CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217806Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 139721

MEETING MINUTES

Eli Lilly and Company
Attention: Ingrid Hensley, PhD
Senior Director, Global Regulatory Affairs-North America
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Hensley:

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

We also refer to the teleconference between representatives of your firm and the FDA on August 11, 2022. The purpose of the meeting was to gain agreement with the Division on the proposed New Drug Application to support the filing and review of tirzepatide as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with obesity, or overweight with weight-related comorbidities.

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, call, Martin White, M.S., Regulatory Project Manager, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Director
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 11, 2022, 10:00 AM - 11:00 AM ET
Meeting Location:	Teleconference
Application Number:	IND 139721
Product Name:	tirzepatide for injection
Indication:	as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m^2 or greater (obesity) or • 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes).
Sponsor Name:	Eli Lilly and Company
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	John Sharretts, MD
Meeting Recorder:	Martin White, MS

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Lisa Yanoff, MD, Deputy Director

Division of Diabetes, Lipid Disorders, and Obesity
John Sharretts, MD, Director
Laura Higginbotham, MD, MPH, Clinical Team Lead
Raymond Soccio, MD, Clinical Reviewer
Julie Golden, MD, Clinical Reviewer
Ovidiu Galescu, MD, Clinical Reviewer
Mary Roberts, MD, Clinical Reviewer
Ginger Winston, MD, Clinical Reviewer

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology
Calvin (Lee) Elmore, PhD, Deputy Director
Patricia Brundage, PhD, Nonclinical Team Lead

Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology
Edwin Chow, PhD, Clinical Pharmacology Team Leader
Harisudhan Thanukrishnan, PhD, Clinical Pharmacology Reviewer
Leslie Kenna, PhD, Clinical Pharmacology Reviewer

Office of Biometrics II, Division of Biometrics II
Feng Li, PhD, Team Leader
Mengjie Zheng, PhD, Reviewer

Office of Scientific Investigations, Division of Clinical Compliance Evaluation
Ling Yang, M.D., Ph.D., FAAFP, Reviewer

Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (OMEPRM), Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Idalia E. Rychlik, PharmD, DMEPA 1, Team Leader
Sarah K. Vee, PharmD, DMEPA 1, Safety Evaluator

Office of Surveillance and Epidemiology (OSE), Office of Pharmacovigilance and Epidemiology (OPE), Division of Pharmacovigilance 1 (DPV 1)
Daniel Woronow, MD, FACC, DPV 1 CardioRenal Metabolic Team, Team Leader
Christine Chamberlain, PharmD, DPV 1, Safety Evaluator
Melissa Murfin, DPV 1, PharmD, PA-C, Safety Evaluator
Ali Niak, MD, Medical Officer

OSE, OPE, Division Risk Management
Yasmeen.Abou-Sayed, PharmD, Team Leader
Ingrid Chapman, PharmD, BCPS, Reviewer
Courtney Cunningham, PhamD, Reviewer

Office of Pharmaceutical Quality
Ted Carver, PhD, CMC reviewer
Nowrin Kakon, MLS (ASCP), Regulatory Business Process Manager

OND, Office of Regulatory Operations, Division of Regulatory Operations for Diabetes, Lipid Disorders, and Obesity
Martin White, MS, Senior Regulatory Project Manager
Elizabeth Solomon, MSHS, RAC-Drugs, Chief, Project Management Staff

SPONSOR ATTENDEES
Ruth M. Belin MD, MPH - Associate VP, GRA-NA
Jennie Walgren, PhD - Associate VP, GRA-NA
Ingrid Hensley, PhD - Sr. Director, GRA-NA
Allison Wolf, MS - Sr. Director, GRA-CMC

James Sagen - Advisor, GRA-Drug Delivery/Digital Health
Juli Curtis, MBA - Associate VP, GRA-Drug Delivery/Digital Health
Geoff Swope, PhD - Sr. Principal Engineer, Delivery Devices & Connected Solutions
Nadia Ahmad, MD, MPH - Sr. Medical Director, Tirzepatide Development
Mathijs C. Bunck, MD, PhD -Associate VP, Medical Tirzepatide Obesity & NILEX
Adam Stefanski, MD - Executive Medical Director, Tirzepatide Development
Martin Bohm, DO - Sr. Medical Director, Global Patient Safety
Anthony Beardsworth, MD - Associate VP, Global Patient Safety
Shuyu Zhang, MS - Director, Statistics
Xiaosu Ma, PhD - Director, Global PK/PD Pharmacometrics
Lukasz Biernat, MD - Associate VP, Exploratory Medicine & Pharmacology
Amy Chesterfield, MS - Sr. Director, COO Tirzepatide
James Croaning, MBA - Head of Global Brand Development, Tirzepatide
Jeffrey Emmick, MD, PhD - VP, Diabetes Product Development
Carlos Garner, PhD – VP, Global Regulatory Affairs
Jingyi Liu, PhD - Associate VP, Statistics
Rona Wang, MD, MBA – Executive Director, GRA-NA
Laura Fernandez Lando, MD, Associate VP, Medical Tirzepatide Development

1.0 BACKGROUND

The purpose of this meeting is to discuss the proposed New Drug Application (NDA) to support the filing and review of tirzepatide as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management (CWM) in adults with obesity, or overweight and weight-related comorbidities.

Tirzepatide is a 39-amino acid synthetic peptide dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist (RA). Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety. IND 139721 was submitted on October 30, 2019.

At the Type C meeting on June 26, 2019, Lilly proposed, and FDA aligned that, four phase 3 registration studies (SURMOUNT-1, -2, -3, and -4) in participants with obesity or overweight were adequate to support an NDA for the proposed indication.

However, according to the Sponsor, they intend to establish substantial evidence of effectiveness for tirzepatide in CWM (b) (4)

FDA sent Preliminary Comments to Eli Lilly and Company on August 9, 2022.

2.0 DISCUSSION

Question 1: Does FDA agree that the proposed submission package, including chemistry, manufacturing and controls (CMC), device, nonclinical, clinical pharmacology, and clinical data, is adequate to support review of tirzepatide for a New Drug Application (NDA) with the following indication?

