

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215866Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 128801

MEETING MINUTES

Eli Lilly and Company
Attention: John Kaiser, Pharm.D., R.Ph.
Director, Global Regulatory Affairs – North America, Diabetes
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Kaiser:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tirzepatide (LY3298176) for injection.

We also refer to the teleconference between representatives of Eli Lilly and the FDA on June 24, 2021. The purpose of the meeting was to gain agreement with the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) that the proposed new drug application (NDA) submission provides a complete application for tirzepatide as an adjunct treatment to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

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 Lindsey Kelly, Regulatory Project Manager at 301-837-7654.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics
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: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 24, 2021, 1-2 pm
Meeting Location: WebEx

Application Number: IND 128801
Product Name: tirzepatide (LY3298176) for injection
Indication: adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM)

Sponsor Name: Eli Lilly and Company
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Patrick Archdeacon, M.D., Associate Director for Therapeutics
Meeting Recorder: Lindsey Kelly, PharmD, Regulatory Project Manager

FDA ATTENDEES

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

Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Patrick Archdeacon, M.D., Associate Director for Therapeutics
Frank Pucino, Pharm.D., M.P.H., Primary Reviewer

Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology
Federica Basso, PhD, Nonclinical Team Lead (Acting)

Office of Biostatistics (OB), Division of Biometrics II
Yun Wang, Ph.D., Team Leader

Office of Clinical Pharmacology (OCP), Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
S.W. Johnny Lau, Ph.D., Primary Reviewer

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Julie Van der Waag, M.P.H., Director, Project Management Staff

Lindsey Kelly, Pharm.D., Regulatory Project Manager

Office of Pharmaceutical Quality

Ee-Sunn Chia, Ph.D, Division Director, Drug Product

Muthukumar Ramaswamy, Ph.D., Team Lead, Drug Product

Paresma Patel, Ph.D., Branch Chief, Drug Substance

Raymond Frankenwich, Ph.D., Primary Reviewer, Drug Substance

Office of Pharmaceutical Manufacturing and Assessment

Vidya Pai, Ph.D., Branch Chief, Manufacturing

Kshitij Patkar, Ph.D., Primary Reviewer, Manufacturing

Valerie Huse, Ph.D., Primary Reviewer, Microbiology

Office of Surveillance and Epidemiology

Ariane O. Conrad, Pharm.D., Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)

Neil Vora, Project Manager

Office of Scientific Investigations, Division of Clinical Compliance Evaluation

Cynthia Kleppinger, MD, Senior Medical Officer

Office of New Drugs, Division of Cardiology and Nephrology

B. Nhi Beasley, Pharm.D., Associate Director of Biomedical Informatics

Office of the Commissioner/Office of Clinical Policy and Programs/Office of Combination Products

Maryam Mokhtarzadeh, M.D., Senior Medical Officer

SPONSOR ATTENDEES

- John J. Kaiser, Pharm.D., Director, Global Regulatory Affairs – North America
- Jennie Walgren, Ph.D., Senior Director, Global Regulatory Affairs – North America
- Ruth Belin, M.D., Sr. Director, Global Regulatory Affairs – North America
- Linda Kelly, Manager, Global Regulatory Affairs – North America
- Allison Wolf, M.S., Principal Research Scientist, Global Regulatory Affairs – CMC
- Laura Fernandez Lando, M.D., Sr. Medical Director, Diabetes Product Development
- Sheryl Allen, M.D., M.S., Medical Director, Diabetes Product Development
- Anthony Beardsworth, M.D., Sr Director, Global Patient Safety
- Govinda Weerakkody, Ph.D., Senior Research Advisor, Statistics
- Xuewei Cui, Ph.D., Principal Research Scientist, Statistics
- Natalie Martinez, Manager, Statistics

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- Corina Loghin, M.D., Medical Advisory, Clinical Pharmacology
- Shweta Urva, Ph.D., Sr. Research Scientist, PK/PD
- Laronda Morford, Ph.D., Sr. Research Advisor, Toxicology
- Jeffrey Emmick, M.D., Ph.D., Vice President, Diabetes Product Development
- James P Croaning, M.B.A., Global Brand Development Leader, Tirzepatide
- Paul Owens, Ph.D., Senior Advisor, Tirzepatide Project Management

1.0 BACKGROUND

Tirzepatide for injection (also referred to as LY3298176) is a 39-amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. The product is being investigated under IND 128801 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. (b) (4)



Eli Lilly and Company (Lilly) intends to submit NDA 215866 in September of 2021, to gain approval for the use of tirzepatide as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Lilly formally notified FDA on May 24, 2021, that it is Lilly's intent to use a Priority Review Voucher for this application. A total of 19 Phase 1, 2, and 3 studies will be submitted in support of the tirzepatide NDA for the adult T2DM indication. The planned submission data cutoff date for the NDA is June 4, 2021.

A type C meeting was held between Lilly and FDA on August 27, 2020, to discuss the analysis plans and other various administrative topics supporting the NDA. The submission has been planned in accordance with the Agency's comments and agreements from that meeting.

Lilly has requested this Type B meeting to gain agreement with the DDLO that the proposed NDA submission provides a complete application for tirzepatide as an adjunct treatment to diet and exercise to improve glycemic control in adults with T2DM.

FDA sent Preliminary Comments to Eli Lilly on June 22, 2021.

2.0 DISCUSSION

2.1. Overview of Chemistry, Manufacturing, and Control

Question 1: Does FDA agree that the proposed organization of Module 3 is suitable for review?

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FDA Response to Question 1:

(b) (4)

We agree that the proposed organization of Module 3 is suitable for review according to the Table of Contents provided in Appendix 3.

Discussion Question 1:

No discussion occurred.

Question 2: Due to travel restrictions, are there additional actions Lilly can take to facilitate the use of alternative tools for any needed prior approval inspections, as appropriate, to assist the agency in ensuring the manufacturing of tirzepatide meets applicable FDA requirements?

FDA Response to Question 2:

Upon submission, should a pre-approval inspection be needed, the Agency would be in communication with the facility and/or sponsor to make requisite requests and/or arrangements.

FDA is utilizing alternative approaches to inspections, where possible, to mitigate the need of inspections during the COVID-19 pandemic. The alternative tools described in FDA's guidance for industry, *Manufacturing, Supply Chain, and Drug and Biological Inspections During COVID-19 Public Health Emergency Questions and Answers*¹, are used to facilitate remote assessments of facilities if an inspection cannot be conducted. As noted in the FDA guidance for industry, *Remote Interactive Evaluations of Drug Manufacturing and Bioresearch Monitoring Facilities During the COVID-19 Public Health Emergency*, the FDA will not accept requests from applicants or facilities for FDA to perform remote interactive evaluations. Such decisions depend on many factors and information not always known to applicants or facilities. FDA will use existing risk management methods and related tools to determine when to request a facility's participation in a remote evaluation.

For more information, please see the FDA guidances related to COVID 19².

¹ We update guidances periodically. 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/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>

Please confirm on your Form 356h that all facilities are ready for inspection at the time of NDA submission.

Discussion Question 2:

No discussion occurred.

2.2. Overview of the Nonclinical Program

Question 3: Does FDA agree that the nonclinical data package is sufficient to support review of the tirzepatide NDA?

FDA Response to Question 3:

Yes. We agree that the scope of the nonclinical information described in the pre-NDA briefing document (pharmacology, safety pharmacology, general toxicity in rats and monkeys, genotoxicity, developmental and reproductive toxicity, and carcinogenicity in mice and rats) should be sufficient to support review of the tirzepatide NDA. However, additional nonclinical studies may be required if the formulation changes in purity, composition, or degradant profile or if there are unexpected results in the clinical or nonclinical studies that merit further nonclinical investigation. The adequacy of the nonclinical data remains a review issue.

Chronic toxicity of tirzepatide was assessed in 6-month toxicity studies in rats and monkeys. As a peptide of < 40 amino acids, tirzepatide is considered a drug and is subject to safety evaluation in accordance with the recommendations outlined in ICH M3(R2) *Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*. ICH M3(R2) recommends a duration of 9 months for non-rodent studies to support the safety of chronic dosing in humans. Your rationale for conducting chronic studies in non-rodents of 6-months in duration to support chronic clinical dosing of tirzepatide should be included in the NDA submission.

Discussion Question 3:

No discussion occurred.

2.3. Overview of the Clinical Pharmacology Program

Question 4: Does FDA agree that the presented clinical pharmacology package is sufficient to support review of the tirzepatide NDA?

