CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA Sufficiency Templates

Version: 2018-01-24

Date:	April 29, 2022
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Subject:	ARIA Sufficiency Memo: An assessment of the Sentinel Active Risk Identification and Analysis (ARIA) system to evaluate the association between tirzepatide and Medullary Thyroid Carcinoma (MTC) during the postmarketing safety surveillance
Drug Name(s):	MOUNJARO (tirzepatide)
Application Type/Number:	NDA 215866
Applicant/sponsor:	Eli Lilly
OSE RCM #:	2021-1826

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	
-Interim	
-Final	X
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

On November 14, 2021, Lilly submitted a New Drug Application (NDA 215866) to the Food and Drug Administration (FDA) for MOUNJARO (tirzepatide), a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist, for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. NDA 215866 is under priority review. The targeted action due date is May 15, 2022.

1.2. Describe the Safety Concern

Medullary Thyroid Carcinoma (MTC) is a rare malignant neuroendocrine tumor of the parafollicular C cells of the thyroid gland, characterized by the production of calcitonin.[1] About 25% of MTC cases are hereditary.[1] MTC accounts for about 3% of all thyroid cancer cases,[2] and the Surveillance, Epidemiology, and End Results (SEER) registry data showed that the age-adjusted incidence of MTC was 0.2 per 100,000 person-years during 2010-2013 in the United States.[3]

Nonclinical toxicology data shows that long-acting GLP-1 receptor agonists cause dose-related and treatment-duration-dependent thyroid C-cell tumors (adenomas and/or carcinomas) in rodents.[4-12] Increases in thyroid C-cell hyperplasia and neoplasia were also observed in male and female rats in a nonclinical tirzepatide carcinogenicity study.[a] A hypothesized carcinogenic mechanism by long-acting GLP-1 receptor agonists includes the increase in cyclic adenosine monophosphate (cAMP) and calcitonin secretion, and C-cell proliferation with GLP-1 receptor stimulation on rodent thyroid C-cells.[13-15]

The effects of GLP-1 receptor agonists on human thyroid cells are not clear. A study shows that human thyroid C-cells have low GLP-1 receptor expression, and that GLP-1 receptor agonists do not cause the release of calcitonin,[14] a specific and sensitive biomarker for human MTC.[16] In contrast, another study showed that GLP-1 receptor expression was frequent in MTC and C cell hyperplasia and "not infrequently present" in normal C cells in humans.[17] MTC cases have been reported in patients treated with GLP-1 receptor agonists in both clinical studies and the postmarketing period.[4, 6, 8, 18-20] However, no treatment-emergent adverse events of thyroid malignancies, including MTC or thyroid C-cell hyperplasia were reported in the tirzepatide clinical development program.[a] Understanding the causal relationship between GLP-1 receptor agonists and humans MTC is complicated because of the long latency period and the relative rarity of the disease, and difference in GLP-1 receptor expression on thyroid C cells between rodents and humans.[21]

Table 1 listed the FDA approved single long-acting GLP-1 receptor agonists as of January 4, 2022.

[a] Dr. Frank Pucino in DDLO provided a draft of his clinical review of MOUNJARO (tirzepatide, NDA 215866). The document summarized the results of nonclinical carcinogenicity study and safety outcomes reported in the tirzepatide clinical development program (communication date: December 11, 2021).

Table 1. List of FDA-approved single long acting GLP-1 receptor agonists with a PMR for MTC risk, as of January 4, 2022

Brand Name[i]	Active Ingredient	Sponsor	Application Number	FDA Approval Date	FDA Approved Indications[ii]			Marketing Status
					Glycemic Control	Reduce the risk of MACE	Chronic Weight Management	
Victoza	Liraglutide recombinant	Novo Nordisk	NDA 022341	January 25, 2010	Yes	Yes		Prescription
Bydureon	Exenatide synthetic	AstraZeneca	NDA 022200	January 27, 2012	Yes			Discontinued
Tanzeum[iii]	Albiglutide	GlaxoSmithKline	BLA 125431	April 15, 2014	Yes			Discontinued
Trulicity	Dulaglutide Injection	Eli Lilly	BLA 125469	September 18, 2014	Yes	Yes		Prescription
Saxenda	Liraglutide recombinant	Novo Nordisk	NDA 206321	December 23, 2014			Yes	Prescription
Bydureon BCise	Exenatide synthetic	AstraZeneca	NDA 209210	October 20, 2017	Yes			Prescription
Ozempic	Semaglutide (injection)	Novo Nordisk	NDA 209637	December 5, 2017	Yes	Yes		Prescription
Rybelsus	Semaglutide (tablets)	Novo Nordisk	NDA 213051[iv]	September 20, 2019	Yes			Prescription
Wegovy	Semaglutide (injection)	Novo Nordisk	NDA 215256	June 4, 2021			Yes	Prescription

[i] All FDA approved long acting GLP-1 receptor agonist contained products have a class wide Boxed Warning of thyroid C-cell tumor including MTC. Xultophy (BLA 208583) is a combination product of insulin degludec and liraglutide. FDA did not issue a MTC PMR for Xultophy because there have been MTC PMRs for single liraglutide products and most Xultophy users would use less than 1.8 mg of liraglutide (communication with Dr. Tania Condarco in DDLO regarding a MTC PMR for Xultophy. Date: January 6, 2022).

[ii] Detailed indications may be found in product labeling.[4-7, 9-12, 20]

[iii] GlaxoSmithKline (GSK), the Sponsor of Tanzeum, voluntarily revoked the license of Tanzeum on October 20, 2021 based on a business decision.[22, 23] FDA released the product from all postmarketing requirements.[22] However, GSK agrees to continuously update FDA annually regarding Tanzeum exposed MTC case till 2029, 15 years after the drug' approval in 2014 (emails dated September 14 and September 20, 2021).

[iv] Novo Nordisk, the Sponsor of Rybelsus, submitted NDA 213182 for the addition of efficacy and safety information to the Rybelsus prescribing information based on the data from the PIONEER 6 cardiovascular outcomes trial. FDA administratively closed NDA 213182 on January 16, 2020 and required the Sponsor to make submissions to the original NDA 213051.[24]

Abbreviations: MACE, major adverse cardiovascular events

Because of the potential safety concern related to exposure to long-acting GLP-1 receptor agonists and increased MTC found in animal studies, all FDA approved long-acting GLP-1 receptor agonists have a Boxed Warning of the risk of thyroid C-cell tumors (with Victoza labeling[4] for thyroid C-cell tumor listed verbatim below).

WARNING: RISK OF THYROID C-CELL TUMORS
See full prescribing information for complete boxed warning.

- **Liraglutide causes thyroid C-cell tumors at clinically relevant exposures (b) (4) It is unknown whether VICTOZA causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance (b) (4) not (b) (4) determined (5.1 (b) (4).**
- **VICTOZA is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). (b) (4) (b) (4) 5.1).**

Under Sections 505(o)(3), 505(k)(1), and 505(k)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA issued postmarketing requirements (PMRs) for the Sponsors of long-acting GLP-1 receptor agonists to participate in a MTC case series registry to evaluate the relationship between long acting GLP-1 receptor agonist treatment and the development of MTC in humans. The Sponsors and the American Thyroid Association (ATA) established the MTC case series registry[b] in 2010 to address these PMRs.

The MTC case series registry aims to systematically monitor the annual incidence of MTC in the United States through the North American Association of Central Cancer Registries (NAACCR) to identify any possible increase in incidence related to the introduction of long-acting GLP-1 receptor agonists into the U.S. market. The MTC Registry also collects case data from participating State Cancer Registries (SCRs) to characterize medical histories and possible risk factors. The MTC case series registry verifies prior GLP-1 receptor agonist treatment through treating physicians. The study will continue for at least 15 years after the addition of the last long-acting GLP-1 receptor agonist to the MTC registry.