TRADENAME (tirzepatide) is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m^2 or greater (obesity) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes mellitus)

Sponsor Background: At the Type C meeting on 26 June 2019, Lilly proposed, and FDA aligned that, four Phase 3 registration studies (SURMOUNT-1, -2, -3, and -4) in participants with obesity or overweight were adequate to support an NDA for the proposed indication. (b) (4) These studies provide substantial evidence of effectiveness for tirzepatide as a CWM treatment. In light of the serious health risks of obesity and the magnitude of weight reduction observed with tirzepatide across these studies, a timelier filing and review of tirzepatide for the indication of CWM in adults with obesity, or overweight and weight-related comorbidities, is warranted.

FDA Response to Question 1:

Clinical: No, we do not agree with the proposed NDA submission package. We recommend completion of the SURMOUNT-2 trial prior to NDA submission. An NDA package that included SURMOUNT-1 and SURMOUNT-2, presuming positive results and adequate conduct, would be acceptable to support filing of an application. We agree that submission of SURMOUNT-3 and SURMOUNT-4 would not be necessary for inclusion in your initial NDA package. Provide an update on the expected completion date of SURMOUNT-2.

(b) (4)

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Therefore, we recommend completion of SURMOUNT-2 as the clearest path to show substantial evidence of effectiveness for tirzepatide in CWM; inclusion of SURMOUNT-1 and SURMOUNT-2 would constitute two adequate and well-controlled trials and an adequate safety database.

Clinical Pharmacology: The clinical pharmacology data as outlined in the pre-NDA submission package seems adequate to support the review of NDA for the proposed indication.

Nonclinical: Nonclinical agrees that the data submitted under NDA 215866 is adequate to support review of tirzepatide for a NDA for the proposed indication.

CMC: Refer to response to Question 2.

Discussion: The Sponsor presented a summary of their response provided to the Agency on August 10, 2022 (see attached), (b) (4)

The Division continued to recommend two AWCTs of sufficient duration (at least 1 year at maintenance dose) to capture concepts of initial weight loss, weight maintenance, and long-term treatment adherence to support filing of an NDA for the indication of CWM. The Division did not agree that this application would represent a situation in which the Agency should exercise regulatory flexibility (b) (4)

(b) (4)

(b) (4)

(b) (4)

Therefore, the Division recommended the Sponsor submit an NDA package that included SURMOUNT-1 and SURMOUNT-2 as two AWCTs. The Sponsor stated that SURMOUNT-2 would be finished in Q3 2023 but reiterated its position that SURMOUNT-2 is not expected to significantly add to the understanding of tirzepatide's effect on weight in patients with T2D (b) (4)

The Sponsor reiterated the seriousness of obesity and public health urgency as reasons to exercise regulatory flexibility to give earlier access to tirzepatide to the American public. The Division informed the Sponsor that the meeting responses had been discussed with the Office of New Drugs Policy to see if there were other options for regulatory flexibility, and none were identified.

(b) (4)

The Division suggested potential options that could expedite the review of a tirzepatide NDA application while including results from the completed SURMOUNT-2 trial. Fast Track Designation (FTD) would allow for rolling review, and would not require demonstration of substantial improvement over available therapy, only potential to address unmet medical need. An initial NDA submission, with a clinical package that includes SURMOUNT-1, could be followed by later submission of SURMOUNT-2 data once the trial is complete. While the review clock would not start until the package is complete, the Division expressed openness to granting a Priority Review timeline under this scenario.

The Sponsor plans to request FTD and consider the options presented by the Division. (b) (4)

(b) (4)

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Question 2: Does the FDA agree with the proposed approach to cross-reference NDA 215866 for CMC content and agree with the strategy proposed for planned manufacturing supplements to NDA 215866?

Sponsor Background: The CMC elements of the drug substance, drug product, and device are consistent across the T2DM indication and the CWM indication, including the same 6 dose strengths. Tirzepatide NDA 215866 for T2DM contains approved CMC content (Modules 2.3 and 3) that meets FDA and ICH requirements. For the CWM NDA, Lilly intends to provide CMC content via a cross reference to NDA 215866 to avoid duplication of content across 2 applications. (b) (4)

FDA Response to Question 2: **Your proposal to provide CMC content via a cross-reference to NDA 215866, to avoid duplication of content across two applications, is generally acceptable.** (b) (4)

Note that CMC evaluation of your proposed CWM NDA will be based on CMC information provided at the time of NDA submission and/or cross-referenced information that we have previously reviewed under approved NDA 215866 (b) (4)

Post-approval, you have the option of submitting appropriate post-marketing supplements to support any manufacturing changes pertaining to the CWM NDA.

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 3: Does FDA agree that the application for a chronic weight management indication with tirzepatide can be submitted with a unique proprietary name?

Sponsor Background: Lilly proposes to seek an indication for tirzepatide as a CWM treatment under a non-NME original NDA (Type 10) with a unique proprietary name. Using dual proprietary names for tirzepatide when treating T2DM and CWM represent an approach that is consistent with other incretin mimetics (e.g., liraglutide and semaglutide) that have been safely marketed for both indications. Lilly recently submitted a proprietary name request that includes supporting information for why having a dual proprietary name is the most effective approach to communicate product information. For example, dual proprietary names may minimize patient perceived

stigma associated with therapy. Lilly plans to propose distinctive packaging for the tirzepatide CWM product. The cartons and container labels will have multiple, prominent elements to differentiate the tirzepatide CWM product line from the tirzepatide T2DM product (MOUNJARO).

FDA Response to Question 3: **Developing and introducing a unique proprietary name for the CWM indication is your business decision. The acceptability of your proposed proprietary name for a CWM indication for tirzepatide will be a review issue.**

> ***Discussion:*** At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 4a: Is FDA supportive of the strategy of the additional prominent labeling elements, in conjunction with the unique tirzepatide CWM proprietary name to appropriately differentiate, by way of multiple distinguishing carton and container labeling features, the CWM multi-strength product line from the MOUNJARO (tirzepatide T2DM product) cartons and container labels?