FDA Response to Question 4:

In Section 7 of the Pre-NDA Briefing Document, you described the following:

- 3 studies for the Biopharmaceutics Package, namely Studies GPHI, GPGS, and GPGE

- 7 studies for the Clinical Pharmacology Package, namely Studies GPGR, GPGA, GPGG, GPGQ, GPHX, GPGT, and GPGC

In general, the presented Biopharmaceutics Package and Clinical Pharmacology Package appear sufficient to support filing of the tirzepatide NDA. However, we recommend that you address the following in the Clinical Pharmacology section of NDA 215866:

- Justification for the doses and dosing regimen used in the registration trials to support your marketing application. Identify individuals who may require dose modifications in support of the proposed dose and administration.
- Exposure-response relationships for efficacy, safety and biomarkers.
- Discuss the effect of immunogenicity on tirzepatide pharmacokinetics, pharmacodynamics, efficacy, and safety.
- Discuss the potential of tirzepatide to prolong the QT interval of electrocardiogram.
- Discuss the effect of age, sex, race, and ethnicity on tirzepatide clinical pharmacology.
- Discuss the difference in pharmacokinetics between patients with type 2 diabetes mellitus and healthy participants.
- Submit the validation report for the assessment of norgestimate and ethinyl estradiol for Study GPGR in Section 5.3.2.2.

Submit the following for the population pharmacokinetic analysis reports:

- Standard model diagnostic plots.
- Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results. Refer to the pharmacometrics data and models submission guidelines³.

Submit the following information and data to support the population pharmacokinetic analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation.
- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

³<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>

- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to the FDA guidances for industry, *Population Pharmacokinetics and Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*. For pharmacometrics data and models submission guidelines, refer to <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

Submit the PBPK model and validation files. Provide a table summary to link the results in PBPK study report and the corresponded modeling files. Refer to the FDA guidance for industry, *Physiologically Based Pharmacokinetic Analyses — Format and Content*.

Discussion Question 4:

No discussion occurred.

2.4. Overview of Clinical Program

Question 5: Does FDA agree that the clinical data package is sufficient to support review of the tirzepatide NDA?

FDA Response to Question 5:

To support your tirzepatide NDA for the adult T2DM indication, your clinical data package will include two phase 2 trials (GPGB, GPGF), five global phase 3 registration trials (GPGK, GPGL, GPGH, GPGM, GPGL), and two regional Japanese phase 3 trials (GPGO, GPGP). The five phase 3 registration trials will include subjects with both early and long-standing T2DM (including individuals at increased cardiovascular risk), evaluate tirzepatide as monotherapy or as add-on to background antihyperglycemic therapy with 1-3 medications or as add-on to basal insulin, and compare tirzepatide (5, 10, or 15 mg using the same dose escalation regimen) to placebo (GPGK, GPGL), basal insulins (i.e., insulin degludec [GPGH], insulin glargine [GPGL]) or selective GLP-1 receptor agonists (i.e., semaglutide [GPGL]). The primary efficacy endpoint will be change from baseline in hemoglobin A1c (HbA1c) at Weeks 40 (trials GPGK, GPGL, GPGL) or 52 (GPGH, GPGM). Trials GPGB and GPGF will be used to support efficacy, while trials GPGO and GPGP will be used to support safety. Of the 5415 subjects randomized to tirzepatide (4833.1 patient years of exposure) in the nine completed phase 2/3 trials, 2375

subjects received tirzepatide for ≥ 52 weeks, 535 subjects received tirzepatide for ≥ 78 weeks.

The proposed clinical data package is in alignment with the clinical program discussed in previous meeting correspondence and appears to be sufficient to review your NDA submission. Please refer to the FDA Additional Comments below that would facilitate our review.

Discussion Question 5:

No discussion occurred.

2.5. Statistics

Question 6: Does FDA have any feedback regarding the submitted Pinnacle 21 validation report?

FDA Response to Question 6:

In response to FDA Type C meeting written responses (i.e., NDA Logistics Meeting, dated August 27, 2020), you submitted the Pinnacle 21 (P21) validation report for trial GPGK. Based on review of this document and the associated Analysis Dataset Model (ADaM) and Study Data Tabulation Model (SDTM) datasets, we have the following comments/recommendations:

- The Reference Range Upper Limit (LBSTNRHI) values were missing for 26,721 of 121,812 laboratory records for which the Numeric Result/ Finding in Standard Units (LBSTRESN) was populated in the submitted Laboratory Test Results (LB) dataset. The P21 Compliance Summary acknowledges that reference ranges were not available for these lab records. Please ensure that laboratory reference ranges will be provided for affected records where reference ranges are expected.
- Approximately 77 laboratory test results in the LB dataset appeared to be duplicates as they had the same Unique Subject Identifier (USUBJID), Lab Test Short Name (LBTESTCD), Category (LBCAT), Subcategory (LBSCAT), Specimen Type (LBSPEC), Location (LBLOC), Laterality (LBLAT), Method (LBMETHOD), Derived Flag (LBDRVFL), Evaluator (LBEVAL), Visit Number (VISITNUM), Date/Time of Specimen Collection (LBDTC), and Planned Time Point Number (LBTPTNUM). According to the P21 Compliance Summary, retests were performed on the given test and thus there were more than one record given the test and collection date/time. Additionally, two different tests came in with the same start date and mapped to the same Clinical Data Interchange Standards Consortium (CDISC) test. The laboratory datasets (i.e., LB and ADLB) to be submitted with your NDA should be manipulated to avoid double counting of laboratory findings, and the above potential duplicate record issues and how they were handled should be explained.

Discussion Question 6:

No discussion occurred.

2.6. Administrative Topics

Question 7: Does FDA have any preliminary comments on Lilly's plans for post marketing communication of safety information and the plan not to submit a REMS?

FDA Response to Question 7:

Based on your preliminary review of the safety data, you believe that safety risks associated with tirzepatide can be adequately communicated to patients and healthcare professionals through product labeling and therefore do not plan to submit a Risk Evaluation and Mitigation Strategy (REMS). You also plan to review integrated safety data to assess the need for postmarketing studies to further characterize the safety profile of tirzepatide in real-world conditions.

It is premature to determine whether a REMS will be required without reviewing the totality of evidence (safety information/data) submitted to your NDA. However, given the information provided in the briefing document, it appears that risk management strategies beyond the recommended labeling may not be necessary.

Discussion Question 7:

No discussion occurred.

Question 8: Does FDA agree that the planned contents of the NDA constitute a complete application for the proposed indication?

FDA Response to Question 8:

Based on review of the Draft NDA Submission Table of Contents for the T2DM Indication provided in your briefing document, the planned contents of your NDA appear to be sufficient for filing of your application. From a technical perspective (and not content related), most of the sections proposed in the electronic common technical document (eCTD) Table of Contents are acceptable, but we have the following comments/recommendations:

- The Introduction to the Quality Overall Summary should be placed in Section 2.3. The Proposed eCTD Table of Contents for the planned submission contains the Introduction in Section 2.3.1.

- The Appendices to the Quality Overall Summary should be placed in a subsection of 2.3.A.1, (if more than one, 2.3.A.2, 2.3.A.3, etc...). The Proposed eCTD Table of Contents for the planned submission contains the Appendices to the Quality Overall Summary in Section 2.3.A.

Please refer to *The Comprehensive Table of Contents Headings and Hierarchy*⁴ for the comprehensive listing of headings and hierarchy and a section mapping the headings to their respective regulations, and to the FDA Guidance for Industry, *M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use*, (page 12) for more details on each section referred to in our response.

Discussion Question 8:

No discussion occurred.

Question 9: If requested, can FDA comment on specific topics that would be covered in an application orientation meeting, and is there an expected timing of such a meeting?

FDA Response to Question 9:

Should FDA request an application orientation meeting, we would be interested in an overview of Module 5, Section 5.3.5 (Reports of Efficacy and Safety Studies), with an emphasis on orientation to the submitted datasets, key efficacy and safety analysis results, and programs you used for those analyses. Should we request this meeting, it would generally be held within the first 45 days after receipt of the application.

Discussion Question 9:

No discussion occurred.

Question 10: Does FDA agree with the proposed approach to the 120-Day safety update?

FDA Response to Question 10:

You plan to include safety data from 15 clinical trials (b) (4) that will be ongoing at the time of data cutoff for the 120-Day Safety Update (i.e., August 16, 2021). The proposed content and data presentation of the 120-Day Safety Update were discussed and aligned in Type C Written Responses (dated August 27, 2020), (b) (4) and an FDA Advice/Information Request response letter (dated October 23, 2020). Based on an anticipated submission date of September 2021, and the use of a

⁴ See <https://www.fda.gov/media/76444/download>

Priority Review Voucher, you plan to submit the 120-Day Safety Update for your NDA no later than January 2022.

