CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761458Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 146742

MEETING MINUTES

GlaxoSmithKline LLC
Attention: Sanni Rana, PharmD
Post-Doctoral Fellow, Global Regulatory Affairs
1250 S Collegeville Road
Collegeville, PA 19426

Dear Dr. Rana:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK3511294; depemokimab.

We also refer to the video conference between representatives of your firm and the FDA on December 11, 2023. The purpose of the meeting was to obtain feedback and concurrence with plans for filing the original Biologic License Application (BLA) for depemokimab.

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

If you have any questions, call me at (301) 796-9017.

Sincerely,

{See appended electronic signature page}

Ji Hyun LaRose, PharmD
LCDR, U.S. Public Health Service
Senior Program Management Officer
Pulmonology, Allergy, and Critical Care
Division of Regulatory Operations for -
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 11, 2023 @ 1:00 PM – 2:00 PM EST

Meeting Location: Zoom

Application Number: 146742
Product Name: depemokimab; GSK3511294

Indication: (b) (4)
Asthma

Sponsor Name: GlaxoSmithKline LLC

Regulatory Pathway: 351(a)

Meeting Chair: Kelly Stone, MD, PhD
Meeting Recorder: Ji Hyun LaRose, PharmD

FDA ATTENDEES

Kelly Stone, MD, PhD, Associate Director for Therapeutic Review (ADTR), DPACC
Stacy Chin, MD, Clinical Team Leader, DPACC
A'ishah Ali, MD, Clinical Reviewer, DPACC
Yunzhao Ren, MD, PhD, Master Pharmacokineticist, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP)
Qianni Wu, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Tim Robison, PhD, Pharmacology/Toxicology Supervisor, Division of Pharmacology-Toxicology for Immunology and Inflammation (DPT-II), Office of Immunology and Inflammation (OII), OND
David Klein, PhD, Pharmacology/Toxicology Reviewer, DPT-II, OII, OND
Brian Roelofs, Product Quality Team Leader, Division of Biotechnology Review and Research II (DBRRII), Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ)
Alexander Sorh, Product Quality Reviewer, DBRRII, OBP, OPQ
Yongman Kim, PhD, Biometrics Team Leader, Division of Biometrics III (DB III), Office of Biostatistics (OB)
Dong-Hyun Ahn, PhD, Biometrics Reviewer, DB III, OB
Xin Yuan, MS, MEd, Patient-Focused Statistical Scientists (PFSS) Reviewer, DB III, OB

Y. Veronica Pei, MD, MEd, MPH, Associate Director of Biomedical Informatics, Division of Biomedical Informatics, Research, and Biomarker Development (BIRBD), Office of Drug Evaluation Sciences (ODES), OND
Onyeka Illoh, OD, MPH, Team Leader, Division of Clinical Outcome Assessment (DCOA), ODES, OND
Ji Li, MD, PhD, Reviewer, DCOA, ODES, OND
Christopher Smith, PharmD, BCPS Clinical Analyst, DBIRBD, ODES, OND
Eliford Kitabi, PhD, Pharmacometrics reviewer & OCP-QT Lead, Division of Pharmacometrics (DPM), Office of Clinical Pharmacology (OCP), Office of Translational Science (OTS)
Ji Hyun LaRose, PharmD, Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations (DRO-II/ORO)

SPONSOR ATTENDEES
Douglas Smith Vice President, Medicine Development Leader
Loretta Jacques Senior Clinical Development Director
Richard Follows Senior Clinical Development Director
James Zangrilli Senior Clinical Development Director
Tope Adeloye Medical Director, Safety/Pharmacovigilance
Natalia Karkoszka Director, Safety/Pharmacovigilance
Stein Schalkwijk Director, Clinical Pharmacology
Tom Keeley Director, Patient-Centered Outcomes
Erica Zaiser Associate Director, Patient-Centered Outcomes
Nick Bird Director, Biostatistics
Dawn Edwards Director, Biostatistics
Ben White Associate Director, Programming
Deepthi BM Programming Manager
Mark DeSiato Vice President, Global Regulatory Affairs
Kevin Fitzgerald Senior Director, Global Regulatory Affairs
Lauren Fanton Associate Director, Global Regulatory Affairs
Bea Tilt Director, Global Regulatory Affairs
Sanni Rana Post-Doctoral Fellow, Global Regulatory Affairs