FDA Response to Question 4a: **Your proposed strategy sounds reasonable; however, the proposed labeling will be a review issue.**

Question 4b: Is FDA supportive of the strategy of the additional prominent labeling elements, in conjunction with the unique tirzepatide CWM proprietary name to distinguish the CWM product line from MOUNJARO (tirzepatide T2DM product) such that confirmation of differentiation of carton and container labeling between the two product lines through a human factors study is neither warranted nor required?

FDA Response to Question 4b: **We note your intention to cross-reference all device information to NDA 215866. You indicate that the device constituent part is functionally identical to the device constituent part of already approved products Trulicity (BLA 125469) and Mounjaro (NDA 215866). You also indicate that the user characteristics are same or similar as that of NDA 215866 Mounjaro (T2DM), and therefore, the use-related risks are identical. However, you have not submitted a comprehensive risk analysis for our review and concurrence for your proposed product for the indication of CWM.**

We also note your plans to conduct a human factors (HF) differentiation study to compare the tirzepatide for CWM and T2DM indication products and that the study results will not be submitted to the NDA but maintained in the usability/device history file. We agree that you do not need to submit the results of your differentiation study in your marketing application and that this information can be added to your design history file.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on the aforementioned information and data, you should determine whether you need to submit the results of a HF validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that an HF validation study does not need to be submitted for your product, submit your risk analysis, comparative analyses, and justification for not submitting the HF validation study to the Agency for review under the IND. We will notify you if we concur with your determination. You may choose to refer to our draft guidance for industry and FDA staff titled, *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*[1] for the content of a HF validation study protocol submission.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on HF procedures to follow can be found in the following guidance documents:

- **Applying Human Factors and Usability Engineering to Medical Devices**
- **Guidance on Safety Considerations for Product Design to Minimize Medication Errors**
- **Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.**

Note that we published two draft guidance documents that, while not yet finalized, you may choose to refer to in order to understand our current thinking and our approach to HF for combination products, product design, and labeling:

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

- **Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development**

- **Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications.**

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 5: Does FDA agree with the planned analysis and presentation of clinical efficacy in the SCE and that no ISE is warranted?

Sponsor Background: Key results from the clinical efficacy data package will be discussed in the SCE (Module 2.7.3). Section 11.1 describes the analyses planned to be conducted for presentation in the SCE, including the strategy for the statistical analyses. Lilly does not plan to submit a separate Integrated Summary of Efficacy (Module 5.3.5.3) as all relevant data will be presented within the SCE. Lilly does not plan to pool any studies for efficacy assessments. Since each study was adequately powered to assess weight reduction with tirzepatide, it is not necessary to conduct pooled analyses. Additionally, pooling of the data across these studies would not be informative due to interstudy differences, including treatment durations, comparators, study populations, and background therapies. Key efficacy results are provided in Section 10.3.

FDA Response to Question 5: **See the response to Question 1. Although we agree, in principle, that an ISE is not required, we disagree with the overall proposed clinical package intended to demonstrate substantial evidence of effectiveness.**

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 6: Does FDA agree with the
- safety populations,
- analysis sets,
- AESIs,
- special safety topics, and
- analyses proposed for the SCS and ISS?

Sponsor Background: Clinically relevant results from the clinical safety data package will be discussed in the Summary of Clinical Safety (Module 2.7.4). Section 11.2 describes the analyses planned with clinical safety data collected in the tirzepatide CWM and T2DM programs for presentation in the Summary of Clinical Safety (Module 2.7.4) and the Integrated Summary of Safety (Module 5.3.5.3), including the strategy for

pooling studies and statistical methods. Four safety analysis datasets are planned, and the details are provided in Section 11.2. Key safety results are provided in Section 10.4.

FDA Response to Question 6: **We defer discussion of the clinical safety data package until there is agreement on the clinical efficacy package. See the response to Question 1. A safety database that includes complete results from SURMOUNT-1 and SURMOUNT-2 could be considered adequate.**

> ***Discussion:*** At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 7: Does FDA agree with the criteria for identifying participant narratives that will be included in the submission?
Sponsor Background: Lilly plans to provide participant narratives consistent with prior FDA agreement in January 2020. Narratives will be submitted for deaths, SAEs, pregnancies, and permanent discontinuation of study treatment due to AEs in accordance with the ICH E3 Guideline for Industry: Structure and Content of Clinical Study Reports (Section 12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events) (ICH 1996).

FDA Response to Question 7: **We agree with the plan for patient narratives.**

> ***Discussion:*** At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 8: Does FDA agree that the information, as outlined in the Table of Contents in Appendix 4, including the use of cross-references to the tirzepatide T2DM NDA 215866, constitutes a complete application for the new, non-NME NDA for tirzepatide as a chronic weight management treatment?

Sponsor Background: A draft Table of Contents for the overall NDA submission is provided in Appendix 4. The submission Table of Contents contains information reflecting the location of CSRs; quality, nonclinical, and clinical summary documents; draft labeling; and other standard submission components.

FDA Response to Question 8: **We defer discussion of the Table of Contents until there is agreement on the trials included in the clinical package. See the response to Question 1.**

> ***Discussion:*** At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 9: Does FDA agree with the proposed plan for submission of the electronic datasets and statistical programs?

Sponsor Background: For studies supporting the CWM NDA, datasets used for statistical analysis will be provided to the FDA in both SDTM and ADaM formats for each individual study and in the ADaM format only for the integrated Phase 2 and Phase 3 safety database. The SDTM CRT package will include the SDTM datasets in SAS XPORT format (.xpt), SDTM-annotated CRF, Define.xml, and a Reviewer's Guide. The ADaM CRT package will include ADaM datasets in SAS XPORT format (.xpt), Define.xml, and a Reviewer's Guide. The only analysis programs Lilly intends to submit will be those used to produce any statistical analyses supporting label claims for clinical efficacy.