Previously, FDA also required a class wide Risk Evaluation and Mitigation Strategy (REMS)[c] for approved long-acting GLP-1 receptor agonists to ensure that the benefits outweigh the potential

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[b] As of February 05, 2021, the MTC case-series registry covers Victoza (liraglutide), Saxenda (liraglutide), Bydureon (exenatide), Bydureon BCise (exenatide), Trulicity (dulaglutide), Ozempic (semaglutide), and Rybelsus (semaglutide) (**Table 1**). Of note, Novo Nordisk, the Sponsor of Wegovy, submitted the MTC case-series registry Protocol Amendment 7 (dated October 25, 2021, submitted on December 14, 2021) to add Wegovy in the MTC registry per the 505(o) Postmarketing Requirement.

[c] The GLP-1 receptor agonists REMS was comprised of communication plan activities including dissemination of a REMS Letter for healthcare providers and professional societies, a REMS Fact Sheet, REMS slides, dissemination of the REMS information at scientific meetings and a website to communicate about the potential risk of MTC.[25]

risk of MTC and the risk acute pancreatitis.[25-31] However, based on the available REMS assessment findings, FDA determined that REMS is no longer required for long-acting GLP-1 receptor agonists.[32-39]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

This memo aims to document the assessment of whether the Sentinel Active Risk Identification and Analysis (ARIA) system could be used to evaluate the MTC safety signal in human for postmarketing safety assessment of tirzepatide under Food and Drug Administration Amendments Act (FDAAA) of 2007.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Not applicable. Because this study is for descriptive purposes only, effect size or sample size calculation is not required.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The desired population would consist of patients who received tirzepatide for the treatment of type 2 diabetes. Given that MTC is a rare and long-latency outcome, a large number of exposed patients with sufficiently long-term follow-up would be necessary for an adequate evaluation of MTC risk associated with the product exposure in Sentinel ARIA.

2.2 Is ARIA sufficient to assess the intended population?

No. ARIA is deemed insufficient to monitor MTC after exposure to tirzepatide. Although there has been over 350 million unique patient identifiers in the Sentinel Distributed Database between 2000 and 2021,[40] the number of tirzepatide users with long-term follow-up would likely be insufficient to support an ARIA evaluation for rare, long latency outcomes such as MTC, given the low market uptake of a newly approved product and the availability of several other GLP-1 receptor agonists.

3 EXPOSURES

3.1 Treatment Exposure(s)

The exposure of interest is tirzepatide.

3.2 Comparator Exposure(s)

Not applicable.

3.3 Is ARIA sufficient to identify the exposure of interest?

The post-approval market uptake of tirzepatide is unknown at this point, but the number of tirzepatide users is likely to be insufficient for MTC risk assessments, given potential challenges with market uptake and the availability of many other drugs in the class.

4 OUTCOME(S)

4.1 Outcomes of Interest

The outcome of interest is MTC.

4.2 Is ARIA sufficient to assess the outcome of interest?

No. ARIA is insufficient to assess MTC risk after tirzepatide exposure because of the following reasons:

- MTC is a rare, long latency disease**:** Only about 1,000 people are diagnosed with MTC yearly in the United States,[41] making it infeasible to conduct an ARIA analysis to detect MTC after tirzepatide exposure. In addition, MTC grows slowly, where it may take longer than 10 years for MTC to be visible on imaging evaluation.[42] Because of this slow growth rate, patients can have the disease without symptoms for a long time,[41] requiring very long follow up periods to characterize an increase in MTC risk. However, Sentinel is unlikely to include a sufficient number of tirzepatide users with a duration of follow-up long enough to evaluate the development of MTC. For example, the follow-up time data of new GLP-1 receptor agonist users in the Sentinel Distributed Database from January 01, 2008 to January 31, 2018 show that as of January 31, 2018, only 26.6% of GLP-1 receptor agonist users have longer than three years of follow-up time (**Appendix Table 1**).[43]
- There are no specific codes or validated algorithms to identify MTC: Available ICD-10 code for thyroid cancer (C73 "Malignant neoplasm of thyroid gland") and procedure codes for surgical thyroid removal[d] (**Appendix Table 2**) are nonspecific to MTC. Results of diagnostic tests for MTC including fine-needle aspiration biopsy, calcitonin blood test, carcinoembryonic antigen blood test and genetic testing for germline *RET* mutations are not currently available in Sentinel ARIA. Furthermore, there are no known validated algorithms for MTC using ICD-10 code and other procedure codes, based on a search of published medical literature.

5 COVARIATES

5.1 Covariates of Interest

Insufficiency in population, exposure, and study outcome makes detailed evaluation of these factors unnecessary.

5.2 Is ARIA sufficient to assess the covariates of interest?

Insufficiency in population, exposure, and study outcome makes detailed evaluation of these factors unnecessary.

[d] MTC treatment involves surgical removal of the thyroid gland and surrounding lymph nodes. [44]

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Insufficiency in population, exposure, and study outcome makes detailed evaluation of these factors unnecessary.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Insufficiency in population, exposure, and study outcome makes detailed evaluation of these factors unnecessary.

7 NEXT STEPS

Given ARIA Sentinel is insufficient to adequately assess MTC risk, in alignment with other long-acting GLP-1 receptor agonists in the class, DEPI-I recommends that FDA issue a PMR for tirzepatide to assess the MTC safety signal in accordance with Section 505(o)(3) of the FDCA. DEPI-I concurs with the use of the MTC case-series registry, given the potential challenges in obtaining a population with sufficient tirzepatide exposure with long-term follow-up and number of MTC events.

The finalized PMR language is below:

> *Conduct a medullary thyroid carcinoma registry-based case series study of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of tirzepatide into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of tirzepatide.*

Draft Protocol Submission:	*November 2022*
Final Protocol Submission:	*May 2023*
Interim Report Submission:	*March 2024*
	March 2025
	March 2026
	March 2027
	March 2028
	March 2029
	March 2030
	March 2031
	March 2032
	March 2033
	March 2034
	March 2035
	March 2036
	March 2037
	March 2038
	March 2039
Study Completion:	*June 2039*
Final Report Submission:	*June 2040*

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Appendix Table 1. Summary of Follow-Up Months Since the First Observed Valid Dispensing of GLP-1 RA in the Sentinel Distributed Database from January 1, 2008 to January 31, 2018 [1]

	Total	Number of Patients by Follow-Up Time (Months)					
		< 6	6 to < 12	12 to < 24	24 to < 36	36 to < 48	48 or longer
Overall, N (%)	1158706 (100%)	220070 (19.00%)	199074 (17.2%)	251872 (21.7%)	179662 (15.5%)	113308 (9.8%)	194720 (16.8%)
By Age, N							
18-44		36,705	28,962	35,824	20,869	13,531	24,367
45-54		53,519	44,579	56,268	34,574	22,782	43,913
55-64		63,787	56,238	70,734	45,918	29,729	48,825
65-74		53,144	56,330	72,171	63,335	38,809	64,002
75+		12,915	12,965	16,875	14,966	8,457	13,613
By Sex, N							
Female		121,968	108,305	137,700	98,769	62,950	111,920
Male		98,102	90,769	114,172	80,893	50,358	82,800
By year, N							
2008		11,436	15,786	19,852	12,585	8,858	34,740
2009		4,259	4,762	5,990	4,037	2,505	10,345
2010		8,239	7,673	11,968	8,935	8,414	61,489
2011		8,078	8,090	11,114	9,318	7,258	46,527
2012		9,244	8,891	14,410	10,723	47,916	19,357
2013		11,503	12,682	17,375	77,761	11,902	22,212
2014		13,032	13,583	77,341	15,134	26,405	50
2015		58,552	54,834	28,647	41,058	50	
2016		19,906	34,519	65,066	111	-	
2017		75,673	38,254	109	-	-	
2018		148	-	-	-	-	

1. Includes Medicare data from 1/1/2010 to 12/31/2015

Appendix Table 2. Current Procedural Terminology (CPT) Codes for thyroid surgical procedures

CPT Code	CPT Code Description
60210	Partial thyroid lobectomy: unilateral; with or without isthmusectomy
60212	Partial thyroid lobectomy with contralateral subtotal lobectomy, including isthmusectomy
60220	Total thyroid lobectomy, unilateral with or without isthmusectomy
60240	Total thyroidectomy
60260	Completion thyroidectomy
60271	Thyroidectomy – cervical approach
60225	Thyroid lobectomy with contralateral subtotal lobectomy, including isthmusectomy
60252	Thyroidectomy with limited neck dissection
60254	Thyroidectomy with radical neck dissection
60270	Thyroidectomy – sternal split or transthoracic approach