1.0 BACKGROUND

In a submission dated October 13, 2023, GlaxoSmithKline requested a meeting to obtain feedback and concurrence with plans for filing the original Biologic License Application (BLA) for depemokimab. The video conference meeting was granted for December 11, 2023, at 1:00 PM – 2:00 PM EST. GlaxoSmithKline's specific questions from the briefing document dated, November 6, 2023, are listed below in *italics* and the FDA responses are provided in normal font.

FDA sent Preliminary Comments to GlaxoSmithKline on December 7, 2023.

FDA Introductory Comments:
Depemokimab is an IgG1 humanized mAb against IL-5 that blocks binding to the IL-5 receptor. In comparison to mepolizumab, depemokimab contains 7 amino acid changes, 4 in the heavy chain variable region and 3 in the Fc region (YTE modification) that increase the binding affinity and extend the half-life, respectively. Depemokimab is being developed for the same indications as mepolizumab: eosinophilic asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic granulomatosis with polyangiitis (EGPA), and hypereosinophilic syndrome (HES). The proposed dosage for asthma (b) (4) is 100 mg subcutaneous (SC) injection every 26 weeks. The meeting package discusses the planned original BLA submission in December 2024 for depemokimab for the proposed (b) (4) add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma with an eosinophilic phenotype. To demonstrate substantial evidence of effectiveness, GSK plans to submit data from (b) (4) randomized, double-blind, placebo controlled 52-week trials, two (b) (4), that are currently ongoing. (b) (4) Trials 206713 and 213744 (SWIFT 1 and 2) are evaluating 507 adolescents and adults with eosinophilic asthma and assessing the annualized rate of clinically significant exacerbations over 52 weeks as the primary endpoint. Additionally, the safety database will include interim safety data from study 206785 (NIMBLE), a randomized, double-blind, double-dummy, active control, non-inferiority trial in adolescents and adults with severe eosinophilic asthma, and study 212895 (AGILE), an OLE study in participants from SWIFT 1 and 2.

Question 1:
Assuming a positive benefit-risk evaluation arising from the Phase 3 programs, does the Agency agree that the proposed clinical data package, in terms of studies and available data, supports the (b) (4) BLA filing and potential authorization of depemokimab in the US for (b) (4):

a. *Asthma indication: "Add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma with an eosinophilic phenotype"*

(b) (4)

FDA Response:
Based on the information in your meeting package, your proposed clinical data package (b) (4) appears reasonable and sufficient to support filing. Regarding your proposed indication statement for asthma, (b) (4)
(b) (4)

(b) (4)

(b) (4) As such, your study population is consistent with a severe asthma population, and your indication statement should reflect this.

(b) (4)

Meeting Discussion:

In response to the FDA Preliminary Comments, GSK thanked the FDA for their feedback on what would be required to define a (b) (4)

(b) (4)

[1] https://ginasthma.org/2023-gina-main-report/

(b) (4) the indication statement should reflect the study population in the pivotal programs, considering factors such as exacerbation history, background asthma therapy, and control of symptoms. The depemokimab asthma program required two or more asthma exacerbations in the year prior to enrollment, and this baseline severity is consistent with a severe asthma population. (b) (4)

(b) (4)

GSK also noted the FDA's concerns regarding the use of (b) (4) as a key study endpoint to support registration and understands that this endpoint will not be

considered to inform the FDA's review decision, but are useful for other regulatory bodies.