FDA Response to Question 9: **No, we do not agree. You plan to submit only analysis programs that support label claims for clinical efficacy. You should submit all programs used for generating the ADaM datasets and tables and figures in the clinical study report.**

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 10: Does FDA agree with the plan to provide summary-level clinical site data and datasets (b) (4) for SURMOUNT-1 (Study GPHK) for CDER inspection planning (b) (4)

Sponsor Background: Per the FDA Draft Guidance, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (FDA 2018), Lilly intends to provide all site- and study-level data and summary-level clinical site data from the Study GPHK (SURMOUNT-1). (b) (4)

FDA Response to Question 10: **The Office of Scientific Investigation requests that Bioresearch Monitoring (BIMO) data from all major studies to support efficacy and safety evaluations in the application be provided. Per FDA's "Bioresearch Monitoring Technical Conformance Guide-Technical Specifications Document," BIMO data from ALL major (pivotal) studies to support safety and efficacy in the application, including studies with different treatment indications should be provided. In addition to SURMOUNT-1, BIMO data from SURMOUNT-2 should be provided if clinical data generated from the study also support the safety and efficacy evaluation of the proposed indication.**

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 11: Does FDA agree with the plan to provide financial disclosure information within the proposed new, non-NME NDA only for SURMOUNT-1 (Study GPHK) and to incorporate financial disclosure information for SURPASS 1-5 by cross-reference?

Sponsor Background: In compliance with 21 CFR 54, Financial Disclosure by Clinical Investigators, Lilly plans to provide financial disclosures for investigators who participated in Study GPHK (SURMOUNT-1). Financial disclosures for other covered studies that reside in the tirzepatide T2DM NDA 215866 will be incorporated by cross-reference.

FDA Response to Question 11: **We agree that this plan is reasonable.**

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

Question 12: Does FDA agree with the plan for the 4-month safety update?

Sponsor Background: Approximately 16 studies are expected to be ongoing at the time of the data cutoff for the 4-month safety update. Lilly intends to provide in the 4-month safety update blinded safety data for deaths, SAEs, discontinuation of study drug due to AE, and pregnancies that occurred in blinded studies, and unblinded data will be provided for open-label studies. Line listings and CIOMS reports will also be provided for deaths, SAEs, and pregnancies. In the event of a priority review, Lilly proposes to submit the safety update no later than 3 months into the NDA review.

FDA Response to Question 12: **We agree that this plan is reasonable.**

Discussion: At this time, the Sponsor accepted FDA's response. No discussion occurred.

3.0 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*.[2] 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.[3]

4.0 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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

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

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

5.0 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*.[6]

6.0 ISSUES REQUIRING FURTHER DISCUSSION

There were several issues that require further discussion. See discussion sections above.

7.0 ACTION ITEMS

[6] https://www.fda.gov/media/85061/download

There were no action items at this time.

8.0 ATTACHMENTS AND HANDOUTS

Eli Lilly and Company's response to FDA's Preliminary Comments was sent to the FDA on August 10, 2022.

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/s/

JOHN M SHARRETTS
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PIND 139721

MEETING MINUTES

Eli Lilly and Company
Attention: Peter McDonald Morrow
U.S. Regulatory Advisor
Lilly Corporate Center
Drop Code 2543
Indianapolis IN 46285

Dear Mr. Marrow:

Please refer to your Pre-Investigational New Drug Application (PIND) file for tirzepatide for injection.

We also refer to the meeting between representatives of your firm and the FDA on June 26, 2019. The purpose of the meeting was to discuss the phase 3 development program for tirzepatide.

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

If you have any questions, call Martin White, M.S., Regulatory Project Manager at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Advice

Meeting Date and Time: June 26, 2019; 10:00 AM – 11:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 139721
Product Name: tirzepatide for injection

Indication: an adjunct to diet and exercise for chronic weight management in adult patients with an initial body mass index (BMI) of:

- 30 kg/m2 or greater (obese) or
- 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes mellitus)

Sponsor: Eli Lilly and Company

Meeting Chair: William Chong, M.D.
Meeting Recorder: Martin White, M.S.

FDA ATTENDEES

Office of the Center Director
Robert Temple, MD, Deputy Director for Clinical Science

Division of Metabolism and Endocrinology Products (DMEP), ODE II
Lisa B. Yanoff MD, (Acting) Director
William Chong, MD, (Acting) Deputy Director
John Sharretts, MD, Clinical Team Leader
Laura Higginbotham, MD, Clinical Reviewer
Jeffery Quinn, PhD, Non-Clinical Reviewer
Michael White, PhD, Regulator Project Manager
Martin White, MS, Regulatory Project Manager

Office of Biostatistics; Division of Biometrics II
Feng Li, PhD, (Acting) Statistical Team Leader
Jiwei He, PhD, Statistical Reviewer

Office of Clinical Pharmacology, Office of Translational Sciences
Sury Sista, PhD, Clinical Pharmacology Reviewer, (Acting) Team Leader

Clinical Outcome Assessments (COAs)
Selina Daniels, PharmD, COA Team Leader
Jing (Julia) Ju, PhD, Primary Reviewer

Office of Combination Products
Maryam Mokhtarzadeh, MD Combination Products Reviewer

SPONSOR ATTENDEES
Angelyn Bethel, M.D., Sr. Medical Advisor
Mathijs Bunck, M.D., Ph.D., Sr. Medical Director
James Croaning, M.B.A., Global Brand Development Leader
Jenny Chien, Ph.D., Research Fellow - PK/PD
Jeffrey Emmick, M.D., Ph.D., Vice President, Diabetes Product Development
Salvador Garcia, M.D., Sr. Director, Global Regulatory Affairs – North America
Peter Morrow, M.S., Advisor, Global Regulatory Affairs – North America
Kelly Perfield, Ph.D., Advisor, Global Regulatory Affairs
Danise Subramaniam, Ph.D., Sr. Director, Global Regulatory Affairs - North America
D. Bradley Woodward, M.D., Platform Team Leader – Incretins
Shanthi Sethuraman, Ph.D., Sr. Director, Statistics

1.0 BACKGROUND

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptors. Its structure is based on the GIP sequence and includes a C20 fatty di-acid moiety that prolongs the duration of action. It is administered once weekly (QW) by subcutaneous (SC) injection.