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/s/

YOUJIN WANG
04/29/2022 05:28:26 PM

YANDONG QIANG
05/02/2022 04:06:19 PM

WEI HUA
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JUDITH W ZANDER
05/02/2022 04:49:50 PM

PATRICIA L BRIGHT
05/02/2022 05:25:53 PM

ROBERT BALL
05/02/2022 05:32:28 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 13, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866
Product Name and Strength:	Mounjaro[a] (tirzepatide), 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL
Applicant/Sponsor Name:	Eli Lilly and Company (Eli Lilly)
OSE RCM #:	2021-1827-1
DMEPA 1 Safety Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU) and autoinjector labels on May 12, 2022 and quick reference guide (QRG) on May 11, 2022, for Mounjaro. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised IFU, QRG, and autoinjector labels for Mounjaro (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a human factors study results review.[b]

2 DISCUSSION AND ASSESSMENT

The Applicant did not implement all our IFU and autoinjector label recommendations. However, they provided a justification and response for our consideration.

Regarding the IFU, we note the Applicant did not implement our recommendation to number the step, “Preparing to inject Mounjaro” as a step that is to be completed when using each

[a] The proprietary name, Mounjaro, was found conditionally acceptable on December 2, 2021
[b] Kumar, N. Human factors results review for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 FEB 15. RCM No.: 2021-1827.

autoinjector. The Applicant stated, [redacted] (b) (4) *Preparing to Inject Mounjaro" task, this section has been made distinctive, as seen in the attached IFU. However, to assure maximum patient comprehension, numbered steps should be limited to those critical to receiving the complete dose, with remaining pre and post actions clearly explained/displayed within the instructions."* We find the Applicant's proposal to not number the step, "Preparing to inject Mounjaro" acceptable.

Regarding the IFU, we also note that the Applicant did not implement our recommendation to number the step, "Disposing of your used Pen" as a step that is to be completed when using each autoinjector. The Applicant stated, [redacted] (b) (4) *"Disposing of your used Pen" instructions, a statement has been inserted to raise the prominence (see attached IFU). Lilly has addressed the concern of patients not seeing the disposal instructions by way of increasing visibility of the disposal instructions location within the instructions, rather than numbering as an additional step. This approach is consistent with Lilly's rationale for focusing patient comprehension of completing tasks, as provided in response to 1 above."* We find the Applicant's proposal to not number the step, "Disposing of your used Pen" acceptable.

Regarding the autoinjector labels, we note that the Applicant did not implement our recommendation to add text to the autoinjector label to indicate to the user which end is the needle-end. The Applicant stated, *"Lilly proposes to retain the current proposed autoinjector label. Information contained in the IFU clearly identifies the "Needle End." Lilly's proposed approach for the autoinjector label has extensive use in other marketed product*s." We find the Applicant's proposal acceptable.

3 CONCLUSION

We find the revised IFU, QRG, and autoinjector labels acceptable and we have no additional recommendations at this time.

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/s/

NEHA KUMAR
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 13, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866
Product Name and Strength:	Mounjaro (tirzepatide) injection, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
OSE RCM #:	2021-1828-1
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling and container labels for Mounjaro (tirzepatide) on May 11, 2022 and May 12, 2022, respectively. The Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the revised container labels and carton labeling for Mounjaro (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and a human factors validation study results review.[ab]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Conrad, A. Label and Labeling Review for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Feb 9. RCM No.: 2021-1828.

[b] Kumar, N. Human Factors Study Report Review for Mounjaro (NDA 215866). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 Feb 15. RCM No.: 2021-1827.

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ARIANE O CONRAD
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IDALIA E RYCHLIK
05/13/2022 11:36:02 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 29, 2022
To:	Lindsey Kelly, Pharm.D. Regulatory Project Manager **Division of Diabetes, Lipid Disorders, and Obesity (DDLO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	MOUNJARO (tirzepatide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 215866
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On September 14, 2021, Eli Lilly and Company submitted for the Agency's review an original New Drug Application (NDA) 215866 for MOUNJARO (tirzepatide) injection, for subcutaneous use. The proposed indication for MOUNJARO (tirzepatide) is for the treatment of type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) on September 22, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for MOUNJARO (tirzepatide) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft MOUNJARO (tirzepatide) MG and IFU received on September 14, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 25, 2022.
- Draft MOUNJARO (tirzepatide) Prescribing Information (PI) received on September 14, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 25, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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SAMANTHA E BRYANT
04/29/2022 03:30:03 PM

NYEDRA W BOOKER
04/29/2022 03:38:01 PM

LASHAWN M GRIFFITHS
04/29/2022 03:54:46 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 29, 2022

To: Lindsey Kelly, Regulatory Project Manager
Division of Diabetes, Lipid Disorders, and Obesity Products (DDLO)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda Wilson, Team Leader, OPDP

Subject: OPDP Labeling Comments for MOUNJARO™ (tirzepatide) Injection, for subcutaneous use

NDA: 215866

In response to DDLO's consult request dated September 21, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Mounjaro.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDLO (Lindsey Kelly) on April 25, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DDLO (Lindsey Kelly) on April 25, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

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SAMANTHA E BRYANT
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Addendum Memo to the Full PLLR Labeling Review

Date: 3/18/2022 **Date consulted:** 9/19/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Drug: Mounjaro (tirzepatide) Injection, for subcutaneous use

NDA: 215866

Applicant: Eli Lilly and Company

Subject: Pregnancy and Lactation Labeling (PLLR)

Proposed Indication: A dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP 1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Materials Reviewed:

- DPMH PLLR labeling review by Wenjie Sun, MD dated January 19, 2022. DARRTS Reference ID: 4922584
- Applicant's submitted background package and proposed labeling for NDA 215866
- DDLO consult form for DPMH, DARRTS Reference ID 4861517

Consult Question:

The review team requests DPMH's input on the labeling to be consistent with the Pregnancy and Lactation Labeling Rule.

PURPOSE

The purpose of this addendum is to update the labeling recommendations based on recent discussion with the DDLO Clinical Pharmacology Team regarding tirzepatide induced delayed gastric emptying and impact on absorption of concomitantly administerial oral medication including reduced efficacy of orally administered hormonal contraceptives.

REVIEW ISSUE

In recent discussion with the DDLO review team, it was noted there is anticipated drug-to-drug interaction between tirzepatide and oral hormonal contraceptives due to delayed gastric emptying. The Clinical Pharmacology Team notes the following:

> Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean Cmax of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%,66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23% respectively. A delay in tmax of 2.5 to 4.5 hours was observed. (b) (4)

Like other GLP-1 receptor agonist, tirzepatide also delays gastric emptying. Because the efficacy of the oral hormonal contraceptive is affected by administration of tirzepatide secondary to delayed gastric emptying, DPMH recommends insertion of language regarding oral hormonal contraceptive use under subsection 8.3 and section 17 of the labeling. Additional consideration should be given to exposure window based on the half-life of tirzepatide, which is 5.4 days from population pharmacokinetic analysis in patients with type 2 diabetes. Therefore, DPMH recommends patients to use a non-oral contraceptive method during treatment and for 27 days (based on 5 times half-life) after treatment. This was confirmed in discussion with the Clinical Pharmacology Team.

LABELING RECOMMENDATIONS

DPMH edited the language in the draft tirzepatide labeling Highlights, subsections 8.1, 8.2, 8.3, and section 17 for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. Note: The DPMH recommended language for subsections 8.1 and 8.2 are not repeated below and the reader is referred to the DPMH full PLLR labeling review dated January 19, 2022.