Your proposed approach for submission of the 120-Day Safety Update is reasonable. However, please clarify how you plan to convey relevant/updated safety information (e.g., evolving safety issues identified in the 15 ongoing clinical trials after the data cutoff date which could influence the safety profile, approvability, and labeling of your product) to the Agency in a timely manner.

Additionally, although we acknowledge that the proposed date of the 120-Day Safety Update is in accordance with 21 CFR 314.50 (d)(5)(vi)(b), the updated safety information provides the Agency with the latest safety information to adequately make a risk-benefit assessment and ensures that product labeling will accurately reflect the known risks of your product. Therefore, submission of these data prior to January 2022, if possible, would improve the efficiency of the review. We also request that you provide the associated ADaM datasets in addition to your 120-Day Safety Update report.

Lilly's Response to FDA for Question 10:

Lilly acknowledged FDA's comments and wished to further discuss this topic to clarify the following:

1. Briefly, to update FDA of relevant/updated safety information, Lilly proposes to submit a letter of cross-reference to IND 128801 for any event which qualifies under 21 CFR 312.32(c) (b) (4)
2. Regarding FDA's request for ADaM datasets for the 120-Day Safety Update, Lilly noted that the studies included in the safety update will be ongoing at the time of the data cutoff. Therefore, they proposed to only submit the safety report itself and questioned whether this would be acceptable.

Discussion Question 10:

1. *FDA stated that it would be helpful if these data could be cross-referenced to the NDA eCTD Module 1-1.4.4 (with a hyperlink to the relevant safety information). Additionally, FDA requested up-to-date safety information as it was being generated; Lilly agreed.*
2. *FDA indicated that the review of line listings of adverse events is not an efficient way to evaluate safety. It would be helpful if the ADaM datasets, up to the August 2021, Update data cutoff, were provided. Lilly agreed to provide the 120-Day Safety Update within 90 days of their NDA submission and to provide ADaM datasets, if requested following submission of this report.*

Question 11: Does FDA currently believe that an Advisory Committee meeting will be scheduled for tirzepatide?

FDA Response to Question 11:

The decision on whether to hold an FDA Advisory Committee meeting for your application will be made when it is submitted to the Agency for review. Referral of your application to an Advisory Committee is not anticipated at this time.

Discussion Question 11:

No discussion occurred.

Question 12: Does FDA agree with the standards in Appendix 5 Study Data Standardization Plan?

FDA Response to Question 12:

In your briefing document, you provided an updated Study Data Standardization Plan (SDSP Version 2.0) that includes the final data standards for recently completed phase 3 trials (i.e., GPGK, GPGH, GPGI, and GPGL). You plan to provide final data standards for your ongoing phase 3 trials (i.e., GPGM, GPGO, GPGP) and the pooled Integrated Summary of Safety (ISS) in the final SDSP provided in the NDA.

The proposed SDSP seems reasonable. However, we have the following comments/recommendations:

- On page 137 of 164 of Appendix 5 in your briefing document, you mention using CDISC SEND STDM version 1.4 (nonclinical Study 8392063), which is not in the Data Standards Catalog. Please clarify why SEND 3.1 is from SDTM 1.4 and not from SDTM 1.5.
- For the ongoing phase 3 trials and ISS, we recommend that you use the same most recent versions of terminology standards listed in your SDSP as you plan to use for the completed phase 3 trials (i.e., MedDRA final version 23.1., WHO Drug Global B3 format).
- SEND datasets are required to be submitted at the same time as nonclinical PDF study reports for study types that are modeled in an FDA-supported SEND Implementation Guide (SENDIG) version when submitted for a commercial IND or NDA/BLA. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page (<https://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>), lists the supported SENDIG versions and associated implementation dates. This requirement applies to both GLP and non-GLP study reports. However, if a study is exploratory in nature and the information reported to the FDA is primarily summarized in text without line listings for individual

animals, SEND datasets would not be required. Please refer to Section 8.2.2 of the Study Data Technical Conformance Guide for guidance on when to use a simplified ts.xpt file.

Lilly's Response to FDA for Question 12:

Lilly wished to understand whether FDA had any additional comments to the clarifications below:

1. Briefly, there was a typo regarding CDISC SEND STDM version 1.4. This should have been version 1.5 as FDA noted.
2. Regarding versions of terminology standards, Lilly will use MedDRA 23.1 in the reporting version of the ISS and the ongoing Phase 3 trials which are intended to be included in the NDA (GPGM, GPGO, GPGP).
3. For the ISS, the entire Phase 3 program will use WHODrug Global B3, while the Phase 2 studies used WHODrug Global B2 format. Lilly does not believe the use of B2 format for Phase 2 studies in the coding of concomitant medications impacts the conclusions reached.

Discussion Question 12:

FDA acknowledge the clarifications provided and had no additional comments.

FDA Additional Comments:

Clinical and Statistical Trial Materials requested with your NDA submission:

- 1. As described in your September 30, 2020, Regulatory Response (i.e., Written Responses on the Tirzepatide Analysis Plans and NDA Administrative Topics), you plan to provide a Table of Significant and Notable Patients (TOSNP), grouped by deaths, serious adverse events (SAEs), permanent discontinuation of study treatment due to AEs, and adverse events of special interest (AESI) with a severity rating of severe. The TOSNP for completed studies supporting the NDA will contain hyperlinks to the subject narratives, case report forms (CRFs), Council for International Organizations of Medical Sciences (CIOMS) and adjudication packets. Please note that CRFs include all clinical documents collected regardless of whether you label them as "CRFs" (e.g., MedWatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets etc.).**
- 2. Provide a dataset that contains a list of all subjects for whom you submitted a CRF, narrative, CIOMS, or adjudication package. The dataset**

should contain five variables (i.e., unique subject identifier [USUBJID], CRF, narrative, CIOMS, and adjudication packet) with an indicator flag for whether each item was submitted.

Lilly's Response to FDA Additional Comment 2:

Regarding FDA's request for a dataset in Additional Comment #2, Lilly wished to understand and discuss the scope of this request. Lilly felt that the planned TOSNP would provide the requested information. The TOSNP would include the following:

Phase 2 and Phase 3

- Deaths
- Serious adverse events (SAEs)
- Pregnancies
- Discontinuations from study treatment due to adverse events

Phase 3 Adverse events of special interest (AESI)

- Adjudication confirmed major adverse cardiovascular events (Severe)
- Adjudication confirmed pancreatitis (Severe)
- Amputations/ peripheral revascularizations (Severe)
- Dehydration (Severe)
- Diabetic retinopathy complications (Severe)
- Gastrointestinal adverse events (Severe)
- Hepatobiliary disorders (Severe)
- Hypersensitivity events (Severe)
- Hypoglycemia (Severe)
- Injection site reactions (Severe)
- Major depressive disorders/ suicidal ideation or behavior (Severe)
- Malignancies (Severe)
- Metabolic acidosis (Severe)
- Renal events (Severe)
- Supraventricular arrhythmia/ cardiac conduction disorders (Severe)
- Thyroid malignancy and C-cell hyperplasia (Severe)
- Treatment-emergent anti-drug antibodies associated hypersensitivity/ injection site reactions (Severe)

As previously discussed, Lilly felt that the TOSNP serve as a listing which will contain blue hyperlinks to the subject narratives, CRFs, adjudication packets and CIOMS reports, as applicable. Below is an example:

Table of Significant and Notable Patients: Deaths
All Randomized Population
Studies: GPGB, GPGF, GPGB, GPGI, GPGK, GPGL, GPGM, GPGO, GPGP

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Patient Identifier Link to Narrative	Treatment Assignment	Study Day at Onset*	Preferred Term/ System Organ Class	Link to Safety Report (CIOMS)	Link to CRF Link to Adjudication Packet
(b) (6)	T2P 5mg	272	Acute myocardial infarction/ Cardiac disorders	AR202004006106	T8F-MC- T8F-MC- (b) (6).pdf -adj.pdf

Discussion FDA Additional Comment 2:

FDA agreed that the proposed approach would be acceptable but requested that Lilly also provide clear separate headings and to separate each TOSNP for phase 2 and phase 3.

- 3. Submit all data management plans for the five phase 3 registration trials included in your clinical data package. Cite all amendments for each data management plan, including all manual and programmatic checks.**

Lilly's Response to FDA for Additional Comment 3:

See FDA Comment 17.

Discussion FDA Additional Comment 3:

See FDA Comment 17.

- 4. Include all site monitoring plans for the nine phase 2/3 trials used to support efficacy/safety. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.**

Lilly's Response to FDA for Additional Comment 4:

See FDA Comment 17.