The sponsor submitted a breakthrough therapy designation preliminary advice request on July 18, 2018, and FDA discussed this via teleconference with the sponsor on August 22, 2018. On August 28, 2018, the sponsor submitted a type B meeting request, to discuss the phase 3 development of tirzepatide and other topics regarding plans for a future marking application. However, on September 11, 2018, the sponsor requested withdrawal of the meeting request because of business reasons.

In the current meeting request submitted March 19, 2019, the sponsor would like to discuss the phase 3 development program for tirzepatide.

FDA sent Preliminary Comments to Eli Lilly on June 20, 2019.

2.0 DISCUSSION

FDA Preliminary Comment:

There is insufficient information on the dose-response relationship between tirzepatide and heart rate increases in overweight or obese, non-diabetic patients to properly inform dose selection before initiation of phase 3 trials. We recommend that you conduct an additional phase 2 study to better inform dose selection and titration scheme. Therefore, we have re-categorized your meeting from an End of Phase 2 to an Advice meeting. Given our recommendation to conduct additional phase 2 investigation, we consider our responses to your questions regarding the phase 3 program as preliminary.

We note the differential dose-response relationship for heart rate increase between healthy subjects and patients with diabetes in your diabetes clinical program. Although the effect on heart rate in overweight/obese patients has not been studied, we are concerned that the magnitude of heart rate changes in obese patients might be comparable to those in healthy subjects predicted from population PK modeling (predicted mean change from baseline of 13.5 and 15.6 bpm with the 10 mg and 15 mg dose, respectively). The smaller heart rate changes observed in patients with diabetes could be due to other factors that are not relevant to obese, non-diabetic patients, such as loss of autonomic regulation or use of concomitant medications (e.g., beta-blockers).

We strongly encourage you to conduct a phase 2 dose-finding trial to further characterize change in heart rate, as well as general tolerability, in overweight/obese, non-diabetic patients. We recommend inclusion of the 5 mg, 10 mg, and 15 mg doses. We also recommend that you incorporate an ambulatory blood pressure monitoring (ABPM) study in a subset of patients, to rigorously assess the effect of tirzepatide on heart rate and blood pressure, as part of this trial. In the substudy, you might consider stratification by use of rate-controlling concomitant medications, or exclusion of patients on these medications, in order to observe the full heart rate effect. Additionally, we suggest use of the titration scheme proposed for phase 3, as this may mitigate heart rate increase or improve tolerability. We expect that results of this phase 2 study will better inform critical elements of your phase 3 weight management program, including dose selection and whether additional safety monitoring is required.

> ***Discussion:*** The sponsor agreed with the Division's concerns about the unknown effect of tirzepatide on heart rate in overweight/obese patients, and that it would be advisable to obtain additional data. The sponsor proposed to collect heart rate data in an initial phase 3 study that would achieve the equivalent aim to the Division's proposed phase 2 study. Their proposal is listed below:
>
> - Treatment groups will be placebo and tirzepatide 5, 10, and 15 mg using the planned registration titration scheme.

- An Assessment Committee will evaluate heart rate and blood pressure results at multiple time points.
  - Heart rate (vital signs, ECG) will be assessed at steady state for each dose group (16, 24, and 32 weeks for 5, 10, and 15 mg, respectively)
  - ABPM will be included in a subset of patients at 32 weeks
- Provisionally, sample size will be estimated primarily based on heart rate using 4 bpm as a non-inferiority margin, which would translate to approximately 150 subjects per group.
- Co-primary endpoint is mean percent change in body weight baseline and at least 5% body weight reduction, both at 72 weeks.
- We would await the results of the 32-week interim analysis described above before initiating the remaining Phase 3 studies. In addition, the remaining studies would be modified as appropriate based on these findings.

The Division reiterated the concerns outlined in the preliminary comments. The Division requested to review the protocol prior to trial initiation but agreed that 32 weeks was a reasonable timepoint to conduct the ABPM, to allow for 12 weeks of treatment at steady-state. In addition, the Division recommended that the sponsor add an earlier heart rate assessment at 8-12 weeks to ensure observation of the peak heart rate effect. The Division pointed out that the sponsor would need to provide details on how they plan to maintain blinding after the interim 32-week ABPM analysis. The Division also questioned if the data was going to be submitted to the Agency for review prior to the sponsor completing the study. The sponsor provided two options for the Division to consider regarding the initial phase 3 data:

- Option 1: FDA would agree to stopping rules, and data would not be submitted prior to completing the phase 3 study.
- Option 2: FDA would agree to stopping rules, and data would be submitted prior to completing the phase 3 study.

The Division also stated that the proposed study should have sufficient monitoring, stopping rules, and should be adequately powered.

The Division stated that the sponsor's initial plan appears reasonable pending review of the full protocol. The sponsor will submit an outline of the protocol, including proposed stopping rules, for the Division's feedback prior to submission of the full trial protocol.

2.1 Nonclinical

<u>Question 1:</u> Does FDA agree that the nonclinical studies that will support the type 2 diabetes mellitus (T2DM) indication will be sufficient to support the

registration of tirzepatide for chronic weight management in adults who are obese overweight?

FDA Response to Question 1: *Yes, the nonclinical program conducted in support of the T2DM indication would also be sufficient to support NDA submission for the obese/overweight indication.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

2.2 Clinical Pharmacology

Question 2: ***Does FDA agree that the clinical pharmacology program for the type 2 diabetes mellitus (T2DM) indication, including the drug-drug interaction (DDI) evaluation (see note below), when supplemented by a single gastric emptying study (see Question 3 below), is adequate to support the planned chronic weight management indication?***

FDA Response to Question 2: *Yes, the proposed clinical pharmacology program is adequate to support the filing of an NDA. Whether further information is needed for registration will be a review issue.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 3: ***Does FDA agree with the design of the proposed clinical pharmacology study to evaluate the gastric emptying effect of tirzepatide in patients without type 2 diabetes mellitus (T2DM) who are obese/overweight versus patients with T2DM who are obese/overweight (Note: In both cases, obese/overweight means body mass index [BMI] ≥27 kg/m^2)?***