(b) (4)

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/s/

WENJIE SUN
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TAMARA N JOHNSON
03/21/2022 07:04:57 AM

LYNNE P YAO
03/24/2022 10:58:14 AM

Clinical Inspection Summary

Date	March 17, 2022
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Frank Pucino, Pharm. D., Clinical Reviewer Michael Nguyen, M.D., Clinical Team Leader Patrick Archdeacon, M.D., Associate Director Lindsey Kelly, Pharm.D., Regulatory Project Manager Division of Diabetes, Lipid Disorders and Obesity (DDLO)
NDA #	215866
Applicant	Eli Lilly and Company
Drug	Tirzepatide (LY3298176)
NME (Yes/No)	Yes
Review Priority	Priority
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Consultation Request Date	October 20, 2021
Summary Goal Date	February 15, 2022; extended to March 25, 2022
Action Goal Date	April 15, 2022
PDUFA Date	May 15, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies I8F-MC-GPGH, I8F-MC-GPGI and I8F-MC-GPGL were submitted to the Agency in support of New Drug Application (NDA) for tirzepatide (LY3298176) injection, for the proposed indication of as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Five clinical investigators (CIs): Drs. Rizwana Mohseni (US; Site #115 for Study I8F-MC-GPGH and Site #118 for Study I8F-MC-GPGL), Stanley Hsai (US; Site #116 for Study I8F-MC-GPGH and Site #114 for Study I8F-MC-GPGL), Juan Frias (US; Site #118 for Study I8F-MC-GPGH and Site #113 for Study I8F-MC-GPGL), Dominik Dahl (Germany; Site #300 for Study I8F-MC-GPGI) and Helga Zeller-Stefan (Germany; Site #309 for Study I8F-MC-GPGI) were selected for clinical inspections. In addition, the sponsor Eli Lilly and Company was selected for inspection.

Inspections of the investigators and the sponsor found no significant regulatory violations. Based on the results of inspections and regulatory assessments, Studies I8F-MC-GPGH, I8F-MC-GPGI and I8F-MC-GPGL appear to have been conducted adequately, and the data generated by the CI sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Eli Lilly and Company (Lilly) submitted NDA 215866 on 09/15/2021 for tirzepatide (TZP) injection, with the proposed tradename of MOUNJARO, as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Tirzepatide is a dual GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptor agonist administered once-weekly by subcutaneous (SC) route of injection. Data from 5 pivotal Phase 3 clinical studies (I8F-MC-GPGH, GPGI, GPGK, GPGL, GPGM) were submitted to support the application. Inspections were requested for 3 of the studies (GPGH, GPGI and GPGL).

Study I8F-MC-GPGH (GPGH)

Study I8F-MC-GPGH (GPGH) was a Phase 3, international, multicenter, randomized, open-label, parallel-group, 52-week, active comparator-controlled study to assess the efficacy and safety of three once-weekly doses of tirzepatide (5 mg, 10 mg and 15 mg) compared with titrated insulin degludec in patients with T2DM naive of insulin treatment who had inadequate glycemic control on stable doses of metformin with or without a sodium-glucose cotransporter-2 inhibitor (SGLT-2i). The primary efficacy endpoint was the mean change from baseline in glycosylated hemoglobin A1c (HbA1c) at Week 52.

Eligible patients were randomized 1:1:1:1 to receive once-weekly (QW) injectable (SC via a single-dose pen) tirzepatide 5 mg, 10 mg, 15 mg, or once-daily injectable insulin degludec. For patients randomized to tirzepatide groups, the starting dose of tirzepatide was 2.5 mg QW for 4 weeks and then increased by 2.5 mg every 4 weeks until the maintenance dose was reached. The study drug escalation period was 24 weeks, which allowed 20 weeks to escalate to tirzepatide 15 mg and an additional 4 weeks to reach steady state.

Dosing for patients randomized to insulin degludec group started at 10 units once daily. Patients adjusted their insulin degludec doses QW to a target fasting blood glucose (FBG) of < 90 mg/dL based on the median value of the last three self-monitored blood glucose values according to a treat-to-target algorithm.

The study screened a total of 1947 subjects, randomized 1444 subjects in 121 study sites in Argentina, Austria, Greece, Hungary, Italy, Poland, Romania, South Korea, Spain, Taiwan, Ukraine and the US. The first subject's first visit was on (b) (6) and the last subject's last visit was on (b) (6) A total of 1437 subjects received at least 1 dose of study drug, and 1325 subjects completed the study (1230 on the study drug). The analyses are based on two database locks. The primary outcome database lock concluded on 02/05/2021 and included all data except immunogenicity data. The final database lock concluded on 03/18/2021 and included immunogenicity data.

Study I8F-MC-GPGI (GPGI)

Study I8F-MC-GPGI was a Phase 3, international, multicenter, randomized, double-blind, parallel-group, 40-week, placebo-controlled study that assessed the safety and efficacy of 5 mg, 10 mg, or 15 mg tirzepatide, as compared with placebo in patients with T2DM, as an add-on to titrated basal insulin glargine with or without metformin. The primary efficacy endpoint was the mean change from baseline in glycosylated HbA1c at Week 40.

Eligible patients were randomized 1:1:1:1 to receive QW SC injectable tirzepatide 5 mg, 10 mg, 15 mg, or placebo via a single-dose pen (SDP). The starting dose of tirzepatide was 2.5 mg and the dose was increased by 2.5 mg every 4 weeks until the assigned maintenance dose was reached. The study drug escalation period was 24 weeks, which allowed 20 weeks to escalate to tirzepatide 15 mg and an additional 4 weeks to reach steady state. Background insulin glargine was titrated by patients using a protocol defined treat-to-target algorithm to reach a target FBG of < 100 mg/dL.

The study screened a total of 586 subjects, randomized 475 subjects at 45 study sites in Czech Republic, Germany, Japan, Poland, Slovakia, Spain and the US (including Puerto Rico). The first subject's first visit was on (b) (6) and the last subject's last visit was on (b) (6) A total of 471 subjects completed the study (424 on the study drug). The primary database lock was on 02/05/2021.

Study I8F-MC-GPGL (GPGL)
Study I8F-MC-GPGL was a Phase 3, international, multicenter, randomized, open-label, parallel group, 40-week, active-controlled study designed to assess the efficacy and safety of three QW doses of tirzepatide (5 mg, 10 mg and 15 mg) compared with QW SC semaglutide (1 mg) in patients with T2DM who have inadequate glycemic control with metformin monotherapy (≥ 1500 mg/day) and had not been treated with any other oral anti-hyperglycemic medications during the 3 months prior to the start of the study. The primary efficacy endpoint was the mean change from baseline in HBA1c at Week 40.

Eligible patients were randomized 1:1:1:1 to receive QW injectable tirzepatide 5 mg, 10 mg, 15 mg or semaglutide 1 mg SC via an SDP. The starting dose of tirzepatide was 2.5 mg, and then increased by 2.5 mg every 4 weeks until the assigned maintenance dose was reached. The drug escalation period was 24 weeks, which allowed 20 weeks to escalate to tirzepatide 15 mg and an additional 4 weeks to reach steady state. The starting dose of semaglutide was 0.25 mg QW, and the dose was doubled every 4 weeks until the 1 mg dose was reached.

The study screened a total of 2526 subjects, randomized 1879 subjects at 128 study sites in Argentina, Australia, Brazil, Canada, Israel, Mexico, the United Kingdom and the US. The first subject's first visit was on (b) (6) and the last subject's last visit was on (b) (6) A total of 1783 subjects completed the study (1678 on the study drug). The primary outcome database lock concluded on 02/21/2021 that included all data except pharmacokinetic (PK), glucagon and immunogenicity results. The second database lock concluded on 03/30/2021 and included glucagon and PK data. The final database lock concluded on 04/16/2021 and included immunogenicity data.

Rationale for Site Selection
Five CIs: Drs. Dominik Dahl, Helga Zeller-Stefan, Juan Frias, Stanley Hsai and Rizwana Mohseni were requested for clinical inspections in support of the application. These sites were selected based on enrolling a high number of subjects to the study that may have an impact in the review division's clinical decision-making process. In addition, the sponsor Eli Lilly was requested for inspection, particularly to review its site monitoring system and Interactive Web

Response System (IWRS) validation process that led to overdose episodes in Studies I8F-MC-GPGH and I8F-MC-GPGI.