Question 2:
Does the Agency agree with the acceptability of the Clinical Pharmacology package, specifically:

a. *Does the Agency agree with the proposed analysis to characterize PK and the effect of intrinsic and extrinsic factors on depemokimab PK to inform if any dose adjustments are required?*

b. *Does the Agency agree with the strategy to characterize the relationship of depemokimab exposure and blood eosinophil count (BEC) using patients with asthma and CRSwNP in order to generate supportive information and justification for the proposed dose and dose frequency* (b) (4) *?*

c. *Does the Agency agree with the Exposure/QTc analysis strategy to mitigate QTc liability for depemokimab?*

FDA Response:
We expect you to provide a descriptive summary of depemokimab PK results, including concentration-time profiles and the necessary PK comparison results in all the study reports.

a. We recommend that you more precisely estimate the allometric scaling of effect of body weight on CL/F and V/F in lieu of fixing the exponents at 0.75 and 1, respectively, in your popPK model.

b. Given the low blood eosinophil counts (BEC) in healthy subjects, the utility of using healthy subjects to build the initial PK/PD model is unclear. We recommend that you evaluate the PK/PD relationship in target patient populations. It is reasonable to combine the asthma patients and CRSwNP patients in the same model if there is no apparent difference in the PK/PD relationship observed between two populations.

   Other than using the proportional change of BEC from baseline as the PD endpoint, we encourage you to explore the relationship between PK and absolute value of BEC in your pharmacometrics program.

c. Yes, we agree with your proposed QT assessment strategy. We also recommend that you should include by-time analysis and categorial analysis of absolute and change from baseline in QTc, HR, QRS and PR intervals for all ECGs collected in the included studies. When you submit your QT evaluation report, please include a completed version of the most recent "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-

fda/center-drug-evaluation-and-research-cder/interdisciplinaryreview-team-cardiac-safety-studies-formerly-qt-irt).

Meeting Discussion:
GSK stated in their responses to the Preliminary Comments that they intend to include descriptive summaries of concentration data and concentration-time profiles in all reports of clinical studies with PK. For clinical pharmacology studies, all necessary PK comparisons are included in the study report. PK subgroup analysis for region will be included in the phase 3 ISEs. Further, necessary PK comparisons will be provided in the popPK report.

FDA stated the GSK's clinical pharmacology proposal outlined in their responses to the preliminary comments is reasonable. No meeting discussions occurred around comments a or b.

GSK stated in their response to the preliminary comments that they are not proposing to provide categorical analyses for HR, QRS, and PR. GSK also proposed to provide by-time analyses for change from baseline and not absolute values. GSK proposed the same strategy for the pooled analyses by indication.

GSK acknowledged the request to include the QT Evaluation Report Submission Checklist in the planned BLA. GSK stated they intend to include relevant information for QT evaluation in the ISS and not to generate a stand-alone "QT evaluation report", and asked if this approach was acceptable.

In response, FDA stated GSK should conduct categorial analyses for HR, QRS, and PR. FDA agreed the QT assessment report can be submitted in the Integrated Summary of Safety. FDA stated that by-time analysis for change from baseline and not absolute value is recommended and agreed that the Sponsor can conduct pooled analyses but should also provide separate analyses by indication.

Question 3:
Does the Agency agree with the proposed safety interim analysis (IA) for study 206785 in support of the BLA and the associated planned blinding strategy to preserve the integrity of the study?

FDA Response:
Yes, we agree with your planned cutoff date of July 15, 2024, for the IA of study 206785, which is expected to provide approximately 481 participants who have received 2 doses of study drug and 56 weeks of follow-up. The blinding charter for study 206785 that outlines the strategy to preserve study integrity following the IA also appears reasonable.

Meeting Discussion:
No discussion occurred.

Question 4:
Does the Agency agree that the size and extent of the safety database is sufficient to allow the assessment of the overall safety profile of depemokimab to support (b) (4) (b) (4) *?*

FDA Response:
The size and extent of the safety database is anticipated to include 1702 total exposed subjects, with approximately 1030 subjects from the completed/ongoing asthma studies, approximately 237 subjects from the CRSwNP studies, and approximately 210 subjects from the long-term OLE asthma study. You anticipate that 1267 participants will have received ≥ 2 doses of depemokimab and at least 52 weeks of follow-up, and 210 participants from long-term OLE asthma study will have received 4 doses of depemokimab and 2 years of follow-up. Provided no new safety signals emerge, your proposed safety database appears adequate to support filing and review (b) (4) (b) (4)

Meeting Discussion:
No discussion occurred.