Discussion FDA Additional Comment 4:

See FDA Comment 17.

5. Provide a description of the responsibilities of each academic research organization (ARO) or contract research organization (CRO) used in these nine trials.
6. Provide a copy of all newsletters and all other communications to investigational sites and national coordinators from the groups responsible for the conduct of the nine trials. Please bookmark the communication by date.

Lilly's Response to FDA for Additional Comment 6:

See FDA Comment 17.

Discussion FDA Additional Comment 6:

See FDA Comment 17.

7. Submit all code and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and phase 3 trial clinical study reports. Ensure your tables and figures are footnoted with the name of the code used to create them.

Lilly's Response to FDA for Additional Comment 7:

See FDA Comment 13.

Discussion FDA Additional Comment 7:

See FDA Comment 13.

8. Provide a list of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. If applicable, submit code that was used to create or clean up your analysis datasets.

Lilly's Response to FDA for Additional Comment 8:

Lilly wished to understand the extent of FDA's request. Specifically, is FDA's request focused on the creation of the analysis datasets? It is Lilly's position that this information is contained in the compliance section included in the SDTM/ADaM Reviewer's Guide.

Discussion FDA Additional Comment 8:

FDA expects Lilly's datasets to match the primary source of data in their trials. FDA would like reassurance that the data are reviewable. Submitting the data management plans, Pinnacle 21 reports, and other relevant information would help to assure that the data are suitable for review.

Lilly felt that the data to be submitted would be high quality and stated that the Reviewer's Guide would identify compliance issues and provide a description of the corrective actions taken.

- 9. For the blinded trials, include a dataset that contains all subjects that were unblinded. Include the USUBJID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.**
- 10. The structure of the submitted adjudication dataset (adaj.xpt) is reasonable. However, we recommend that you add one variable to describe the trigger for the event sent for adjudication (i.e., investigator, laboratory result, etc.).**

Lilly's Response to FDA for Additional Comment 10:

Lilly proposed to provide the requested information as a listing, as the requested variable to the adjudication dataset was not included in the database.

Discussion FDA Additional Comment 10:

FDA agreed that this would be acceptable.

- 11. Provide a Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board (IRB) and with adequate informed consent procedures. If you were granted an IRB Waiver during the conduct of these trials because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.**
- 12. Provide a rationale for assuring the applicability of foreign data to the United States (U.S.) population/practice of medicine in the submission for those phase 3 trials conducted primarily outside of the United States (OUS).**

There are two major pieces to applicability of foreign data:

- Are the subjects the same (U.S. versus rest of the world)?**
- Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?**

- 13. For us to be able to reproduce your results, in addition to the datasets, please provide clear and well commented analysis codes that you utilized to produce all your major results for primary and secondary endpoints, and codes you used to derive ADAM datasets for primary and secondary endpoints from SDTM datasets. Also, to improve clarity of your analyses, we recommend that you include a program flow, i.e., a detailed description of your program, in each of your codes. Please include detailed flow charts in the ADRG (analysis data reviewers guide).**

Lilly's Response to FDA for Additional Comments 7 & 13:

Regarding FDA Additional Comment #7, Lilly acknowledged FDA's request but wished to clarify the scope of this request.

1. Briefly, Lilly plans to submit all datasets used to create the analyses found in the main sections of the Summary of Clinical Efficacy, Summary of Clinical Safety, and Phase 3 trial clinical study reports. As the SCE does not contain integrated efficacy data, Lilly noted that the efficacy datasets would be contained in the individual study reports.
2. Lilly stated that there are several hundred tables, figures, and listings (TFLS) contained in the main sections of the SCE, SCS, and CSRs. As per agreement from the Type C Logistics meeting in 2020 (reference to FDA response to Question 11), Lilly intends to only provide the programs used to support labeling claims of clinical efficacy and sensitivity analysis of primary endpoints to explore the impact of missing data on the estimated treatment effect.
3. Regarding FDA Additional Comment #13, Lilly requested clarification for what information should be contained in a detailed flow chart.

Discussion FDA Additional Comments 7 & 13:

1. *FDA agreed that Lilly's proposal to provide programs used to support labeling claims and sensitivity analyses for efficacy would be acceptable. However, it would be helpful for Lilly also to provide the code for programs that involved analytical modeling as predefined in their Program Safety Analysis Plan (PSAP) for their P3 trials and SCS (e.g., MMRM on log-transformed data, ANCOVA, time-to-event analyses). To minimize the volume of code, FDA suggested that Lilly submit just the main safety analysis and not every variation of the main analysis.*
2. *Lilly agreed to provide a list of what they plan to submit in their TFLS for safety, which the FDA would then review and provide comment.*

3. *To replicate analyses, Lilly was asked to provide documentation for analysis codes and programs used for deriving analysis datasets and performing the analyses for primary and secondary endpoints to support labeling claims. FDA stated that it would be helpful to have a flowchart displaying the flow from raw datasets to derived analysis datasets and what derived analysis datasets are used for primary and secondary analyses. Lilly agreed to provide a detailed flowchart.*

14. Submit all versions of the protocol and statistical analysis plan for the seven studies used to support efficacy in your clinical data package and the date when changes were implemented. Include a Summary of Changes for each version.

15. Provide a table which includes the following information for the nine phase 2/3 trials:

- **Dates of first patient and last patient visits**
- **Date of data lock**
- **Dates of all versions of the SAP (with a hyperlink to each SAP)**
- **Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).**

16. Submit all charters for committees involved in conducting five phase 3 registration studies (e.g., Data and Safety Monitoring Board [DSMB], Steering Committee, etc.).

17. Submit all meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

Lilly's Response to FDA for Additional Comments 3, 4, 6, & 17:

Lilly wished to understand and discuss (i) the intent and (ii) the scope of this request. Lilly felt that the requested information in these comments is typically reviewed as part of a sponsor inspection and not normally provided in the Electronic Common Technical Document (eCTD). Lilly asked to discuss the possibility of providing the requested information through another mechanism (i.e., FDA Box). Lilly proposed to not include the Japan studies (i.e., GPGO and GPGP) in the requests made in these Additional Comments as translation would be required.

Discussion FDA Additional Comments 3, 4, 6, & 17:

FDA acknowledged that for remote regulatory assessments performed by the Office of Regulatory Affairs, there has been limited use of an FDA drop box. However, for an efficient review of the application, the requested data should be submitted to the NDA (i.e., not to an FDA drop box). Submitting the requested documents, such as the newsletters and meeting minutes, provides insight into any issues that occurred during the conduct of each trial. Such documents have been requested from other sponsors and submitted with their application via eCTD.

FDA is requesting Lilly's data management plans to better understand the handling of study data generated during the course of the trial; how it was managed, analyzed, and stored, as well as access, sharing and oversight of the data. FDA stated that submission of at least the final version would be informative.

FDA acknowledged that the requested information in these comments is typically reviewed as part of a sponsor inspection. They are being requested for the review team to gain additional knowledge regarding the implementation of the trials. If an inspection were to occur, the documents would be requested onsite for compliance needs and used for any enforcement actions.

FDA agreed that Lilly's proposal to not submit the additional documents requested above in Comments 3, 4, 6, & 17 for studies conducted in Japan (GPGO and GPGP) is acceptable.

- 18. Provide an annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1 (e.g., Section 1.6.3, with correspondence regarding meetings).**

Combination Product:**19. Combination product manufacturing**

Please note that Part 3 combination products are subject to 21 CFR Part 4 Current Good Manufacturing Practice Requirements for Combination Products⁵. Related guidance is available in the FDA guidance for industry, Current Good Manufacturing Practice Requirements for Combination Products.

⁵ <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-product>

20. eCTD Location of combination product information

For information on the location of device related information, see Section 5 of the agency eCTD Technical Conformance Guide: Technical Specifications Document: *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.⁶

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA and sponsor agreed that a complete application will be provided in the original submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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

⁶<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>.

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*.⁷ 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.⁸

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 Information⁹ and Pregnancy and Lactation Labeling Final Rule¹⁰ 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.

⁷ 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>.

⁸ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

¹⁰ <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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial

period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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.¹¹

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.¹²

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.

¹¹ <http://www.fda.gov/ectd>

¹² <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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 356h¹³ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*¹⁴. 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

¹³ <https://www.fda.gov/media/84223/download>

¹⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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*.¹⁵

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items identified.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor sent responses to the FDA preliminary comments by email on June 23, 2021. Their responses have been integrated into the meeting minutes document and therefore there will be no attachment.

