria at 9 months and 2-year total eGFR slope from the Inker, et al publication (AJKD vol. 78 Iss. 3 Sep 2021) were used to power the trial such that the proposed study had at least 95% power to detect a 30% reduction in UPCR at 9 months.

The Division acknowledged that the Inker publication provides important information on the relationship between changes in proteinuria at 9 months and 2-year eGFR slope and recommended that the Sponsor use the size of the treatment effect on UPCR seen in their phase 2 trial to power the phase 3 trial. The Division emphasized that showing a statistically significant effect on UPCR would not be sufficient to support accelerated approval. There would also need to be confidence that the confirmatory phase of the trial was adequately powered to verify the benefit, taking into account the various sources of uncertainty (see preliminary responses above).

The Division request that the Sponsor submit information on the treatment effect on UPCR and eGFR seen in phase 2 when the data become available, as well as information on the model used to predict treatment effects on eGFR, including how the model handles the various sources of uncertainty. The Division explained that it would need this information to determine whether the Sponsor's assumptions for powering the confirmatory phase of the study are reasonable. See also discussion under Question 3.

The Division requested clarification on the timing of the UPCR analysis (i.e., whether the UPCR endpoint would be assessed at 1 year or at 9 months). The Sponsor confirmed that the primary endpoint, UPCR, will be evaluated at 9

months. In response to a question from the Division, the Sponsor indicated that they plan to continue the trial and collect eGFR data even if the treatment effect on UPCR is not statistically significant. The Division voiced concern, noting that the statistical approach currently proposed by the Sponsor does not preserve any alpha for assessing the eGFR endpoint at 2 years in such a setting. The Division recommended that the Sponsor preserve some alpha.

c. Given the limitations of the analyses submitted by sponsors to date on the quantitative relationship between changes in proteinuria at 9 months and eGFR slope at 2 years and because available data indicate that treatment effects on 1-year eGFR slope are likely predictive of treatment effects on eGFR over 2 years, we have generally held that sponsors should provide analyses of eGFR data at the time submission of an application for accelerated approval to provide additional confidence that the confirmatory trial is adequately powered to confirm the treatment benefit. Such analyses of 1-year eGFR data could provide further verification of the sample size assumptions used for eGFR slope over 2 years.

See also our responses to Question 3 for additional comments related to the design of your study.

Sponsor Response:
We acknowledge FDA feedback. eGFR data will be provided at the time of BLA filing.

Discussion during the meeting:
The Division reiterated that 1-year eGFR data would be needed to provide additional confidence that the confirmatory phase of the trial is adequately powered and emphasized the importance of enrolling a sufficient number of patients with rapid rates of disease progression.

Question 3:
Does the agency agree with the proposed statistical design and analysis plan for the phase 3 trial (417-201-00007)?

Preliminary FDA Response:
You state that you will conduct an interim analysis for the UPCR endpoint after 62.5% of the randomized patients complete the 9-month visit (b) (4) You also indicate that the overall Type 1 error will be controlled at the 5% level for all planned multiple comparisons, interim (Interim 1) and final analyses of the primary endpoint (Interim 2), analysis of key secondary endpoint of eGFR (assumed to be your final analysis), and other secondary endpoints. In Section 9.6 of your draft protocol, you provide some additional information on the proposed interim analysis and in Section 9.1.1 you list possible changes to the endpoint and the sample size of the study. Specifically, you note the following:

- Depending on the results of the phase 2 study, the UPCR endpoint may be revised to be evaluated at 1 year.
- To address uncertainties around the sample size calculation for the difference in eGFR slopes over 24 months, you will conduct two checks on the assumption for the within and between standard deviation for eGFR. You note that no alpha adjustment will be made but do not provide a rationale.

Based on the provided information, we have the following comments:

a. You have not provided compelling justification for your sample size calculations for your UPCR and eGFR endpoints. We recommend that you delay initiation of your phase 3 trial until you have additional data from your phase 2 trial on your product's effect on UPCR, including the time course of the effect. Data from this trial may also be needed to determine how to power the confirmatory phase and analyze your eGFR-based endpoint (see our response to Question 4 for further discussion of this issue).