Question 5:
Does the Agency agree with the proposed safety analysis strategy for the Integrated Summary of Safety (ISS)?

FDA Response:
Your plan to provide a single ISS with indication-specific sections and subgroups and your overall pooling strategies for the ISS appear reasonable. See Additional Comments below.

Meeting Discussion:
No discussion occurred.

Question 6:
GSK proposes a comprehensive evaluation of safety but does not plan to provide data relating to FDA Medical Queries in the BLA submission. Does the Agency agree?

FDA Response:
We agree that you are not required to conduct your safety evaluation using FDA Medical Queries. However, you will need to submit complete safety data to support a comprehensive safety review of your marketing application. Additionally, you should plan to evaluate all AEs based on logical groupings of preferred terms (PTs) using standard MedDRA queries or other appropriate groupings of PTs. Include in your submission the procedures and rationale used for grouping of PTs. The intent of safety analyses based on grouped PTs is to avoid splitting of PTs so that adverse events are adequately captured (e.g., “ABDOMINAL PAIN, UPPER”, “ABDOMINAL PAIN,

LOWER", "ABDOMINAL PAIN" should be grouped together in the assessment for abdominal pain).

Meeting Discussion:
The Sponsor acknowledged the FDA's feedback and requested confirmation that in addition to the integrated safety summaries of AEs by HLT, SOC, and PT, and AESIs, the planned analysis as described in the Briefing Document are sufficient to evaluate all AEs based on logical groupings of preferred terms (PTs).

Based on the FDA's review of the meeting package and responses, the plan for evaluating AEs is reasonable; the FDA had no additional comments.

Question 7:
Does the Agency agree that the safety data lock point for the submission will be the LSLV date for the rate-limiting study contributing to the integrated safety analysis (expected to be study 217095), acknowledging that earlier data cut-offs are being used in the interim reporting of studies 206785 and 212895?

FDA Response:
Yes, we agree. Your safety data lock plan appears reasonable.

Meeting Discussion:
No discussion occurred.

Question 8:
Does the Agency agree with the proposed integrated efficacy analysis strategy with respect to:

- *The efficacy endpoints that will be included in the integrated analysis* (b) (4)
- *The efficacy endpoints for which subgroup analysis are proposed*
- *The proposal that subgroup statistical analyses are focused on integrated pivotal study data,* (b) (4)

FDA Response:
Yes, we agree. Your proposed integrated efficacy analysis strategy plan appears reasonable.

Meeting Discussion:
No discussion occurred.

Question 9:
Does the Agency consider that the proposed submission package, including partial extrapolation approach, is sufficient to assess the benefit-risk of depemokimab as an

add-on treatment of [redacted] *severe asthma in adolescents (aged 12 to 17 years old)?*

FDA Response:
The efficacy assessment in adolescents will be based upon matching PK/PD parameters to that in adults to support full extrapolation, and given the relatively small number of adolescents enrolled, safety will be partially extrapolated from adults. We consider your proposed partial extrapolation strategy using Bayesian dynamic borrowing to be supportive.

Meeting Discussion:
No discussion occurred.

Question 10:
Does the Agency agree that the evidence submitted has demonstrated that the ADSD and ANSD are fit-for-purpose PRO measures for use as study endpoints to support the depemokimab asthma indication?

FDA Response:
Whether or not the ADSD and ANSD are fit-for-purpose for the proposed context of use will be determined during the review of the BLA. As conveyed in the DDT Qualification Statement (dated March 28, 2019; https://fda.report/media/122726/DDT+COA+006+Qualification+Statement.pdf), the key evidence needed to determine fitness-for-purpose under the proposed context of use are longitudinal measurement properties of the ADSD and ANSD and information to support thresholds for clinically meaningful within-patient changes on the 0 to 10 average scores. That said, we note that the ADSD and ANSD study endpoints are listed as "other endpoints" and do not appear to be controlled for multiplicity. It is therefore unclear how these PRO measures are intended to be used to support your development program. Before commenting further, we ask that you clarify the intended use of the ADSD and ANSD (e.g., exploratory endpoint, labeling claims, etc.).