III. RESULTS

1. Dominik Dahl, M.D. (Sites #300 for I8F-MC-GPGI)
Besetlerstr. 2a, Diabeteszentrum Hamburg West
Hamburg, Hamburg, 22607
Germany

This CI was inspected on 01/24-28/2022 as a data audit for Study I8F-MC-GPGI. This was the first FDA inspection for Dr. Dahl.

The study site screened and enrolled 18 subjects, with all 18 subjects completed the study. The first subject consented on (b) (6) and the last subject's last visit was on (b) (6) Source records were reviewed for all 18 screened subjects.

Source records reviewed during the inspection included the study protocol and amendments, Informed Consent Forms (ICFs) and versions, documentation of eligibility criteria and enrollment logs, medical records [including laboratory tests, HbA1c, adverse events (AEs) and serious AEs (SAEs)], investigation product (IP) accountability records, visit data, electronic Case Report Forms (eCRFs) and electronic data capture (EDC) entries, protocol deviations and related regulatory documents [e.g., Central Ethics Committee (CEC) and regional Component Authority (CA) approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy data source for HbA1c was verified. The secondary efficacy data sources for body weight changes, serum glucose, serum calcitonin, blood pressure and heart rate were also verified. There were no underreporting of AEs or SAEs.

The following observations were noted and discussed at the end of the inspection:

Protocol deviations:

- Subject (b) (6) (TZP 15 mg) was dispensed 15 mg instead of 10 mg at visit 13 due to an IWRS error. This was not reported as a protocol deviation.
- Subjects (b) (6) (TZP 10 mg) and (b) (6) (placebo) both used insulin 20 U/day that did not meet the inclusion criteria #3 of > 20 U/day insulin use and were both enrolled. The sponsor allowed the enrollment of both subjects and reported the enrollments as protocol deviations.
- The site had about 38 episodes of out of window PK sampling errors due to subjects' schedules and the site's scheduler.

Reviewer's Comments: *The sample collection times were accurately recorded, and these episodes were reported as protocol deviations. The site already implemented correction actions with a new standard operation procedure (SOP) to improve the scheduling and*

provided appropriate staff training. This was discussed with the review division and PK analysis is based on actual sample collecting times.

Record keeping and transcription errors:

- Subject (b) (6) (TZP 10 mg) SAE of "heart failure" on (b) (6) was submitted as (b) (6)
- Subject (b) (6) (placebo) heart rate at visit 22 was listed as 70, instead of 76.
- Subject (TZP 15 mg) body weight for the baseline was listed as 77.1 kg, instead of 81.1 kg.

In general, the protocol deviations, record keeping, and transcription errors found at this site do not appear to importantly affect subject safety or data reliability. A Form 483 (Inspectional Observations) was not issued.

2. **Helga Zeller Stefan, M.D.** (Site #309 for I8F-MC-GPGI)
Elenorastr. 42, InnoDiab Forschung Gmbh
Essen, North Rhine-Westphalia, 45136
Germany

This CI was inspected on 01/17-20/2022 as a data audit for Study I8F-MC-GPGI. This was the first FDA inspection for Dr. Zeller.

The study site screened 18 subjects, enrolled 14 subjects, with 10 subjects completed the study. The first subject consented on (b) (6) and the last subject's last visit was on (b) (6) Source records were reviewed for all the 14 enrolled subjects.

Source records reviewed during the inspection included the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (laboratory tests including HbA1c levels, AEs and SAEs), visit data, paper subject diaries, paper CRFs with eCRFs entries and EDC audits, protocol deviations, related regulatory documents (e.g., CEC and regional CA approvals and communications, financial disclosures, and delegation of authority), monitoring logs, staff training logs and record retention.

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint for HbA1c levels was verified with no discrepancies noted. The secondary endpoints for body weight changes, serum glucose and calcitonin values, blood pressure and heart rate were also verified with no discrepancies noted. There was no underreporting of SAEs.

Examples of protocol deviations that were noted and discussed at the end of the inspection are listed below:

- Subject (b) (6) (TZP 15 mg) basal insulin dose at visit 4 on (b) (6) was adjusted to 24 units instead of 22 units.
- Subject (b) (6) (TZP 15 mg) was dispensed 15 mg instead of 10 mg at visit 13 due to an IWSR error.

In general, the inspection verified source data for most of inspected study subjects, with no significant deficiencies reported. A Form 483 (Inspectional Observations) was not issued.

3. Juan Frias, M.D. (Site #118 for I8F-MC-GPGH; Site #113 for I8F-MC-GPGL)
2010 Wilshire Blvd. Suite 302
Los Angeles, CA 90057

This CI was inspected on 01/12-20/2022 as a data audit for Studies I8F-MC-GPGH and I8F-MC-GPGL. This was the second FDA inspection for Dr. Frias. Previous inspection in 03/2016 was classified as No Action Indicated (NAI).

For Study I8F-MC-GPGH, the study site screened 30 subjects, enrolled 23 subjects, with 19 subjects completed the study. The first subject consented on (b) (6) and the last subject completed the study on (b) (6). Source records of all 23 enrolled subjects were reviewed.

For Study I8F-MC-GPGL, the study site screened 20 subjects, enrolled 11 subjects, with all 11 subjects completed the study. The first subject consented on (b) (6) and the last subject completed the study on (b) (6) Source records of all 11 enrolled subjects were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit logs, laboratory tests of HbA1c, ECGs, AEs and SAEs), visit data, paper CRFs with eCRFs entries and EDC audits, protocol deviations and related regulatory documents [e.g., Institutional Review Board (IRB) approvals and communications, Clinicaltrial.gov registration, staff training logs, and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy data source for HbA1c was verified with no discrepancies noted. The secondary efficacy data source for changes in body weight was also verified with no discrepancies noted. Adverse events were captured except the following:

- For Study I8F-MC-GPGH, Subject (b) (6) (insulin control group) AE of "exacerbation of HTN" with blood pressure of 158/62 at visit 19 (b) (6) was not entered into the EDC and it was not included in the NDA.

Reviewer's Comment*: The isolated unreported AE occurred in subject in the insulin control group.*

In general, the inspection verified source data documentation for most of the inspected study subjects, with no significant deficiencies reported. At the end of the inspection, a Form 483 (Inspectional Observations) was not issued.

4. Stanley Hsai, M.D. (Site #116 for I8F-MC-GPGH; Site #114 for I8F-MC-GPGL)
6011 Pacific Blvd. Suite 116
Huntington Park, CA 90255

This CI was inspected on 12/06-10/2021 as a data audit for Studies I8F-MC-GPGH and I8F-MC-GPGL. This was the first FDA inspection for Dr. Hsai.

For Study I8F-MC-GPGH, the study site screened 56 subjects, enrolled 40 subjects, with 32 subjects completed the study. The first subject consented on (b) (6) and the last subject completed the study on (b) (6). Source records of 25/56 screened subjects were reviewed.

For Study I8F-MC-GPGL, the study site screened 36 subjects, enrolled 27 subjects, with 24 subjects completed the study. The first subject consented on (b) (6) and the last subject completed the study on (b) (6). Source records of 27/36 screened subjects were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit logs, laboratory tests including HbA1c levels, AEs and SAEs), visit data, eCRFs and EDC entries with audit, protocol deviations, IP accountability and related regulatory documents (e.g., IRB approvals and communications, study monitoring, Clinicaltrial.gov registration, financial disclosure, staff training logs, and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies found. There were no underreporting of AEs or SAEs.

It was noted that, for Study I8H-MC-GPGH, Subject (b) (6) (TZP 10 mg) met the exclusion criteria #12 (baseline eye examination was not fully evaluable due to presence of a cataract) and should not be enrolled. The sponsor identified the issue after the subject completed the study and reported it as a protocol deviation.

The inspection verified adequate source data documentation for the inspected study subjects, with no significant deficiencies reported. A Form 483 (Inspectional Observations) was not issued.