¹⁵ <https://www.fda.gov/media/85061/download>

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/

PATRICK ARCHDEACON
07/23/2021 11:16:06 AM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128801

MEETING MINUTES

Eli Lilly and Company
Attention: John Kaiser, PharmD
Advisor, Global Regulatory Affairs – North America, Diabetes
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Kaiser:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY3298176 for injection.

We also refer to the meeting between representatives of your firm and the FDA on September 6, 2018. The purpose of the meeting was to discuss your Phase 3 program and other topics regarding your plans for a future marketing application.

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

If you have any questions, call Peter Franks, Regulatory Project Manager, at (240) 402-4197.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, 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



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: September 6, 2018; 10:00 AM – 11:00 AM EDT
Meeting Location: White Oak Building 22, Conference Room: 1415

Application Number: IND 128801
Product Name: LY3298176 for injection

Indication: Improvement of glycemic control in patients with type 2 diabetes mellitus

Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Lisa Yanoff
Meeting Recorder: Julie Van der Waag

FDA ATTENDEES

Office of Drug Evaluation II

Mary T. Thanh Hai, M.D.; Director (Acting)

Division of Metabolism and Endocrinology Products

William Chong, M.D.; Director (Acting)

Lisa Yanoff, M.D.; Deputy Director (Acting)

Patrick Archdeacon, M.D.; Clinical Team Lead - Diabetes (Acting)

Frank Pucino, Pharm.D., MPH; Clinical Reviewer - Diabetes

John Sharretts, M.D.; Clinical Team Lead - Lipid/Obesity (Acting)

Ovidiu Galescu, M.D.; Clinical Reviewer - Lipid/Obesity

Federica Basso, Ph.D.; Nonclinical Team Lead (Acting)

Jessica Hawes, Ph.D.; Nonclinical Reviewer

Julie Van der Waag, MPH; Chief, Project Management Staff

Martin White, MS; Regulatory Project Manager

Office of Biostatistics

Yun Wang, Ph.D.; Statistical Team Lead

Eugenio Andraca-Carrera, Ph.D.; Statistical Team Lead

Jiwei He, Ph.D.; Mathematical Statistician

Bo Li, Ph.D.; Mathematical Statistician

Office of Clinical Pharmacology

Manoj Khurana, Ph.D.; Clinical Pharmacology Team Lead
Lian Ma, Ph.D.; Clinical Pharmacology Team Lead, Division of Pharmacometrics
Dipak Pisal, Ph.D.; Clinical Pharmacology Reviewer
Lars Johannesen, Ph.D.; QT/IRT Lead, Division of Pharmacometrics
Junshan Qiu, Ph.D.; Clinical Pharmacology Reviewer, Division of Pharmacometrics
Nan Zheng, Ph.D.; Clinical Pharmacology Reviewer, Division of Pharmacometrics

Office of Biotechnology Products

Bruce Huang, Ph.D.; Reviewer, Division of Biotechnology Review and Research II
William Hallett, Ph.D.; Team Lead, Division of Biotechnology Review and Research II

Office of New Drugs/Clinical Outcomes Assessment (COA) Staff

Selena Daniels, Pharm.D., M.S.; Team Leader

Center for Devices and Radiological Health

Sarah Mollo, Ph.D.; Reviewer, General Hospital Devices Branch
Carolyn Dorgan, Ph.D.; Acting Senior Lead Reviewer, General Hospital Devices Branch

Office of Combination Products

Maryam Mokhtarzadeh, M.D.; Senior Medical Officer

SPONSOR ATTENDEES

Jeffrey Emmick, MD, PhD; Vice President, Diabetes Product Development
Laura Fernandez, M.D., Sr. Medical Director, Diabetes Product Development
Salvador Garcia, M.D., Sr. Director, Global Regulatory Affairs – North America
Sirel Gurbuz, M.D., Sr. Medical Advisor, Global Patient Safety
John Kaiser, Pharm.D., Advisor, Global Regulatory Affairs – North America
Dawn Brooks, Ph.D., Chief Operating Officer, Diabetes
Zvonko Milicevic, M.D., Sr. Medical Fellow, Diabetes
Peter Morrow, M.S., Advisor, Global Regulatory Affairs – North America
Jeffrey Riesmeyer, M.D., Sr. Medical Director, Cardiovascular
Danise Subramaniam, Ph.D., Sr. Director, Global Regulatory Affairs – North America
Shweta Urva, Ph.D., Sr. Research Scientist, PK/PD
Govinda Weerakkody, Ph.D., Senior Research Advisor, Statistics
D. Bradley Woodward, M.D., Platform Team Leader-Incretins
Allison Wolf, M.S., Principal Research Scientist, Global Regulatory Affairs – CMC

1.0 BACKGROUND

LY3298176 for injection (also referred to by the sponsor as tirzepatide) is a 39-amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, and is being developed as an adjunct to

diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The sponsor submitted a breakthrough therapy designation preliminary advice request on May 2, 2018, and FDA discussed this via teleconference with the sponsor on May 14, 2018. On May 24, 2018, the sponsor submitted a type C meeting request, seeking FDA guidance on immunogenicity testing and assay validation. FDA issued written responses on August 1, 2018. On June 15, 2018, the sponsor submitted a type B EOP2 meeting request to discuss their Phase 3 program and other topics regarding plans for a future marketing application. The sponsor submitted specific questions in a meeting package, which was received on July 17, 2018, including nonclinical, clinical, clinical pharmacology, statistical, and device-related questions.

(b) (4)

FDA sent Preliminary Comments to Eli Lilly and Company on August 30, 2018. The sponsor responded by email on August 31, 2018, stating that they plan to discuss Questions 3, 4, 6, 16, and Additional Comments 2 and 6. The sponsor's responses to the preliminary comments follow in italicized font. The meeting discussion follows in underlined font.

2. DISCUSSION

2.1. Nonclinical Safety

Question 1: Does the FDA agree that the nonclinical studies conducted to date, together with the additional ongoing and proposed studies, will provide sufficient nonclinical safety information to support registration of tirzepatide in adults?

FDA Preliminary Response to Question 1:

The proposed nonclinical safety program appears generally reasonable to support the planned Phase 3 clinical studies with LY3298176; however, we have the following suggestions to support submission of an NDA.

- a. **Characterization of the genotoxicity potential of LY3298176 should be conducted, as communicated on July 13, 2018.**
- b. **Given that LY3298176 contains an organic linker that may be uncapped or released during catabolism, you should conduct an evaluation of the metabolic fate of the linker, including an assessment of in vivo exposures to free linker and/or linker-related materials. Based on the results of this evaluation, provide a hazard assessment for the linker and any linker-related materials unique to humans and/or >10% of total drug, as per ICH M3(R2) and the FDA Safety Testing of Drug Metabolites.**
- c. **Conduction abnormalities in monkeys appear to be more severe with LY3298176 than with other GLP-1 agonists in the class. Provide a rationale and/or any**

comparative assessment information you may have between LY3298176 and other GLP-1 agonists, and consider mechanistic evaluations of LY3298176 and potential linker-related metabolites (see above) on Na, K, and Ca channel activities, based on the following drug-related cardiovascular findings in Cynomolgus monkeys:

- **Cardiovascular effects consistent with decreased cardiac contractility after single doses of 0.05 and 0.15 mg/kg LY3298176 in the safety pharmacology study #8328700.**
- **Evidence of increased heart rates at 0.15 and 0.5 mg/kg/week in the 1-month and 6-month toxicology studies (#8325823 and #8336517, respectively).**
- **Evidence of PR prolongation compared to pre-dose values in all females at 0.5 mg/kg/week in the 6-month toxicology study #8336517.**
- **Second-degree atrioventricular block with PR prolongation and increased heart rate correlating with C_{max} increased creatine kinase levels, and minimal epicardium inflammation in 1 female at 0.5 mg/kg/week in the 6-month toxicology study #8336517.**

We note that additional studies may be required, as appropriate, if the formulation is modified or if there are unexpected results in clinical or nonclinical studies that merit further nonclinical investigation.

Meeting Discussion:

The sponsor plans to comply with the requests.

2.2. Clinical Pharmacology

Question 2: Does the FDA agree that the proposed clinical pharmacology program is adequate to support the planned New Drug Application for tirzepatide in patients with T2DM?

FDA Preliminary Response to Question 2:

Your proposed clinical pharmacology studies appear reasonable, however the adequacy of the planned studies depends on the data obtained from these studies and will be a review issue.

Meeting Discussion: None

Question 3: Does the FDA agree with the proposal to utilize integrated model-based approaches that are sufficiently qualified to evaluate potential drug-drug interactions with tirzepatide?