Sponsor Response:
See slides

Discussion during the meeting:
The Division asked about the basis for the assumed effect size (i.e., whether there were data from the development program indicating that sibeprenlimab reduces proteinuria by 30%). The Sponsor indicated that in the subset of patients in the phase 2 trial with data collected for up to 5 months, there was a roughly 30% reduction in UPCR. The Division recommended that the Sponsor submit the UPCR and eGFR data from the phase 2 trial when it is completed and before launching the phase 3 trial. The Division indicated that although this was not a hold issue, such data would be needed to determine whether the phase 3 program was adequately designed to support approval. See also discussion under Questions 1 and 2.

b. It is critical to maintain the integrity of a trial following the conduct of an unblinded interim analysis and a submission for accelerated approval. To address this issue, we have advised sponsors to submit a detailed data access plan for Agency review. We also expect sponsors to submit their DMC charter along with the monitoring rules for the proposed interim analysis for FDA review.

Sponsor Response:
We acknowledge FDA feedback. The DMC Charter and SAP will be submitted for FDA review.

Discussion during the meeting:
None.

c. According to Section 9.6, if the primary efficacy endpoint of UPCR at 9 months does not meet the prespecified level of significance based on the group sequential design

(i.e., at either of the interim analyses), then there is no alpha reserved for evaluating the eGFR endpoint at 2 years. If you plan to continue your trial and evaluate for a treatment effect on eGFR regardless of the results of your interim analysis, then you will need to propose an approach to control the overall Type 1 error.

Sponsor Response:
We acknowledge FDA feedback.

Discussion during the meeting:
None.

d. Your first interim analysis to be conducted at 62.5% of the randomized patients is based on a sample size of 434 patients in total. You state later that the sample size may be increased to 484 to account for dropouts. We note the following:
   - For a group sequential design, the total information needs to be prospectively specified to determine the operating characteristics.
   - Increasing the sample size of the study to account for missing data from dropouts only addresses the variability of the estimate of the treatment effect but does not correct for the bias induced by the missing data. We recommend that you implement aggressive measures to reduce the risk of missing data.

Sponsor Response:
The target of 484 subjects enrolled was for operational planning purposes. The final protocol will include the target enrollment number. All randomized patients will be included in the analysis, which will be detailed in the SAP.

Discussion during the meeting:
None.

e. Please clarify how the sample size of the study will be increased based on the two proposed interim checks of the standard deviation of eGFR. Clarify how your design controls the overall type I error rate with the sample size re-estimation for a different endpoint.

Sponsor Response:
The sample size re-estimation is not a traditional unblinded re-estimation; this will be a pooled assessment of standard deviation and therefore has no impact to the Type I error.

Discussion during the meeting:
None.

We recommend that you address these issues when you submit your protocol. When you submit your protocol, you should also submit a draft SAP or include sufficient details on your planned statistical analysis in the protocol to facilitate review. With a

group sequential design in place, we recommend that the SAP be locked prior to the first interim analysis.

Sponsor Response:
We acknowledge the FDA feedback. The draft SAP will be submitted to the FDA for comments approximately 3 months after the first patient is enrolled in the study.

Discussion during the meeting:
None.

Question 4:
Does the agency agree with the proposed statistical analysis plan for efficacy?

Preliminary FDA Response:
According to Section 9.5.1.1 of your Trial Synopsis (Appendix 4), you propose to target the hypothetical estimand for UPCR at 9 months. The endpoint will be analyzed using an analysis of covariance model with multiple imputatio (b) (4) We have the following comments:

a. In general, the estimand should reflect the clinical question of interest and be estimated with minimal and plausible assumptions. While a hypothetical estimand may be acceptable, (b) (4) we cannot agree to the proposed approach at this time. You should address this issue in your SAP and when you submit the protocol.

   Sponsor Response:
   We acknowledge the FDA feedback. Further details will be provided in the protocol and/or SAP.

   Discussion during the meeting:
   None.

b. The proposed eGFR analysis based on a random coefficient model relies on a strong linear assumption in addition to missing at random assumptions. You should provide additional data on the pattern of changes in eGFR in your phase 2 trial; such data are needed for us to assess whether your therapy could have an acute effect on eGFR and hence whether the assumptions underlying your analysis are acceptable.

   Sponsor Response:
   Based on the mechanism of action of sibeprenlimab(APRIL suppression) we do not anticipate an acute effect on eGFR. Data from the Phase 2 study will be provided in the final clinical study report.

Discussion during the meeting:
None.

Question 5:
Does the agency agree with the proposed plan for handling corticosteroid use in the Phase 3 trial?

Question 6:
Does the agency agree with the proposed plan for handling new supportive care regimens in the phase 3 trial?