Meeting Discussion:
In response to the FDA Preliminary Comments, GSK stated that a substantial portfolio of validation work to fulfill the key evidence needs identified in the FDA 2019 qualification statement for ADSD and ANSD has been completed. The results of this work indicate that the longitudinal measurement properties are robust and the estimation of clinically meaningful thresholds for the measures has been successful. GSK believes that this evidence demonstrates that the ADSD and ANSD are fit-for-purpose PROs that can provide important data for the benefit-risk assessment, and important information for prescribing clinicians and patients. [redacted] GSK would welcome any further feedback from the Agency on the validation work completed and

the suitability of these measures to inform benefit-risk assessment for the SWIFT studies.

GSK also inquired if these PRO measures would be considered ready for secondary endpoint elevation in the hierarchy.

The FDA thanked the Sponsor for developing new PROs for asthma and noted that if they intend to seek labeling claims for the PROs, the endpoints should be controlled for multiplicity. However, the determination of whether a PRO measure is considered fit-for-purpose to support regulatory decision making and labeling is made at the time of BLA review. Therefore, the FDA cannot advise whether or not to elevate the ADSD and/or ANSD to secondary endpoints; GSK must make the decision based on their confidence in the quantitative and qualitative data obtained thus far. If the Sponsor chooses to include the ADSD and/or ANSD endpoints in the hierarchical control strategy, the FDA recommends submitting an amended protocol and/or SAP for review and comment. In addition, it may be beneficial to request a Type C, COA-focused meeting for the FDA to provide preliminary review and comments on the proposed PRO endpoints because these discussions typically occur earlier than at the pre-BLA stage. Given that the data lock point is soon approaching, GSK noted that it might be difficult to submit an amended protocol and inquired if a revised SAP would be sufficient. FDA stated that this plan was reasonable from the statistical perspective.

GSK stated that the psychometric analyses were conducted using data from the SWIFT 1 trial and asked whether FDA had any concerns if the same data is used for both the psychometric analyses and efficacy analyses. FDA stated that once agreement is reached on the positioning of the PRO-based endpoints in the testing hierarchy, FDA will conduct their review of the psychometric analyses and provide comments on the approaches GSK used for the analyses.

Post-Meeting Comments:
Ideally, psychometric evaluation of the proposed COAs should be conducted prior to the initiation of the phase 3 trials. Given that the phase 3 trials are ongoing, quantitative measurement properties of the ADSD and ANSD will be a review issue.

Question 11:
On 01 September 2023, GSK was notified by (b) (4) that it was investigating some suspected GCP violations in several clinical studies involving a (b) (4) SMO. On 17 October 2023, (b) (4) confirmed GCP violations in several clinical studies involving the (b) (4) SMO, (b) (4) The studies included depemokimab asthma studies 213744 and 212895 (b) (4). GSK is proposing that all data, including safety data, from participants enrolled at sites overseen by (b) (4) are excluded from the primary analyses, and included in supplementary analyses of these studies.

Does the Agency agree?

FDA Response:
We agree with your plan to exclude all data from the (b) (4) sites from your primary analyses and to provide supplementary analyses with these sites included.

Meeting Discussion:
No discussion occurred.

Question 12:
Does the Agency agree with the proposed data standards and SDTM/ADaM data package for completed, ongoing, and integrated clinical studies?

FDA Response:
In general, your proposed approach to data standardization for clinical and nonclinical studies as described in the draft Study Data Standardization Plan appears to be acceptable. Note FDA no longer supports use of WHO Drug Dictionary (WHO-DD) as of March 15, 2019. Your data submission will need to align with the current supported medical terminology dictionary (i.e., WHO Drug Global Version-B3 Format) as outlined in the FDA Data Standards Catalog (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-catalog).