FDA Response to Question 3: *Yes, the design of proposed clinical pharmacology study GPHU is reasonable.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 4: ***Does FDA agree that the proposed population pharmacokinetics (popPK) analysis plan, involving samples from approximately 1250 subjects in 3 of the 4 pivotal phase 3 studies in participants who are obese/overweight, together with available data from all phase 1 to phase 3 studies from the type 2 diabetes mellitus (T2DM) program, is sufficient for investigating the effects of prespecified covariates on the pharmacokinetics (PK) and pharmacodynamics (PD) of tirzepatide in participants who are obese/overweight?***

FDA Response to Question 4: *In general, the proposed population PK and PK/PD approach is acceptable. For NDA submission, submit the data, NONMEM control streams, and scripts used to generate the final population PK model, PK/PD model,*

*and associated plots. Data files should be submitted as SAS transport files with *.xpt format (e.g. Data1.xpt) and other files be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_out.txt).*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

2.1. Clinical

Question 5: ***Assuming that the data are supportive, does FDA agree that the proposed phase 3 weight management program is adequate to support a New Drug Application (NDA) for the proposed indication below, considering the number and type of studies and total patient exposures for safety evaluation?***

Intended indication: "TRADENAME® (tirzepatide) is a dual agonist of GIP (glucose-dependent insulinotropic peptide) and GLP-1 (glucagon-like peptide 1) receptors and is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of:

- ***30 kg/m2 or greater (obese) or***
- ***27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or T2DM)"***

FDA Response to Question 5: *Final labeling and the adequacy of the clinical data to support an indication will be review issues. In general, the number and type of studies appear adequate for your phase 3 weight management program. We may have additional comments upon review of the full protocols.*

To achieve the recommended total patient exposure in the clinical safety database, it is acceptable to supplement your phase 3 weight management database with data from the T2DM clinical program if patients are on the same dose as intended for the weight management program for a one-year maintenance period beyond the titration phase.

Discussion: The sponsor proposed supplementing safety data from their phase 3 weight management program with patient exposures from the phase 3 diabetic program. The Division stated that the heart rate effect observed in the initial weight management study would help determine if this plan is reasonable. If the heart rate effect in overweight/obese patients is similar to the effect observed in diabetes patients, the Division would be willing to accept exposures from the open-label, high CV risk trial in diabetes where minimum treatment duration is 18 months. The Division will consider whether placebo exposures from shorter-term trials of 40 weeks are acceptable. To inform this decision, the Division recommended that the sponsor provide a table that outlines which T2DM studies

the sponsor plans to use for supplementation. The table should include sample size, trial duration, and patient exposure based on patient years.

Question 6: ***Does FDA agree with the dose levels*** (b) (4) ***including dose escalation schemes, proposed for phase 3 registration trials to support the chronic weight management indication for tirzepatide?***

FDA Response to Question 6: *No, we do not agree with the proposed dose levels. Refer to the preliminary comment for our recommendations.* (b) (4)

More generally, we recommend that you consider how your analytic approach influences the apparent efficacy of your selected doses as well as dose dependence. The phase 2 results you provided for body weight (kg) change from baseline are based on a mixed model for repeated measures (MMRM) model that assumes data is missing at random (MAR) and treats the behavior of missing data for those patients who are off-treatment to be the same as that of observed data for those patients who are on-treatment in the same treatment arm. The apparent larger treatment effect for the 15 mg group is highly dependent on this implausible assumption, considering the high rate of treatment discontinuation and dropout in this group, and therefore we question whether the 15 mg dose is in fact more efficacious than the 10 mg dose. Refer to Question 12 for our recommendations on the statistical analysis of efficacy in weight loss. It may be reasonable to include the 15 mg dose based on the efficacy data as it is plausible that the proposed titration scheme might mitigate the problem of intolerance and drug discontinuation. However, you should consider the dose selection and expected treatment effect in the context of all safety findings, including elevated heart rate.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 7: ***Does FDA agree that the planned safety assessments are adequate to support registration of tirzepatide in weight management, considering especially the following?***

- ***body composition assessment with dual-energy X-ray absorptiometry (DEXA)***
- ***depression and suicidality risk evaluation***
- ***abuse potential assessment***

FDA Response to Question 7: *Your proposed safety assessments for body composition, depression and suicidality risk, and abuse potential appear reasonable. You should ensure that the 240 participants selected for DEXA scan are representative of the enrolled trial population. We will consult the Controlled Substance Staff to address whether your plan to not perform a dedicated abuse potential study in animals or humans is sufficient, and we will follow-up with a post-meeting comment or general advice letter.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 8: ***Does FDA agree that the evaluation of the listed adverse events of special interest (AESI) are adequate to support registration of tirzepatide in weight management?***

The AESI assessments below will be included in the phase 3 clinical trial program for chronic weight management (see Appendix 2 for SURMOUNT-1 (Study GPHK) Draft Protocol):

- ***Severe hypoglycemia***
- ***Pancreatitis (adjudicated)***
- ***Major adverse cardiovascular events (adjudicated)***
- ***Treatment-emergent supraventricular arrhythmias and cardiac conduction disorders***
- ***C-Cell hyperplasia and thyroid malignancies***
- ***Acute renal events***
- ***Hepatobiliary disorders***
- ***Severe gastrointestinal events***
- ***Depression/suicidal ideation or behavior***
- ***Allergic/hypersensitivity reactions. Includes injection site reactions and antidrug antibody formation.***
- ***Diabetic retinopathy complications****
- ***Metabolic acidosis, including diabetic ketoacidosis****
- ***Amputation/peripheral revascularization****

**** will be collected as AESI only in the clinical trials which will recruit participants with T2DM who are obese/overweight***

FDA Response to Question 8: *Your proposed adverse events of special interest (AESI) appear reasonable. We also suggest inclusion of the Vasculitis SMQ under the assessment of hypersensitivity reactions.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 9: ***Does FDA agree with the design of the 4 individual phase 3 studies, considering especially key design aspects such as primary and***

secondary endpoints, inclusion and exclusion criteria, background lifestyle modification, treatment duration, and safety monitoring?