FDA Preliminary Response to Question 3:

We acknowledge your submitted PBPK modeling report and proposal to use a PBPK approach to evaluate the potential effect of your investigational drug on gastric emptying time and on the PK of co-administrated drugs. The acceptability of PBPK modeling will be a review issue.

We note that the PBPK modeling report should describe in detail the rationale to support the development of the PBPK model and assumptions being made. Refer to the draft *Guidance for Industry- Physiologically Based Pharmacokinetic Analyses-Format and Content*, available at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm531207.pdf>.

Sponsor's Response to FDA's Preliminary Response:

We wish to discuss the possibility of obtaining a definitive FDA response on the acceptability of PBPK modeling prior to filing our NDA.

Brief Explanation: The Division's preliminary comment stated, "The acceptability of PBPK modeling will be a review issue". We are grateful for this reply, which we understand to mean that (i) in principle, the proposal seems reasonable based on the briefing document information, and (ii) a final FDA determination will require additional, complete information. Complete details of the PBPK model should be available in April 2019. We propose to request a Type C meeting around that time in order to seek definitive FDA advice. Our object here is to avoid potential delays on review due solely to DDI considerations (i.e. in the fortunate event that our application is judged approvable in all respects but DDI evaluation, we would not wish to have a delay).

Meeting Discussion:

As complete details of the PBPK model were not available at the time of this meeting and will be available before April 2019, FDA asked that the sponsor submit the request for advice as an amendment to the IND, with complete details of the PBPK model and their rationale for DDI studies, but not as a meeting request. The sponsor should clearly state in the cover letter of the submission that a response is requested.

Question 4: Does the FDA agree with the design of the proposed oral contraceptive drug-drug interaction study? The study will evaluate the effect of a single 5-mg dose of tirzepatide on the PK of a combination oral contraceptive.

FDA Preliminary Response to Question 4:

The design seems reasonable, however as 15 mg is the proposed highest dose planned in the Phase 3 program, we recommend using a 15 mg dose for this DDI study.

Sponsor's Response to FDA's Preliminary Response:

We wish to understand and discuss (i) the basis for the FDA's recommendation to use tirzepatide 15 mg in the planned oral contraceptive DDI study and (ii) the potential acceptability of using a single 5 mg tirzepatide dose.

Meeting Discussion:

FDA stated that the sponsor may consider a study design which they have used for a multiple dose study utilizing acetaminophen as a probe substrate for their DDI study with oral contraceptive (OC). However, the sponsor discussed the difficulties in giving 15 mg as a single dose due to tolerability issues. FDA noted that in general, DDI designs should evaluate the 'worst case' scenario. Provided an adequate rationale is submitted, the 5 mg dose may be reasonable for DDI assessment with OC. FDA agreed to review the study design prior to study initiation. The sponsor should provide their rationale for the study design when it is submitted to the IND and should clearly state in the cover letter of the submission that a response from FDA is requested.

Question 5: Does the FDA agree that the proposed population pharmacokinetic analysis plan, involving samples from approximately 1150 subjects in 3 of the 5 pivotal Phase 3 studies in T2DM, is sufficient for investigating the pharmacokinetics of tirzepatide?

FDA Preliminary Response to Question 5:

We recommend you combine all available PK data from Phase 1 to 3 studies for your final population PK analysis.

Meeting Discussion: None

Question 6: Does the FDA agree with the proposed approach for evaluating potential QTc prolongation with tirzepatide and, specifically, that no thorough QTc study is required?

FDA Preliminary Response to Question 6:

We do not agree that you have characterized the potential of LY3298176 to prolong the QTc interval as per the ICH E14 guideline. The dosing regimen and PK/ECG sampling schedule in the three studies used for the concentration-QTc analysis do not cover the steady state therapeutic exposure (i.e., $C_{max,ss}$) at the highest proposed clinical dose (15 mg QW).

We recognize that conducting a TQT study for LY3298176 is challenging given the long half-life and the titration schedule to obtain steady state concentrations. We recommend that you conduct in vitro evaluation (hERG assay) on LY3298176, and collect at least one additional safety ECG in the Phase 3 studies after patients achieve steady state exposure on the 15 mg QW dose (e.g., Week 24). The potential of LY3298176 to prolong the QTc interval will be inferred from the totality of data collected from your in vitro assays and in vivo safety pharmacology studies, the concentration-QTc analysis of data collected in your Phase 1 and Phase 2 clinical trials, and safety ECGs obtained in the Phase 3 clinical trials.

Sponsor's Response to FDA's Preliminary Response:

We acknowledge and understand the FDA's recommendation to, "collect at least one additional safety ECG in the Phase 3 studies after patients achieve steady state exposure on the 15 mg QW dose (e.g. Week 24)", and are committed to providing all necessary QTc information. However, because all Phase 3 studies already include a safety ECG collection at steady state (36 weeks), we wish to understand better the basis for the FDA recommendation.

Meeting Discussion:

The sponsor stated they will evaluate the effect of LY3298176 on hERG. FDA agreed that safety ECG collection at Week 36 instead of Week 24 is acceptable.

2.3. Clinical Development

Question 7: Assuming that the data are supportive, does the FDA agree that the proposed Phase 3 program is adequate to support a New Drug Application for the following indication, considering the number and type of studies, patient safety, exposure requirements, and other relevant factors?

FDA Preliminary Response to Question 7:

Whether the Phase 3 development program and clinical data will support the intended indication will be a review issue. Although the proposed program may be reasonable, we have the following comments for consideration:

- a. We note that subjects with varying stages of renal impairment may participate in your Phase 3 program, and that the impact of renal impairment on LY3298176 PKs at clinical doses/regimens in patients with T2DM will be investigated as part of the Phase 3 population PK analyses. Please clarify your plan to evaluate the use of LY3298176 in diabetic subjects with impaired renal function for your Phase 3 trials. Patients with renal impairment may constitute a significant proportion of the target population for your product, and therefore, the relative efficacy and safety of**

LY3298176 needs to be assessed in an adequate number of subjects from this special population.

Meeting Discussion:

The sponsor noted that the planned patient populations for their Phase 3 program would include patients with renal impairment, including patients with eGFR < 30 mL/min and patients with end stage renal disease. FDA indicated that the sponsor will need to ensure that adequate numbers of subjects with various stages of renal impairment are enrolled to evaluate the use of LY3298176 in this population.

- b. We recommend that the following adverse events (AEs) relevant to antihyperglycemic pharmacologic classes, particularly incretin mimetics, be considered prespecified AEs of special interest (AESI), or provide justification for why these events would not be applicable to the LY3298176 Phase 3 clinical program: pancreatitis, cardiovascular events (including clinically relevant rhythm and conduction disorders), diabetic retinopathy complications, severe/serious hypoglycemia (per 2017 ADA/EASD classification) ¹, dehydration/acute kidney injury/chronic renal failure exacerbation, serious hypersensitivity reactions (e.g., anaphylaxis/hypotension/shock, angioedema, asthma/dyspnea/bronchospasm, rash, pruritus, urticaria), severe/serious injection site reactions (e.g., abscess, cellulitis, erythema, hematomas/hemorrhage, exfoliation/necrosis, pain, subcutaneous nodules, swelling, induration, inflammation), malignancies (e.g., medullary and papillary thyroid carcinomas), hepatobiliary disorders (e.g., cholelithiasis /cholecystitis, drug-induced liver injury), major depressive disorder (e.g., suicidal behavior and ideation), metabolic acidosis (e.g., ketoacidosis, lactic acidosis), severe/serious gastrointestinal adverse reactions, amputations/peripheral revascularization procedures, and antidrug antibody formation associated with reduced efficacy or severe hypersensitivity/ injection site reactions.**
- c. Please provide the data safety monitoring and adjudication/clinical endpoint committee (CEC) charters when these documents become available.**
- d. Although the planned safety exposures (i.e., 4116 subjects exposed; ≥1600 subjects exposed for ≥12 months; and ≥300 subjects exposed for ≥18 months) appear to be in accordance with both the 2008 Diabetes Guidance ² and the International Council for Harmonisation (ICH) E1A Guidance ³, the adequacy of your safety database will**

¹ Agiostratidou G, Anhalt H, Ball D, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRE International, the Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care 2017;40:1622-30.

² Guidance for Industry. Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. Rockville, MD: Food and Drug Administration, February 2008. Accessed August 13, 2018, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071624.pdf>.

³ Guideline for Industry. The extent of population exposure to assess clinical safety: for drugs intended for long-term treatment of non-life-threatening conditions. Silver Spring, MD: Expert Working Group (Efficacy) of the

depend on whether any new/emerging safety issues become apparent during Phase 3 clinical development.