Meeting Discussion:
No discussion occurred.

Question 13:
For studies and integrated data packages included in the BLA, GSK plans to provide the software programs used in development of outputs and analyses dataset (ADaM) in non-executable format. The software program details will be included in the Analyses Data Reviewers Guide Section 7 and codes will be shared in ASCII file format. Does the Agency agree with this approach?

FDA Response:
Your plan to provide all programs used to create ADaM data sets and your analyses to support determination of efficacy or safety appears reasonable. Please include any Macros used. We may have additional requests during the BLA review.

Meeting Discussion:
No discussion occurred.

Question 14:
Does the Agency agree with GSK's proposal regarding the inclusion of electronic case report forms (eCRFs)?

FDA Response:
No, we do not agree. You need to submit narratives and eCRFs for all serious adverse events (SAEs) (which includes deaths), AESIs, adverse events leading to permanent

treatment discontinuation, and patients who experienced treatment emergent pregnancy for all 9 studies (205722, 214099, 206713, 213744, 206785, 212895, 208021, 217095 and 218079). We remind you that narratives and CRFs for patents meeting the aforementioned criteria should be submitted regardless of attribution to the investigational drug product or treatment arm.

We have the following additional comments that pertain to narrative format and content:

a) The subject's unique identifier should be used as the title of the document and the file name. These names are used to assist reviewers in finding the CRF for an individual.

b) Narrative summaries should provide a complete synthesis of available relevant clinical data and an informed discussion of the case. This summary should include, but not limited to, the patient's medical history, medical/surgical management of the event, the outcome, study treatment and enrollment disposition, and the event's potential relationship to the investigatory treatment.

c) Narratives should be comprehensive enough for the reader to be able to reach a reasonable conclusion regarding the subject and the adverse event.

d) For subjects who had more than one related event requiring a narrative (whether in the same trial or in the core study and an extension), present a single narrative rather than separate narratives for the various events. Unrelated events that are separated in time may be submitted as separate narratives.

Meeting Discussion:
No discussion occurred.

Question 15:
Does the Division agree with GSK's proposal for providing information for the Office of Scientific Investigations?

FDA Response:
Yes, we agree with your plan to submit clinical study-level information and participant-level data line listings by clinical site for all asthma (b) (4) phase 3 studies (206713, 213744, (b) (4)). Submitting a summary-level clinical site dataset is not yet mandatory. The main purpose of submitting the summary level clinical site dataset is to facilitate the timely identification of sites for inspection and to support regulatory review of your marketing application.

Meeting Discussion:
No discussion occurred.

Question 16:

Meeting Discussion:
No discussion occurred.

Question 17:
Financial Disclosure information will be provided in accordance with 21 CFR 54.2 (e) for these (b) (4) pivotal studies: 206713, 213744, (b) (4). Does the Agency agree?

FDA Response:
Yes, we agree.

Meeting Discussion:
No discussion occurred.

Additional Comments Pertaining to Data Submission:

1. The ISS dataset should include flags to permit evaluation of the relevant analysis populations as outlined in the ISS SAP and CSR.
2. The data definition file (i.e., Define.xml) should include adequate detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. Submit corresponding Define.pdf files in addition to the Define.xml files.
3. For each study, provide a flag in the ADAE dataset or a separate dataset that maps preferred terms to the adverse events of special interest (AESIs).
4. Laboratory data from all visits (i.e., unscheduled and scheduled visits, central and local laboratory) should be included in outlier analyses. Include a flag or variable in the ADLB data set that identifies central vs. local lab data. Laboratory

[2] Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees, December 2004 (https://www.fda.gov/media/72397/download)

results obtained during unscheduled study visits that occur outside of a protocol-specified visit window should be included in the data for the nearest protocol-specified visit or analyzed per the Statistical Analysis Plan.