Preliminary FDA Response to Questions 5 and 6:
You note that systemic corticosteroid use (>14 days), other immunosuppressive therapy, drugs that are contraindicated in IgAN per local practice (e.g., NSAIDs >1 week, aminoglycosides, trimethoprim, cimetidine, pyrimethamine, fenofibrate, or creatine supplements), and traditional Chinese, Ayurvedic and herbal medications and supplements will be prohibited within 16 weeks before randomization and for the duration of the trial. Patients should be on maximally tolerated doses of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and those already on an SGLT2i must be on stable doses for at least 3 months before screening and remain on those doses for the duration of the trial. Patients will not be allowed to initiate SGLT2i after enrollment.

From a clinical perspective, the proposed approach is acceptable; see our response to Question 4 for comments on statistical considerations related to the handling of prohibited medications in key analyses.

Discussion during the meeting:
None.

Question 7:
Does the agency have any additional comments on the phase 3 Trial 417-201-00007 design?

Preliminary FDA Response:
We have the following additional comments:

a. To provide confidence that the observed treatment effect on eGFR will, over time, translate into a meaningful effect on progression to kidney failure, it will be important to show that the treatment effect continues to accrue across the various stages of disease. To address this issue, the protocol should specify enrollment of minimum numbers of patients at the higher and lower ends of the proposed eGFR range.

Sponsor Response:
We acknowledge FDA feedback.

Discussion during the meeting:
None.

b. In general, we also recommend that sponsors include patients with an eGFR <30 mL/min/1.73 m^2 in trials in settings where the marketed product will likely be used in patients with lower levels of kidney function and when efficacy data in later stages of disease can be important for understanding the likely impact of a treatment on progression to kidney failure.

Sponsor Response:
The protocol will allow enrollment of patients with a broad range of eGFR. The sponsor agrees to include up to 20 patients with eGFR between 20-30 mL/min/1.73 m^2 which will be an additional cohort and will not be included in the primary analysis. Does the agency agree?

Discussion during the meeting:
The Division indicated that, in principle, such an approach could be acceptable, assuming it was prespecified.

c. The post-marketing phase of your trial should be completed in a timely manner following accelerated approval. As such, your trial should be fully enrolled or nearly so at the time of submission of an application for accelerated approval.

Discussion during the meeting:
None.

Question 8:
Does the agency agree that the available safety data support initiating the phase 3 trial (417-201-00007)?

Preliminary FDA Response: We agree that the referenced safety data, including data from completed and ongoing clinical studies using intravenous and subcutaneous dosing in healthy volunteers (single-ascending dose trials VIS649-101 and VIS649-102), data from your ongoing phase 2 study (VIS649-201) in patients with IgAN, as well as data from nonclinical studies, should be sufficient to support initiation of your phase 3 trial from a safety perspective.

Discussion during the meeting:
None.

Question 9:
Does the agency agree that a single phase 3 trial (417-201-00007), with supportive information from the phase 2 trial (VIS649-201) will be sufficient for regulatory decision making?

Preliminary FDA Response:
We agree, in principle, that a single adequate and well-controlled trial plus confirmatory evidence could be used to satisfy the regulatory requirement for substantial evidence of effectiveness. For further discussion of this issue, we refer you to the draft guidance, titled "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products" (https://www.fda.gov/media/133660/download).

Discussion during the meeting:
None.

Question 10:
Does the agency agree that the anticipated patient exposure data at the time of Biologics License Application submission provides sufficient data for regulatory decision making?

Preliminary FDA Response:
You anticipate approximately 219 patients with IgAN will be exposed to multiple doses of sibeprenlimab in the phase 2 and 3 clinical trials at the time of BLA submission for proposed accelerated approval (approximately 219 patients should have >6 months exposure, approximately 82 patients >12 months, and approximately 82 patients >24 months). We recognize that the size of your safety data will be limited by the size of the affected population; whether the safety database is adequate will be determined as part of the NDA review.

Discussion during the meeting:
None.

Question 11:
Does the agency agree with the current method to assess anti-drug antibodies and the proposed method to assess neutralizing anti-drug antibodies?