5. Rizwana Mohseni, D.O. (Site #115 for I8F-MC-GPGH; Site #118 for I8F-MC-GPGL)
5050 Palo Verde Street, Suite 103
Montclair, CA 91763

This CI was inspected on 12/13-17/2021 as a data audit for Studies I8F-MC-GPGH and I8F-MC-GPGL. This was the first FDA inspection for Dr. Mohseni.

For Study I8F-MC-GPGH, the study site screened 28 subjects, enrolled 19 subjects, with 12 subjects completed the study. The first subject consented on (b) (6) and the last subject completed the study on (b) (6) Source records of 13/19 enrolled subjects were reviewed.

For Study I8F-MC-GPGL, the study site screened 45 subjects, enrolled 27 subjects, with 24 subjects completed the study. The first subject consented on (b) (6) and the last subject completed the study on (b) (6). Source records of 10/27 enrolled subjects were reviewed.

Source records reviewed during the inspection included the study protocol and amendments, ICFs and versions, documentation of eligibility criteria and enrollment logs, medical records (including visit logs, laboratory tests including HbA1c levels, AEs and SAEs), visit data, subject diaries, paper CRFs with eCRFs transcription and EDC audit, protocol deviations, IP accountability and related regulatory documents (e.g., IRB approvals and communications, study monitoring, Clinicaltrial.gov registration, financial disclosure, staff training logs, and delegation of authority).

The submitted data were verifiable with source records at the study site. The primary efficacy data source of HbA1c levels were verified with no discrepancies noted. The secondary efficacy data source for changes in body weight were also verified with no discrepancies. There were no underreporting of AEs or SAEs.

The following was discussed with the investigator during the inspection:

- IP storage and accountability documentation: IP to be returned from closed studies was mixed with unused IP from active studies. The master accountability log for both studies were inconsistently used and incomplete, although documentation of each IP shipment to the site, quantities and dates of distribution to subjects, and final disposition (e.g., destruction, return to sponsor) appeared adequate.

The inspection verified adequate source documentation for the inspected study subjects, with no significant deficiencies reported. A Form 483 (Inspectional Observations) was not issued.

6. Eli Lilly & Company (Sponsor)
839 S Delaware Street
Indianapolis, IN 46225

The sponsor was inspected on 01/04-13/2022 as a data audit for Studies I8F-MC-GPGH, I8F-MC-GPGI, and I8F-MC-GPGL. Recent inspections were in 03/2020 (NAI) and 02/2021 [voluntary action indicated (VAI)]. There was also a remote regulatory assessment in 03/2021 with no significant issues identified.

The inspection reviewed the sponsor's organizational structure, overall accountability for quality management, conduct and oversite of the inspected studies, IP management system, CIs selection and training, trial master files, data collection and handling, quality assurance and auditing.

In particular, the inspection reviewed detailed files for 11 of the CIs sites: four sites (#117, #152, #506 and #605) for Study I8F-MC-GPGH; four sites (#300, #309, #403 and #429) for Study I8F-MC-GPGI; and three sites (#133, #301 and #604) for Study I8F-MC-GPGL. The inspection reviewed documents regarding IRB approvals; FDA1572s; data management; site and CIs selection and qualification; monitor qualifications, plan and visit reports; investigator non-compliances; escalation process of non-compliant sites and corrective actions; quality assurance; site correspondence; AE and safety reporting; protocol deviations, drug overdose cases; IWRS use/testing/validation and IP accountability.

IWRS (Interactive Web Response System) Dispensing Error and Improper Dosing

The incorrect IWRS dispensing of the investigational product resulted in improper dosing of patients who were enrolled in Studies I8F-MC-GPGH and I8F-MC-GPGI. A summary of improper dosing due to IWRS dispensing error is presented in Table 1.

Table 1: Summary of Improper Dosing as Result of IWRS Error

Site-Subject#	Visit #	Assigned Dose (TZP)	Dispensed Dose (TZP)	Potentially Related AEs Reported Within 4 Weeks of the Incorrect Dispensation at Visit 13
Study I8F-MC-GPGI				
(b) (6)	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	Diarrhea
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
	13	10 mg	15 mg	Lipase and amylase increased; diarrhea; large intestine polyp
	13	10 mg	15 mg	None
	13	10 mg	15 mg	Vomiting; decreased appetite
	13	10 mg	15 mg	None
	13	10 mg	15 mg	None
Additional Dosing Error				
(b) (6) *	12	7.5 mg	15 mg	No AE
Study I8F-MC-GPGH				
(b) (6)	18/19	15mg	10 mg	No AE

* (b) (6): error identified after the study closed.

As shown in Table 1, for Study I8F-MC-GPGI: on 01/08/2020, there were a total of 17 patients, who were dispensed 15 mg TZP instead of 10 mg on Visit 13 due to incorrect configuration input to IWRS. An additional patient ((b) (6)) received an incorrect dose of 15 mg instead

of the scheduled 7.5 mg at the non-dispensing Visit 12 due to an error in the IWRS. None of the subjects reported any adverse events such as hypoglycemia related to the overdose.

For Study I8F-MC-GPGH: one subject (b) (6) TZP15 mg group), the first subject received any IP for Visit 18, was dispensed TZP 10 mg instead of 15 mg. The site found that the incorrect dose was dispensed to the subject and reported the error to the sponsor on 11/25/2019. The sponsor's checking of the IWRS also found a similar incorrect dose assigned for Visit 19. The dosing error of Subject (b) (6) is reported as a protocol deviation in the submission. No other subject received any incorrect dose for Visits 18 and 19.

At the end of the inspection, the FDA inspector discussed the above observation related to inadequate IWRS dispensing process that has resulted incorrect dosing of subjects with the sponsor. The sponsor acknowledged the issue and stated corrective actions have been taken including implementation of a revised IWRS template and a "Modernization Project" to improve the IWRS dispensing process.

Reviewer's Comments: *Per the sponsor's responses dated on 03/14/2022 to FDA's information request that no other adverse events were identified other than listed above for the 17 impacted subjects who were overdosed due to inadequate IWRS dispensing process. Sixteen (16) of the impacted subjects completed the study and 1 subject was lost to follow up. The dosing errors for all subjects were reported as a protocol deviation in the submission. It is not known if the reported dosing errors potentially impact mean change in glycosylated HbA1c at Week 40, although the sponsor stated that the overdosing issue does not impact the primary efficacy endpoint assessment of the studies. We recommend that FDA's statistical team conduct sensitivity analysis to evaluate the robustness of the reported primary efficacy outcome if the review division has concerns. The sponsor confirmed that there are no additional unreported dosing errors due to inadequate IWRS dispensing errors for all studies submitted in the NDA.*

{See appended electronic signature page}

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

/s/

LING YANG
03/24/2022 11:38:05 AM

ANTHONY J ORENCIA
03/24/2022 12:30:17 PM
Concur: Anthony Orencia, MD, FACP, on behalf of Min Lu, MD, MPH

KASSA AYALEW
03/24/2022 01:11:37 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: February 16, 2022

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst, DCN

To: Lindsey Kelly, RPM
DDLO

Subject: IRT Consult to NDA-215866 (SDN001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/26/2022 regarding the Division's QT related question. We reviewed the following materials:

- Previous IRT review for IND-128801 dated 08/24/2018 in DARRTS (link);
- Sponsor's PK/PD study report (SN0001; link);
- Sponsor's hERG study report (SN0001; link); and
- Sponsor's proposed product label (SN0003; link).

1 IRT Responses

Question 1: Eli Lilly has submitted a new NDA for tirzepatide (IND-128801), a GIP/GLP-1 dual receptor agonist. This application is in The Program and Lilly submitted a priority review voucher, so this will be on an 8-month clock (PDUFA Goal Date: May 15, 2022). We are requesting this consult for IRT to review the applicant's clinical QT assessment as part of the population PK/PD report and the in vitro hERG study report. Please also comment if the dose and concentration versus heart rate relationship is similar between the Japanese and the non-Japanese population.

IRT's Response: The submitted non-clinical and clinical data do not indicate any unexpected or important effects of tirzepatide on the QTc interval at clinically relevant exposures associated with the proposed dose (i.e., up to 15 mg once weekly). The applicant did not propose QT labeling language in Section 12.2 (Cardiac Electrophysiology, link). We agree with the applicant's proposal because it is consistent with our labeling practices for peptides and large targeted proteins when a dedicated QT study has not been conducted.