Additionally, you will need to determine what dose escalation scheme you intend to pursue prior to initiation of your Phase 3 program (see response to Question #8).

Meeting Discussion: Only response 7a was discussed.

Question 8: Does the FDA agree with the dosing regimens [5 mg, 10 mg, and 15 mg], including escalation schemes with intermediate dose steps, proposed for Phase 3 registration trials to support the glycemic control indication for tirzepatide?

FDA Preliminary Response to Question 8:

Based on your preliminary clinical data, the 5 mg, 10 mg and 15 mg doses appear to be reasonable. (b) (4)

Since this trial will determine the preferred dose titration of your product and provide essential information to support the efficacy, safety, and tolerability of this dose escalation approach, this trial will need to be completed prior to initiating your planned Phase 3 trials. The dose titration scheme which you propose for dosing recommendations should be studied in all Phase 3 trials.

Meeting Discussion: None

Question 9: Does the FDA agree with the design of the 5 individual Phase 3 glycemic control studies, considering especially key design aspects such as primary and secondary endpoints, entry criteria, background therapy (choice/dose), treatment duration, safety monitoring, rescue therapy provisions, and choice/dose of comparators?

FDA Preliminary Response to Question 9:

Overall, the key design aspects (e.g., primary and key secondary efficacy endpoints, entry criteria, background therapy, safety monitoring, rescue therapy) appear to be reasonable. However, we note that three of the five Phase 3 trials evaluate the efficacy of the LY3298176 15 mg dose after only 16 weeks of exposure (i.e., GPGI, GPGK, GPGK). To adequately evaluate the durability of hemoglobin A1c (HbA1c) changes, as well as the safety and tolerability of this dose, we recommend that trial durations be extended to provide at least 18 to 24 weeks of exposure to the LY3298176 15 mg dose following the titration phase. Additionally, for trials that allow more than one

background antihyperglycemic medication, it may be helpful to include background therapy as a stratification factor.

For the Phase 3 trials that use insulin as an active comparator (i.e., Trials GPGH, and GPGM), it will be important that the insulin dose is “titrated optimally throughout the entire study” (as stated in your background package) to ensure an unbiased comparison with your product. Additionally, should LY3298176 be associated with similar HbA1c reductions as observed in your Phase 2 program, appropriate safeguards should be in place to minimize the risk of severe hypoglycemia for study participants (e.g., Trials GPGI, and GPGM include LY3298176 as add-on to insulin or insulin secretagogues, respectively).

Meeting Discussion: None

Question 10: Assuming the data are supportive, does the FDA agree that the proposed additional Phase 3 escalation study is adequate to support “Dosage and Administration” labeling for an alternative escalation scheme as the exclusive dosing recommendation?

FDA Preliminary Response to Question 10:

We do not agree. Please refer to our response to Question #8 above.

Meeting Discussion: None

Question 11: Does the FDA agree with the proposed immunogenicity sampling and assessment plan described in Protocol I8F-MC-GPGM, which will serve as a model for the remaining Phase 3 studies (see especially protocol Sections 9.4.4, 10.3.5, 10.3.6, and Table GPGM.1)?

FDA Preliminary Response to Question 11:

We agree that the proposed plan for immunogenicity sampling and assessment appears reasonable.

Meeting Discussion: None

Question 12: Does the FDA agree with the proposed approach for evaluating cardiovascular risk in the tirzepatide clinical program: a meta-analysis of adjudicated cardiovascular events, the majority of which will be contributed by Phase 3 Study GPGM, which will enroll a population with T2DM and increased risk of cardiovascular events?

FDA Preliminary Response to Question 12:

In general, a meta-analysis of adjudicated cardiovascular events from the primary database may be adequate to establish that there is not an unacceptable increase in CV risk at the time of NDA submission. However, we strongly suggest that your program

be designed to avoid using interim data from trial GPGN to rule out the 1.8 risk margin. An interim analysis of the ongoing GPGN trial carries the risk to impact its conduct and interpretability.

Based on Table 8.1 (page 157) in your briefing document, the primary database at the time of NDA submission is expected to include as few as 107 MACE-4 events. Under the example described in Section 8.1.2, if your primary database includes 100 total events, the first pre-specified analysis (based on the primary database alone) would have a probability of approximately 80% to rule out the pre-specified 1.8 risk margin (assumptions: 1:1 randomization, true HR=1, $\alpha_1 = 0.0389$). This scenario would result in an approximately 20% chance to not rule out the 1.8 risk margin based on the primary database and consequently to require an interim analysis of trial GPGN.

We recommend that you consider modifications to your proposed program such that an interim analysis of GPGN is not needed. One possible way to achieve this goal is to increase the targeted number of MACE-4 in the primary database to be 133 events by increasing the sample size or follow-up time of the single trial GPGM. Alternative approaches may be considered.

Meeting Discussion: None

Question 13: Does the FDA agree with the following design elements for a planned cardiovascular outcomes trial of tirzepatide in T2DM patients with established cardiovascular disease:

- The use of placebo as the control group (both tirzepatide and placebo would be added to the standard of care), and
- A single tirzepatide dose group with dosing to be initiated at 2.5 mg and escalated to a maximum dose of 15 mg in a similar manner to the Phase 3 studies. Dose adjustment will be permitted based on study drug tolerability.

FDA Preliminary Response to Question 13:

These design elements are reasonable.

Meeting Discussion: None

2.4. Statistics

Question 14: Does the FDA agree with the proposed statistical approach to establish that there is no excess cardiovascular risk at the time of initial New Drug Application (NDA) for tirzepatide (ie, that the upper bound of a CI of the hazard ratio for adjudicated MACE-4 [the composite endpoint of CV death, myocardial infarction, stroke, or hospitalization for unstable angina] is <1.8)?

FDA Preliminary Response to Question 14:

Please see our response to Question 12. A meta-analysis of adjudicated MACE-4 events from the primary database may be adequate to rule out the 1.8 risk margin. However, we strongly suggest that your statistical approach does not include an interim analysis of trial GPGN.

Meeting Discussion: None

Question 15: For the FDA, the primary efficacy analysis of HbA1c mean change from baseline will be guided by the “treatment-regimen” estimand, representing the efficacy of tirzepatide doses irrespective of adherence to investigational product or introduction of other rescue antihyperglycemic therapy. Thus, the analysis will be conducted using the full analysis set, all available data from subjects receiving at least one dose of study drug, including data collected from subjects who discontinued drug but remained in the study, using multiple imputation methods for missing data. Does the FDA agree with the proposed primary analysis?

FDA Preliminary Response to Question 15:

The proposed primary efficacy analysis and the method of dealing with missing data are acceptable. In cases where there are not enough retrieved dropouts to provide a reliable imputation model, you may consider alternative analyses, such as multiple imputation with reference to the placebo group in placebo-controlled studies and multiple imputation with reference to baseline in active-controlled studies. That being said, you should try your best to retrieve patients who discontinue study treatment and keep missing data to minimum.

Meeting Discussion: None

2.5. Device-Related

Question 16: Does the FDA agree that the following clinical information is adequate to support approval of the drug delivery device for the tirzepatide combination product, which uses the same marketed autoinjector device as the Trulicity Single-Dose Pen:

- i. use of the autoinjector in 4 of the 5 glycemic control Phase 3 studies in T2DM and
- ii. a relative bioavailability bridging study of the prefilled syringe (clinical trial device) versus the autoinjector?

FDA Preliminary Response to Question 16:

We recommend that you provide verification testing on final, finished product including the proposed drug product. We recommend that the essential performance requirements for the autoinjector (AI) that could be impacted by the drug product (e.g.,

including, but not limited to, injection time, activation force, and dose accuracy) are performed on the final, finished device, including the proposed final drug product. For other device requirements/specifications, if you are leveraging testing from previously approved products (i.e., Trulicity AI), the submission should itemize all design changes and provide a rationale for why the changes would not impact the specification or attribute being evaluated.

The PK comparability study should include the highest dose of the final to-be-marketed formulation.

Sponsor Response to FDA Preliminary Response:

We wish to understand and discuss (i) the basis for the FDA's recommendation to use tirzepatide 15 mg in the planned device PK comparability study and (ii) the potential acceptability of 5 mg.

Meeting Discussion:

The sponsor clarified that they are conducting 4 of the 5 Phase 3 clinical studies with auto-injector (AI) and one study with the pre-filled syringe (PFS) presentation and planning to conduct population PK analysis using the data from Phase 3 studies. FDA agreed with the sponsor's proposal to use the 5 mg dosage strength in the planned device PK comparability study. FDA also stated that the sponsor's approach, to use the single dose PK comparison and population PK analysis from the Phase 3 studies to support PK comparability between the devices, is reasonable.