Preliminary FDA Response:
Based on the limited information provided in the meeting package, your current method to detect anti-drug antibodies (ADA) and the proposed approach to detect neutralizing anti-drug antibodies (NAb) are reasonable. In addition, the drug tolerance of your immunogenicity assays will be confirmed once the steady state concentration of sibeprenlimab from the pivotal clinical study is known. Per FDA Guidance for Industry, Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection (2019), FDA recommends that screening and confirmatory ADA assays achieve a sensitivity of at least 100 ng/mL ADA positive control with on board drugs. Ensure that validated method performance parameter ranges different from those recommended in the FDA guidance, e.g., MRD of 1:4, and parameters recommended for validation by the guidance that are not included in your validation exercise, are adequately addressed and justified in your validation report.

Discussion during the meeting:
None.

2.1. Clinical Pharmacology

Question 12:
The proposed dosing regimen for the phase 3 trial (417-201-00007) is 400 mg of sibeprenlimab administered SC once every 4 weeks. Does the agency agree with the proposed dosing regimen for the phase 3 trial determined by PK/Pharmacodynamic modeling and simulation?

Preliminary FDA Response:
You propose a dosing regimen of 400 mg sibeprenlimab administered subcutaneously (SC) once every four weeks in the proposed phase 3 trial. Your dose selection is based on the reduction in serum IgA (approx. 60%) achieved with monthly doses of 4 mg/kg administered intravenously (IV) to patients with IgAN. Based on the population PK/PD modeling, the 400 mg SC dose is expected to provide similar PK and IgA reduction compared to the 4 mg/kg IV dose.

We agree that your proposed dosing regimen appears reasonable; however, it may be prudent to also use the dose-response data on UPCR that will be obtained from your phase 2 trial to inform dose selection and ensure that the selected dose of 400 mg SC is optimal (and that a higher dose is not needed).

Discussion during the meeting:
None.

Question 13:
The sponsor proposes to allow injection site flexibility in the phase 3 trial including upper arm, abdomen, and thigh. Does the agency agree the proposed plan will provide sufficient information to support a label that provides for the injection sites specified?

Preliminary FDA Response:
None.

We agree with your proposal to allow flexibility in injection site including upper arm, abdomen, and thigh, in the phase 3 trial. Assuming adequate data from each injection site, the proposed approach could support a label that specifies each of these sites, provided injection site is not a significant covariate on the PK or PD of sibeprenlimab.

Question 14:
Does the agency agree that the contents of the clinical pharmacology package are sufficient for approval of sibeprenlimab?

Preliminary FDA Response:
We agree that no additional clinical pharmacology studies are needed.

Discussion during the meeting:
None.

2.2. Nonclinical

Question 15:
Does the agency agree that the completed and proposed nonclinical program is adequate for approval?

Preliminary FDA Response:
Yes, we agree that the completed and proposed nonclinical program appear to be adequate for a BLA submission.

Discussion during the meeting:
None.

2.3. Chemistry, Manufacturing, and Controls

Question 16:
Two receptor-blocking (BCMA and TACI) enzyme-linked immunosorbent assays representing the sibeprenlimab mechanism of action were developed and qualified for sibeprenlimab potency assessment. Does the agency agree that a single potency assay of TACI receptor blocking is adequate for phase 3 development and approval?

Preliminary FDA Response:
We do not have sufficient information to determine whether a single TACI receptor blocking assay is adequate for phase 3 development and approval. We have the following comments about your proposal:

a. The current sibeprenlimab drug substance (DS) and drug product (DP) specifications include an APRIL-binding ELISA assay as a potency assay. It is not clear whether you plan to replace the current APRIL-binding ELISA assay or to add the proposed TACI receptor blocking assay as an additional potency assay. In your meeting package, you indicate that “additional receptor-blocking potency assays were developed” to “augment the APRIL-binding ELISA assay”. Please clarify whether you plan to use two potency assays for release and stability testing. Note that in addition to method validation, bridging data between the current and the proposed potency assays will be needed to replace any assay.
b. You have not justified why the TACI receptor blocking assay was chosen over the BCMA receptor blocking assay, or addressed whether APRIL binding to TACI, BCMA, or both is relevant to clinical efficacy in the proposed patient population. In addition, we note slight differences in Figure 20 between the IC50 values of APRIL-TACI binding and APRIL-BCMA binding inhibition by sibeprenlimab. Provide

justification for choosing the TACI receptor blocking assay, including its relevance to clinical efficacy in the proposed patient population and how it informs and controls the biological activities regulated by APRIL binding to the BCMA receptor if they are important for the proposed clinical indication.

c. Although the TACI and BCMA receptor blocking assays provide more information about the proposed mechanism of action of sibeprenlimab than the APRIL-binding ELISA assay, they do not provide complete information about the signaling and biological activity downstream of APRIL-APRIL receptor binding inhibition. As indicated in the non-hold comments in the safe-to-proceed letter dated October 14, 2018, we recommended that you establish an appropriate cell-based potency method because it would reflect the full mechanism of action of your product in the intended clinical population. Clarify your plans with respect to developing a cell-based potency assay.