2 Internal Comments to the Division

- *Considering we were notified late in the review cycle, we did not conduct an independent review of the sponsor's PK/PD analysis. In absence of independent assessment of submitted raw data, we are unable to comment on the observed concentration-heart rate relationship as well as any differences between Japanese and non-Japanese populations.*
- *We recommend evaluating the presser effects of new drugs used chronically in patient population with a high cardiovascular risk (e.g., type 2 diabetes mellitus) in accordance with pressor effects draft guidance (Feb-2022, link).*

3 Background

3.1 Product Information

Eli Lilly and Company is developing tirzepatide an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (adult patients). Tirzepatide (MW: 4813 Da; synthetic peptide with 39-amino acids) is a dual the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist.

The product is formulated as sterile solution (single-dose pen; 0.5 mL water for injection) containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg tirzepatide (a ready-to-inject, fixed-dose of a single-use) for subcutaneous (self-) administration (the abdomen, thigh, or upper arm). The proposed therapeutic dose includes starting dose of 2.5 mg once weekly which can be increased to 5 mg once weekly after 4 weeks. The maximum recommended dose is 15 mg once weekly which can be achieved with increments of 2.5 mg after a minimum of 4 weeks on the current dose.

The peak concentrations of ~1990 ng/mL (Tmax: ~24 h, range 8 to 72 h; half-life: ~120 h) are expected at steady state with the anticipated therapeutic dose (POP-PK). The sponsor claims that tirzepatide has a low drug interaction potential as a victim drug as it undergoes proteolytic degradation similar to other peptides and is not metabolized by the CYP450 enzymes. The human mass balance study indicates that ~21% of the drug (as TR) is excreted in feces, and ~50% (as TR) in urine (total recovery: ~70% Study # I8F-MC-GPHX) with no intact tirzepatide observed in urine or feces. The exposures of tirzepatide are not expected to be affected significantly in subjects with renal or hepatic impairment. No dose adjustment is proposed in subjects with mild, moderate, or severe renal impairment or mild, moderate, or severe hepatic impairment. In summary, the exposures of tirzepatide are not likely affected by intrinsic and extrinsic factors significantly and therapeutic exposures associated with highest dose (i.e., 15 mg once weekly) represents high clinical exposure scenario.

Tirzepatide was the largest component in plasma accounting for approximately 80% of the circulating radioactivity. The 4 minor metabolites in plasma, M1 + M3 (co-eluting), M4 and M13, resulted from proteolytic cleavage of the peptide backbone and each individually accounted for less than 5.7% of total circulating radioactivity. Plasma metabolites were formed from proteolytic cleavage of the peptide backbone of tirzepatide leaving the linker moiety and intact C20 fatty diacid unchanged. Six metabolites were identified in urine. The 2 prominent metabolites (M5 and M7) in urine, represented 20.6% and 9.4% of the dose and 4 minor metabolites (M8, M11, M17, and M18) each represented less than 3% of the dose. All metabolites in urine were formed by proteolytic cleavage of the peptide backbone and β-oxidation of the C20 fatty acid, with 2

metabolites, M11 and M17, showing additional amide hydrolysis in the linker region. o Six metabolites were identified in feces. The 6 metabolites (M12, M5, M19, M7, M11, and M8) identified accounted for a total of 6.8%, 3.3%, 2.9%, 1.0%, 0.6%, and 0.5% of the dose. All metabolites in feces were formed by proteolytic cleavage of the peptide backbone and β-oxidation of the C20 fatty acid, with 2 metabolites, M12 and M19, showing additional amide hydrolysis in the linker region.

No significant relationship between renal function and tirzepatide exposure was detected. Based on known understanding of tirzepatide metabolism pathways, hepatic impairment is not expected to directly influence tirzepatide PK.

Previously, the IRT reviewed the sponsor's request for substitution of thorough QT study. Considering that it is challenging to conduct a dedicated QT study with given long half-life of tirzepatide and titration schedule to achieve steady state concentrations associated with highest dose, the IRT recommended integrated assessment using non-clinical data and additional ECG collections in planned phase-3 studies. Refer to previous IRT review for IND-128801 dated 08/24/2018 in DARRTS (link).

During the same time frame the IRT was evaluating QT prolongation risk of peptides in general. Based on the IRT's recent assessment of historical clinical and non-clinical data, peptides comprised of naturally occurring amino acids have a low likelihood of direct ion channel interactions and a thorough QT study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies. Considering that tirzepatide is metabolized releasing free linker and that there is a limited data available on the exposures of free linker in the systemic circulation, the IRT reviewed submitted non-clinical and clinical data.

3.2 Sponsor's Position related to the Question

The sponsor requesting substitution of thorough QT study and claims that there is a low risk of QT prolongations associated with subcutaneous administration of tirzepatide based on the data from their non-clinical (Section 3.3) and clinical studies (Studies # GPGA, GPGB, & GPGF).

QT interval corrected using Fridericia's formula (QTcF) prolongation: Tirzepatide did not lead to QTcF prolongation at any of the dose levels investigated in the clinical program and consequently there was lack of concentration effect relationship with corrected QT interval.

In accordance with the ICH guidance on using concentration-QTc (C-QTc) modeling as primary analysis method for assessing QT interval prolongation risk for tirzepatide, popPK model-based analyses were conducted utilizing all data from healthy participants and patients with T2DM who were given either placebo or tirzepatide in Phase 1 Study GPGA and Phase 2 Studies GPGB and GPGF. Tirzepatide concentrations and ECG measurements were collected in Phase 1 Study GPGA and in Phase 2 Studies GPGB and GPGF.

In Study GPGA Part A, which investigated single doses of tirzepatide 0.25 to 8 mg in healthy participants, triplicate ECGs were obtained at pre-dose and 8 hours post dose, and at 24, 48, 72, 96, 120, 168, and 336-hours post-dose at a time matched to pre-dose.

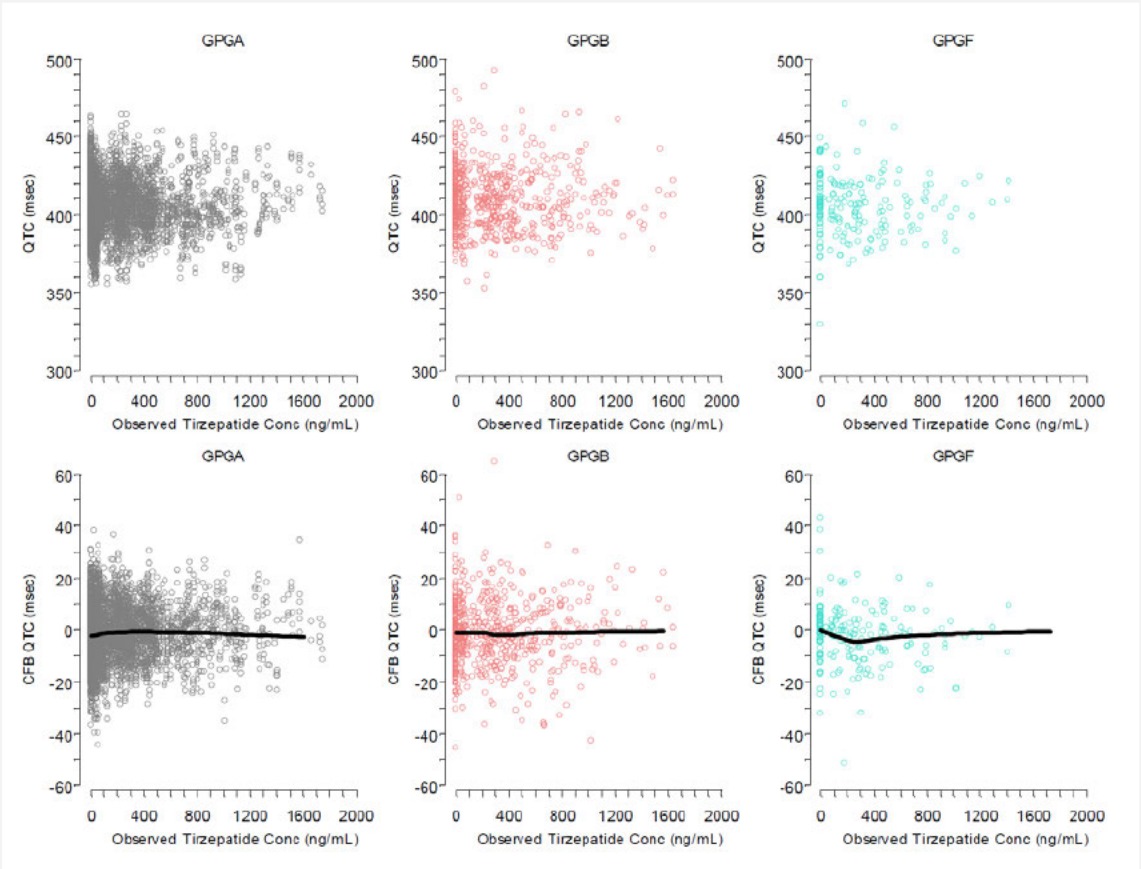
In Study GPGA Parts B and C, which investigated weekly dosing of tirzepatide 0.5 to 15 mg over 4 weeks, triplicate ECGs were measured at pre-dose, and 8 hours after dose administration on Days 1 and 22 and on Days 2, 3, 4, 8, 23, 25, 29, and 36 at a time matched to pre-dose. The ECG prior