FDA Response to Question 9: *We generally agree with the design of the four individual phase 3 studies, which appear consistent with the weight management guidance. Please see the additional comments below for several of our preliminary recommendations. We may have additional comments upon review of the full protocols.*

Additional FDA Comments on the Proposed Phase 3 Trials

1. *We agree with your selected primary endpoints, except as noted below for SURMOUNT-4.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

2. *We recommend that you include metabolic parameters such as lipids, fasting glucose, insulin, blood pressure, pulse, waist circumference, and HbA1c (in diabetic patients) as key secondary endpoints. From both a clinical and regulatory standpoint, improvements in these metabolic parameters would support more convincingly any weight loss benefit detected in your primary endpoint than secondary endpoints that re-analyze or re-present weight loss data.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

3. *The treatment duration of SURMOUNT-1, SURMOUNT-2, and SURMOUNT-3 (20-week titration and 52-week maintenance periods) appears adequate.*

   Discussion: The sponsor sought clarification on the recommended treatment duration for weight management trials contained in FDA's weight management guidance. The Division clarified its expectation that patients should be at maintenance dose for a 52-week period that does not include the titration phase.

4. *We do not agree with your proposal* (b) (4) *The primary analysis should be performed based on the full analysis set using an intent-to-treat (ITT) approach with inclusion of all data until the last study visit.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

5. *We do not agree* [redacted] (b) (4) *Safety analyses should be conducted using an ITT approach on the full safety analysis set.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

6. *Given the historically high degree of missing data in weight management trials, we encourage you to employ efforts to minimize withdrawals and to contact withdrawn patients for body weight measurement at the 72-week primary efficacy timepoint. These retrieved dropouts will provide more accurate body weight data and can inform imputation methods.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

SURMOUNT-1: Non-diabetics with 2-year extension for patients with pre-diabetes

7. *It is unclear whether only patients with normoglycemia or whether both patients with normoglycemia and pre-diabetes are contributing to the primary 72-week endpoint. We encourage you to include data from both patient populations to ensure results are generalizable to a broader patient population.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

SURMOUNT-2: Diabetics

8. *We recommend that you stratify enrollment by baseline HbA1c in addition to baseline antihyperglycemic medication.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

SURMOUNT-4: Weight loss maintenance

9. *We question the* [redacted] (b) (4) *It is unclear that this endpoint is clinically meaningful.*

   Discussion: The sponsor accepted FDA's response, no discussion occurred.

10. *We recommend that you include the proportion of subjects who lose ≥5% of baseline body weight as a co-primary endpoint.*

    Discussion: The Division clarified that the ≥5% weight loss endpoint was intended to reflect weight reduction from baseline weight at screening and not weight reduction from baseline weight at the time of randomized withdrawal. The Division indicated its willingness to consider other endpoints that would reflect whether patients regain weight after drug discontinuation or whether the drug has a carryover effect. The Division is also willing to consider the position of the endpoints within the testing hierarchy. The sponsor will submit the SURMOUNT-4 protocol for Division feedback prior to trial initiation.

11. *You should ensure that the maintenance period of your lead-in phase is long enough to demonstrate plateauing of weight loss prior to drug withdrawal. You might consider a 46-week lead-in (20 weeks titration, 26 weeks maintenance) similar to your Phase 2 T2DM trial. We agree with the proposed 52-week duration following the lead-in phase. To minimize the impact of missing data on your primary endpoint, we recommend that an interim follow-up body weight measurement, e.g. at month 6 post-lead-in, be included as either the primary or a key secondary endpoint. You might also consider a time-to-failure analysis, although the definition of "failure" in this context would warrant additional discussion.*

    Discussion: The sponsor agreed that drug should be withdrawn at the time of maximum weight loss and will reassess after preliminary data from earlier phase 3 studies is reviewed.

Post-Meeting Comment on Question 9, Comments 10 and 11:

We are concerned that a high incidence of dropout at Week 88 could impact the interpretability of your primary endpoint in SURMOUNT-4. We encourage you to consider whether including an additional secondary or co-primary endpoint or assessing the primary endpoint at an earlier timepoint would mitigate the impact of missing data. The Division is willing to consider other study designs or endpoints and is willing to provide feedback on the protocol prior to trial initiation.

12. *It is unclear if all patients who tolerate their assigned dose will enter the randomized withdrawal phase (as stated in the protocol synopsis) or only those patients who tolerate and also achieve ≥5% weight loss (as stated in Table 7.4 primary objective). For this trial of weight loss maintenance, we recommend that all patients who tolerate drug enter the randomized*

withdrawal phase regardless of weight loss success. This approach will more closely mimic drug use in a clinical setting.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

13. *It is unclear if enrollment of patients with significant weight loss (>5 kg within 3 months) pre-screening is permitted in SURMOUNT-4. Inclusion of these patients may confound attribution of weight loss results and interpretation of the treatment effect. We recommend their exclusion.*

    Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 10: ***Does FDA agree*** (b) (4) [redacted]

FDA Response to Question 10: *Your question* (b) (4) [redacted] *is premature. However, we question the clinical value of* (b) (4) [redacted] (b) (4) [redacted]

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 11: ***Does FDA agree with the proposed approach for evaluating cardiovascular risk in the tirzepatide weight management clinical program, and in particular, that it is not necessary to pre-specify a statistically-defined risk margin to assess cardiovascular risk in weight management trials?***

FDA Response to Question 11: *Please refer to our Preliminary Comment. It is premature to discuss evaluation of cardiovascular risk in your phase 3 clinical program. As stated previously, we have concerns with the degree of heart rate increase predicted in your PK/PD population models, which predicts an increase of 6.4 to 7.4 bpm in diabetic patients and 13.5 to 15.6 bpm in healthy subjects.*

Additional data on the dose-response relationship of tirzepatide and heart rate in overweight or obese, non-diabetic patients will inform whether reliance on adjudicated cardiovascular events from the T2DM program is sufficient or whether independent assessment in an obese, non-diabetic population is more appropriate.