Additional CMC Comments
Drug product (DP) is formulated for (b) (4) SC (200 mg/mL) administration (b) (4) You state that the sibeprenlimab SC formulation has been determined (b) (4) (b) (4) by analytical testing; however, information for the SC formulation has not been submitted to the IND. To support use of the SC DP under the IND, update the CMC sections of the IND with the information and data for the SC DP and provide a summary of the updated content. In addition to information on the SC DP manufacturing and control strategy, you should provide information on the SC DP lots intended for use in the phase 3 clinical study, including data supporting their stability during clinical studies and comparability to the materials used in the supporting toxicology and earlier clinical studies. In addition, the submission should include data to support in-use stability and compatibility with the proposed administration materials.

Discussion during the meeting:
None.

2.4. Regulatory

Question 17:
It is anticipated that North America will contribute to approximately 10% to 15% of subjects enrolled in Trial 417-201-00007. Does the agency agree this is sufficient representation for regulatory decision-making?

Preliminary FDA Response:
We do not have a set requirement regarding the number of patients who should be enrolled from sites in the U.S. (or North America). To support approval, you will need to make the case that the findings seen in the trial are generalizable to a U.S. population receiving U.S. standard of care for the treatment of IgAN.

Discussion during the meeting:

None.

Question 18:
The sponsor plans to submit an initial pediatric study plan. Does the agency agree with the proposed pediatric plan?

Preliminary FDA Response:
You propose to conduct an open-label study to assess the PK, PD, safety, and tolerability of sibeprenlimab administered by subcutaneous injection every 4 weeks for 52 weeks in 14 adolescent patients 12 to <18 years of age with IgAN, and an UPCR >0.75 g/g or total urine protein >1 g/day. You plan to extrapolate efficacy from adults based on similar etiology, pathogenesis, and clinical characteristics and plan to determine the dose of sibeprenlimab for adolescent patients using a population PK model to match exposures in adult patients. You plan to defer initiation of the pediatric study until a favorable benefit-risk profile is established from the study of adults with IgAN and plan to request a partial waiver of studies for patients (b) (4) years of age.

We have the following comments on your proposed approach:

a. You have not provided sufficient support for your proposal to extrapolate efficacy from adults to pediatric patients with IgAN. The extent to which one can rely on extrapolation of efficacy depends on the strength of the evidence supporting assumptions regarding the similarity of disease characteristics and response to treatment between adults and pediatric patients. We do not believe the available evidence is sufficient to support such assumptions in IgAN.
b. We encourage you to consider including adolescent pediatric patients at high risk of disease progression in the planned phase 3 trial in adults. If older pediatric patients are included in this trial and the observed treatment effect in the enrolled pediatric population is similar to that observed in adults at similar exposures, the findings in this trial could support extrapolation of efficacy to younger pediatric patients.
c. We believe there is unmet need for therapies for children with IgAN who are at high risk of disease progression. Absent a compelling rationale or safety concern, we are unlikely to agree to a partial waiver of pediatric studies in patients up to (b) (4) years of age. You should reconsider the lower age cutoff for a request for a partial waiver and provide justification for your request.

Discussion during the meeting:
None.

Question 19:
The sponsor proposes that the chronic toxicology studies provide sufficient information on potential juvenile toxicity due to the ages of the monkeys in these studies. Does the agency agree that no additional nonclinical studies are needed to support the proposed pediatric study plan?

Preliminary FDA Response:
We agree that no additional juvenile toxicity studies are needed to support the inclusion of adolescent patients 12 to <18 years of age in the proposed phase 3 clinical study. We note that toxicology studies of up to 6 months duration were conducted in monkeys at ages covering a human age of 12 years and above and did not show significant adverse effects.

Discussion during the meeting:
None.

3.0 OTHER IMPORTANT MEETING LANGUAGE

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

4.0 ATTACHMENTS AND HANDOUTS

Attached below.

12 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALIZA M THOMPSON
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