Post-Meeting Comment: If you plan to use PFS in the monotherapy study and the AI presentation in the add-on studies, then you may benefit from conducting the single dose PK comparability study before initiating the Phase 3 trials with the AI presentation.

2.6. Efficacy Measurement, Proportion of A1c Target

Question 17: Does FDA agree that achieving HbA1c (b) (4) % may be a clinically meaningful assessment of efficacy in a clinical program for type 2 diabetes? Further, would FDA consider including the proportion of the study population achieving HbA1c (b) (4) (if defined as a secondary endpoint, and controlled for multiple comparisons)?

FDA Preliminary Response to Question 17:

The decision to include a prespecified key secondary endpoint (b) (4) would be a review issue. However, the clinical relevance of statistical differences between treatment arms in the proportions of subjects achieving an HbA1c (b) (4) % is uncertain, and limited information was provided in the briefing document (b) (4) sufficient evidence would need to be provided to justify why the observed differences

between treatment arms for the proposed exposure durations are clinically meaningful. Additionally, it will be important for you to clarify whether a stringent HbA1c goal (b) (4) would be an appropriate glycemic target for all patient populations, such as subjects with a history of severe hypoglycemia, limited life expectancy, advanced microvascular (e.g., diabetic retinopathy) or macrovascular complications, extensive comorbid conditions, and long-standing diabetes ⁴.

Meeting Discussion: None

FDA Additional Clinical Comments:

1. We note that all proposed Phase 3 clinical trials include assessments of patient-reported outcomes (PROs). Please clarify the purpose of these assessments.

Meeting Discussion:

The sponsor clarified that the purpose of these assessments is not for labeling.

2. Please provide sample datasets (analysis and tabulation) to be used for the proposed Phase 3 clinical trials. Post-baseline and on-treatment flags would be useful for the CE, LB, VS, and EG (where available) tabulation datasets, as well as a treatment-emergent flag for the AE tabulation datasets. It also would be helpful to flag marked clinical laboratory abnormalities in both the analysis (ADLB) and tabulation (LB) datasets, and to possibly include a grading scale for laboratory changes, adverse events, vital sign changes, and electrocardiogram findings (e.g., Common Terminology Criteria for Adverse Events [CTCAE] toxicity grades) if appropriate.

Sponsor Response to FDA Preliminary Comment:

We will be happy to provide sample datasets. To help us generate the proper information and submit it at the appropriate time, we wish to learn (i) the particular reasons for this FDA request, (ii) ideal timing for FDA receipt of sample datasets, and (iii) desired format (e.g. “.xpt”).

Meeting Discussion:

FDA clarified that this is not a requirement, only a request. FDA recommends that the sponsor submit to the IND sample datasets (SAS transport file format) that include 5-10 non-actual subjects, preferably before initiating their Phase 3 trials, while there is still time for FDA input. Inclusion of both the U.S. conventional units and Système

⁴ American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41:S55-S64.

International (SI) units for the laboratory datasets is requested. The sponsor will work on proposed datasets and will submit to the IND for FDA's review and comments.

3. We note that the proposed Phase 3 trials will exclude subjects with proliferative retinopathy or maculopathy. It will be important that these trials adequately evaluate subjects for diabetic retinopathy at study entry, and to have plans in place to appropriately assess the progression/occurrence of diabetic retinopathy complications and their clinical significance during the trial.
4. The proposed glycemic rescue criteria for persistent hyperglycemia in your Phase 3 trials will be based on once weekly 4-point self-monitored blood glucose profiles or average fasting serum glucose concentrations (≥ 4 values/week), both assessed over a 2-week period. We recommend that you also consider including HbA1c rescue criteria (e.g., after Week 12).
5. For the clinical chemistry panels, it appears that you do not plan to measure serum bicarbonate concentrations. Several of your Phase 3 trials include combination therapy with products associated with metabolic acidosis (metformin, sodium-glucose cotransporter 2 [SGLT2] inhibitors). Further, it is possible, the LY3298176 may be associated with rapid weight loss, volume depletion/renal impairment due to vomiting and diarrhea, and/or reductions in insulin dosing as add-on to background insulin therapy. Therefore, we recommend that serum bicarbonate concentrations be measured as part of the clinical chemistry panel for your Phase 3 program, with appropriate follow-up assessments performed (e.g., serum and urine ketones, serum lactate) when metabolic acidosis is suspected.
6. Serum calcitonin concentrations will be measured at Week 16 for all Phase 3 trials, while a chemistry panel will be assessed at Week 12 for two of the trials. It appears that most of the other on-treatment safety laboratory assessments (including measurement of serum amylase and lipase) will not be performed until Week 36. In your latest Development Safety Update Report (DSUR, dated June 27, 2018), serious adverse events (SAEs) of acute kidney injury and pancreatitis occurred following 65 and 15 days of LY3298176 exposure, respectively. Additionally, the Clinical Study Report (CSR) for Trial GPGB (dated April 13, 2018), reported that four subjects experienced lipase elevations of 2.8-7.8x the upper limit of normal (ULN) within two weeks of a single subcutaneous dose of LY3298176. In your response (dated May 11, 2018) to our May 8, 2018, information request regarding Trial GPGB, you also report that lipase elevations $>3x$ ULN were observed in approximately 6% (13/211) of subjects following 1-26 weeks of exposure, of which two discontinued study (acute pancreatitis and amylase/lipase elevations, respectively), and a third experienced an SAE of acute pancreatitis. Based on these data, and to adequately ensure subject safety, you will need to include additional safety laboratory assessments (e.g., hematology panel, clinical chemistry panel including bicarbonate, serum calcitonin, amylase and lipase, eGFR) prior to

Week 36. Additionally, we recommend that you exclude subjects with abnormal serum amylase and/or lipase concentrations at screening, and appropriate assessment and follow-up should be provided for subjects experiencing symptoms characteristic of acute pancreatitis between laboratory visits.

Sponsor Response to FDA Preliminary Comment:

We will comply with the FDA recommendations for additional laboratory safety assessments and evaluation/follow-up of subjects with symptoms of acute pancreatitis, and wish to briefly describe our plans for doing so. We also wish to understand better, and discuss the basis for, the Division's recommendation to exclude subjects with pancreatic enzyme elevations.

Some key points about pancreatic safety measures in the tirzepatide clinical program:

- *Acute or chronic pancreatitis is an exclusion criterion*
- *As requested, we will revise the Phase 3 studies to add an additional timepoint for laboratory safety assessment prior to week 36, including amylase and lipase.*
- *Concerning the Division's recommendation for evaluation of patients with symptoms characteristic of pancreatitis, the Phase 3 protocols require that such subjects be fully evaluated, including laboratory and imaging diagnostic work-up.*
- *Appropriate pancreatic safety data will be collected on dedicated CRFs.*
- *An independent committee will adjudicate all cases of suspected cases throughout the program.*

We propose not to use pancreatic enzyme elevations as an exclusion criterion in Phase 3 studies.

Evaluation of pancreatic safety in a previous Lilly incretin program yielded the following:

- *Up to 20% of subjects had abnormal amylase or lipase values at screening. An additional approximately 25% of patients in the placebo group had abnormal amylase or lipase at least once at any point from screening through 6 months.*
- *Adjudication of subjects with $\geq 3X$ elevations in amylase or lipase showed that these elevations, in the absence of symptoms, had extremely low predictive value for pancreatitis.*
 - *Asymptomatic pancreatic enzyme elevations are not reliable for the detection of acute pancreatitis.*
 - *For this reason, the Phase 3 protocols require that all patients with clinical symptoms of suspected pancreatitis be fully evaluated.*

- *Given the preceding, in Lilly's view, exclusion of subjects based on amylase/lipase abnormalities is not warranted*

Meeting Discussion:

FDA agreed with the sponsor's proposal not to use pancreatic enzyme elevations as an exclusion criterion in Phase 3 studies. The sponsor stated that they will submit a copy of the CEC charter to the IND.

- 7. Oral antiemetic or antidiarrheal medications (per local country availability and individual subject needs) may be used to manage gastrointestinal symptoms. Since the use of these medications reflect subject tolerance to adverse gastrointestinal symptoms associated with LY3298176, it will be important to adequately document the use of these products, and to record interruptions in therapy and dose reductions due to intolerable/persistent gastrointestinal adverse events.**

3.0 OTHER IMPORTANT INFORMATION

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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. 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: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

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](#) and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

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: <http://www.fda.gov/ectd>.

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 <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

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 INDs not in eCTD format).

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 (February 2018) and the associated 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:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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/

LISA B YANOFF
10/05/2018