5. For liver-related safety analysis, we recommend you incorporate and summarize investigator reports and PTs related to potential hepatic injury in addition to the pre-specified liver biochemistry elevations. Refer to FDA guidance for industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation (available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation) and relevant sections from Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH) (available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-specifications-submitting-clinical-trial-data-sets-treatment-noncirrhotic-nonalcoholic) for additional guidance on liver safety data submission.

Meeting Discussion to Comment 4 and 5:

GSK clarified that there are no local labs data collected in this program and any local lab values that may be mentioned in SAE free-text narratives are not systematically collected as numeric values in the eCRF. Hence local lab data will not be included in SDTM LB and ADaM ADLB datasets or in summaries and analyses of numeric lab values. Central lab data from unscheduled visits will be included in outlier summaries of worst-case post-baseline changes.

FDA recommend all data to be collected, including local labs data, to look for outlier analysis, and fully evaluate potential safety signals.

GSK stated for liver-safety analyses, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced in addition to a scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin. Any hepatobiliary laboratory abnormality data will be included in ADLIVER (Analysis Dataset Liver Enzymes) dataset. System Organ Classes (SOC) and Preferred Terms (PTs) will be consolidated in a comprehensive Adverse Event (AE) summary output. GSK asked if this is acceptable.

The FDA responded that GSK should follow the referenced guidance in their liver safety data submission to the best of their ability but given what is known about the product safety profile and lack of a hepatotoxic signal, the current approach appears reasonable.

GSK inquired if they could submit proposal regarding the inclusion of local laboratory data in their database and analyses.

GSK's Post Meeting Comments:

In a post-meeting email correspondence dated December 17, 2023, the Sponsor provided the following additional information about labs:

We appreciate the clarification provided by the FDA at the December 11, 2023 pre-BLA meeting for depemokimab [IND146742] regarding the inclusion of local laboratory data in our database and analyses.

We want to confirm that central laboratory test results obtained during unscheduled study visits outside of a protocol-specified visit window are included in the data for the nearest protocol-specified visit and analyzed per the Statistical Analysis Plan. Additionally, we confirm that any outliers in the summary of change from baseline analyses are duly reported, taking into consideration maximum postbaseline central laboratory values.

Our current analytical focus primarily centers on the frequent and systematically collected central laboratory data (≤ every 8 weeks through week 28 and then ≤ 12 weeks through end of study, for both the asthma and chronic rhinosinusitis with nasal polyp studies). Potentially clinically important outlier values that occur during the course of the studies may trigger additional unscheduled central testing (e.g. protocolized for liver enzyme elevations). Unscheduled, local laboratory testing could be obtained at the discretion of the PI or e.g. during hospitalisation, to aid in the diagnosis and management of specific, treatment emergent AEs at an individual patient level; however, those data are not captured systematically. Local laboratory data provided by the study sites during reporting of Serious Adverse Events (SAEs) are an integral part of SAE report narrative.

While we understand the rationale behind the request for local lab data in datasets, at the time of initiation of our development program our analytical strategy was focused on central laboratory data. Incorporating local lab data in the reporting of these mature Phase 3 studies (e.g. asthma database locks pending Q1 and Q2 2024) is problematical given the absence of a prospective systematic collection process for local lab data and may introduce complexities that could compromise the reliability in the interpretation of our results.

Therefore, GSK propose to not include any local laboratory data in the SDTM LB or ADaM ADLB datasets in our planned BLA and believe our Integrated Safety Summary strategy and submission of SAE narratives is appropriate. Does the agency agree?

Our commitment is to collaborate transparently to meet regulatory standards and contribute to the advancement of sound scientific practices. Considering the importance of local lab data these recommendations will be considered for future development programs.

FDA Response:
This plan is reasonable.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 24, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[3]

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

[3] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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 guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[4] 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.[5]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

[4] https://www.fda.gov/media/86340/download
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[8]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[9]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[10] and the guidance for industry, *Identification of Manufacturing Establishments in*

[10] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[11]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[12]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[12] https://www.fda.gov/media/85061/download

information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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/

JI HYUN LAROSE
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