Discussion: The Division reiterated that whether it is appropriate to rely on CV risk assessment from the T2DM program will depend on results of the initial phase 3 study in overweight/obese patients. If the degree of heart rate increase observed in obese, non-diabetic patients is similar to that observed in diabetic patients, it may be reasonable to consider supportive evidence from adjudicated cardiovascular events in the T2DM program. However, if a different dose-heart rate relationship is observed, the Division may require independent assessment of CV risk in an obese population.

2.3 Statistics

Question 12: Does FDA agree with the proposed primary efficacy analysis plan, (b) (4) "treatment-regimen estimand" for a sensitivity analysis?

FDA Response to Question 12:

1. We do not agree with your proposed primary efficacy analysis (b) (4) Your primary analysis should account for missing data in the primary endpoint in a fashion consistent with what the measurement would have been, had it been measured. We prefer the proposed sensitivity analysis based on "treatment regimen" estimand as the primary analysis.
2. Missing values of body weight at the endpoint visit for patients who prematurely discontinue the study treatment should be imputed from the observed data in the patients in the same treatment group who prematurely discontinue the study treatment but have the measurement for the endpoint. This should apply to both the use of analysis of covariance (ANCOVA) model for change in body weight from baseline and the use of logistic regression model for categorical endpoints. Alternatively, for analyses of categorical endpoints, patients with missing values at the endpoint visit can be considered as non-responders. Methods for handling missing data need to be pre-specified.

3. You propose [redacted] (b) (4) We do not agree with this approach. The primary analysis population should be the full analysis set (FAS), defined as data obtained during the treatment period from the mITT population, regardless of adherence to study drug.
4. Considering the expected high dropout rate in these trials, it is important to make continued efforts to measure endpoints on all subjects, even those who may have discontinued protocol treatment, so as to minimize missing data.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

2.4 Patient-Reported Outcomes, Target Product Profile

Question 13a: ***Does FDA agree that pending appropriate validation and subject to multiplicity adjustment,*** [redacted] (b) (4)

FDA Response to Question 13a: [redacted] (b) (4) *In general, we are open to the assessment of physical function (e.g., SF-36v2) to inform benefit of weight management treatment.* [redacted] (b) (4)

We generally do not recommend evaluating measurement properties and determining within-patient meaningful change thresholds in a phase 3 clinical trial, given that the instrument may not perform well and may not detect a treatment effect if there is one. However, we acknowledge that some measurement properties for SF-36v2 in overweight and obese patients have been reported in the literature. We are open to the option of confirming the measurement properties of SF-36v2 in one of the trials using blinded data. On the other hand, we would like to remind you using phase 3 trial data to determine within-patient meaningful change thresholds will prohibit you from pre-specifying the thresholds to define responders in the responder analysis. Please note that a responder analysis is not required for demonstrating treatment efficacy. Please provide your rationale for determining the within-patient meaningful change score for each phase 3 clinical trial in which data for the instruments are collected.

For any COA that you propose as a pre-specified alpha-controlled efficacy endpoint intended to be fit-for-purpose to support regulatory decision-making and labeling claims, we recommend that you provide the following for Agency review and comment prior to initiating your phase 3 trial:

1. *Conceptual framework of the instrument;*

2. *Evidence of content validity (e.g., qualitative research with expert clinicians) obtained for this specific context of use;*
3. *Exact copy of the instrument as it will be administered during the clinical trial (e.g., electronic screen shots) and any training materials and user manuals;*
4. *Proposed scoring algorithm(s) with rationale for any weighting of items or response options in the domain scoring and corresponding information on how the instrument's scores will be analyzed as part of an endpoint;*
5. *Plans for, and results from, evaluation of the psychometric properties and performance of the instrument (i.e., reliability, validity, and ability to detect change) after content validity has been established;*
6. *Pre-specified plans for handling missing data;*
7. *A priori threshold representing clinically meaningful within-patient improvement in the instrument's scores.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

***Question 13b:* Does FDA agree with the use of the Impact of Weight on Quality of Life (IWQOL)-Lite Clinical Trials Version, including the Physical Function composite, in the validation of the SF-36v2 acute form Physical Functioning domain?**

FDA Response to Question 13b: *We are open to your proposal to use IWQOL-Lite Physical Function composite as an anchor measure for the psychometric evaluation of SF-36v2. We recommend that you provide more details on how it will be used as an anchor. We further recommend that you provide your plan for the psychometric analysis of SF-36v2, including the anchors (e.g., PGIS) for use to determine the within-patient meaningful change thresholds, for our review.*

Discussion: The sponsor accepted FDA's response, no discussion occurred.

Question 14: What comments does FDA have (b) (4)

(b) (4)

FDA Response to Question 14: *Final labeling will be a review issue.* (b) (4) [redacted] *. Please refer to our response to Question 10.*

(b) (4) [redacted]

Discussion: The sponsor sought clarification on the Division's rationale for inclusion of a stopping criteria in labeling of approved weight management products that instructs patients to discontinue weight loss drugs for lack of efficacy after a specified time (12 or 16 weeks). The Division clarified its position that because decrease in body weight is a surrogate for clinical benefit, such as decreased risk of cardiovascular disease and metabolic comorbidities, a lack of drug efficacy alters the benefit-risk equation. The Division stated that the specific language contained in any label would be a review issue. In general, the Division will provide guidance on the specific components of any stopping criteria on a case-by-case basis.

Additional Clinical Pharmacology Comment:

1. The sponsor clarified to the Division that data from the proposed new initial Phase 3 study will be included in the proposed population pharmacokinetics (popPK) analysis plan.

3.0 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]

4.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards.

[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
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[4] https://www.fda.gov/media/88173/download

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[9]

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

6.0 PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

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[7] https://www.fda.gov/media/88173/download
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/media/109533/download

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide protocol outline for lead-in phase 3 study.	Sponsor	N/A
Submit a proposal to leverage safety or efficacy data from the diabetes development program, including total patient exposure and specific data to be used.	Sponsor	N/A

9.0 ATTACHMENTS AND HANDOUTS

Eli Lilly's Response to FDA's Preliminary Comments sent to the FDA on June 25, 2019.

2 Page(s) 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/

JOHN M SHARRETTS
07/25/2019 04:27:17 PM
John Sharretts signing for William Chong