to the first dose of tirzepatide was taken in triplicate every 15 minutes for 1 hour to establish a baseline. Electrocardiograms were recorded before collecting any blood for safety or PK samples.

In Study GPGB, triplicate measurements of ECG were collected prior to the first dose of tirzepatide and with weekly treatment of tirzepatide 5, 10, and 15 mg at 8, 12, and 26 weeks. During Study GPGF, triplicate ECGs were measured prior to the first dose of tirzepatide and at 4, 8, and 12 weeks of tirzepatide 2.5, 4, 5, 7.5, 10, 12, and 15 mg administered weekly. The ECGs were collected immediately prior to PK sample collection.

The relationship between tirzepatide concentration and corrected QT interval (QTc) and the relationship between tirzepatide concentration and PR interval were evaluated using the guidance and recommended techniques in the recently published scientific white paper on concentration-QTc modeling (Garnett et al. 2018). In the concentration-QTc analysis, baseline-adjusted and Fridericia-corrected QT interval (ΔQTcF) was used at the dependent variable. For the calculation of ΔQTcF, baseline was the average of QTc measurements obtained immediately prior to the first dose of tirzepatide administered during the study period. Each QTc measurement was paired to the tirzepatide concentration sample obtained closest to the time of ECG recording. Tirzepatide concentration for placebo treatment was considered to be zero. Scatter plots of paired ΔQTcF and tirzepatide concentration with a less smooth line are shown in Figure APP.2.7.2.5.1.

Figure APP.2.7.2.5.1. QTcF (top row) and change from baseline QTcF (bottom row) across tirzepatide concentrations for Studies GPGA, GPGB, and GPGF.



Abbreviations: CFB = change from baseline, Conc = concentration, QTC/QTcF = Fridericia-corrected QT interval.
Note: The circles represent study observations and the solid line is a loess smoothing line.

A prespecified direct response linear mixed effects (LME) model was used to evaluate the relationship between tirzepatide concentration and ΔQTcF. The fixed effect parameters included in the model are intercept, slope, influence of baseline QTcF (msec), treatment (active = 1 or placebo = 0), disease status (T2DM = 1 or healthy subject=0), influence of time after most recent tirzepatide dose administration, and time on treatment. Subject was included as an additive random effect on both intercept and slope terms, and additive residual error was estimated. The prespecified LME model was implemented in R version 3.4.4.

Table APP.2.7.2.5.1. Tirzepatide Concentration - ΔQTcF Model Parameter Estimates

Study	**GPGA**	**GPGB**	**GPGF**	**Combined**
N (nobs)	137 (3859)	220 (630)	91 (195)	448 (4684)
Mean baseline QTcF	407	411	408	409
Fixed Effects				
Intercept	-4.16 (1.28) [p=0.0011]	-1.25 (2.38) [p=0.600]	-8.30 (4.94) [p=0.0958]	-4.64 (1.14) [p<0.001]
$Slope_{CONC}$	-0.00109 (0.00156) [p=0.486]	-0.000674 (0.00203) [p=0.741]	-0.00521 (0.00401) [p=0.197]	-0.000331 (0.00111) [p=0.767]
$Slope_{BSLN}$[a]	-0.166 (0.0291) [p<0.001]	-0.204 (0.0346) [p<0.001]	-0.149 (0.0579) [p=0.0114]	-0.187 (0.0216) [p<0.001]
$Slope_{TRT}$[b]	-0.335 (1.39) [p=0.809]	0.0887 (1.83) [p=0.961]	-0.517 (3.12) [p=0.869]	-0.569 (1.04) [p=0.584]
$Slope_{TFDS}$	0.00148 (0.00174) [p=0.395]	0.00946 (0.0118) [p=0.424]	0.0252 (0.0255) [p=0.325]	0.00570 (0.00145) [p<0.001]
$Slope_{STTM}$	0.577 (0.132) [p<0.001]	-0.0886 (0.0550) [p=0.108]	0.481 (0.267) [p=0.0746]	-0.00222 (0.0419) [p=0.958]
$Slope_{T2DM}$[c]	4.83 (1.02) [p<0.001]	NE	NE	3.33 (1.01) [p=0.001]
Random Effects[d]				
IIV Intercept	6.30	8.44	9.56	7.58
IIV Correlation	-0.610	-0.078	-0.777	-0.379
IIV Slope	0.0101	0.00259	0.0117	0.00871
Residual Error[e]	8.01	8.82	8.82	8.16
Model Predicted Mean (90% CI)[f]				
Placebo ΔQTcF	1.58 (-0.325; 3.57)	-4.75 (-9.46; 0.0517)	-10.7 (-22.0; 2.45)	-1.52 (-3.56; 0.594)
Tirzepatide ΔQTcF	1.24 (-0.283; 2.79)	-4.75 (-8.66; -0.928)	-11.4 (-19.9; -2.11)	-2.11 (-3.84; -0.364)
ΔΔQTcF	-0.334 (-0.986; 0.338)	0.0709 (-1.80; 1.87)	-0.773 (-5.44; 3.33)	-0.570 (-1.52; 0.352)

Tirzepatide Concentration - ΔQTcF Model Parameter Estimates Abbreviations: Δ = change from baseline; ΔΔ = placebo-adjusted change from baseline CI = confidence interval; Cmax,ss = maximum concentration at steady state; HV = healthy volunteer; IIV = inter-individual variability; N = number of subjects or patients; NE = not estimated; nobs = number of observations; PK = pharmacokinetic; QTcF = Fridericia-corrected QT interval; QW = once weekly; SD = standard deviation; SlopeBSLN = influence of baseline QTcF; SlopeCONC = influence of tirzepatide concentration; SlopeSTTM = influence of study time period (weeks); SlopeTFDS = influence of time (h) after most recent tirzepatide dose administration; SlopeTRT = influence of treatment (0=placebo, 1=active); SlopeT2DM = influence of disease status (0=HV, 1=T2DM); T2DM = type 2 diabetes mellitus;. Note: Parameters for fixed effects are reported as estimate (standard error) [p-value]. [a] *The influence of baseline QTcF was centered on the mean baseline QTcF (ie, individual baseline QTcF – mean baseline QTcF).* [b] *0 = placebo, 1 = active treatment.* [c] *0 = healthy volunteer, 1 = patient with T2DM.* [d] *IIV reported as SD.* [e] *Additive residual error.* [f] *The PK model predicted mean Cmax,ss = 1560 ng/mL for tirzepatide 15 mg QW. The model-predicted ΔQTcF are calculated based on Cmax,ss,*

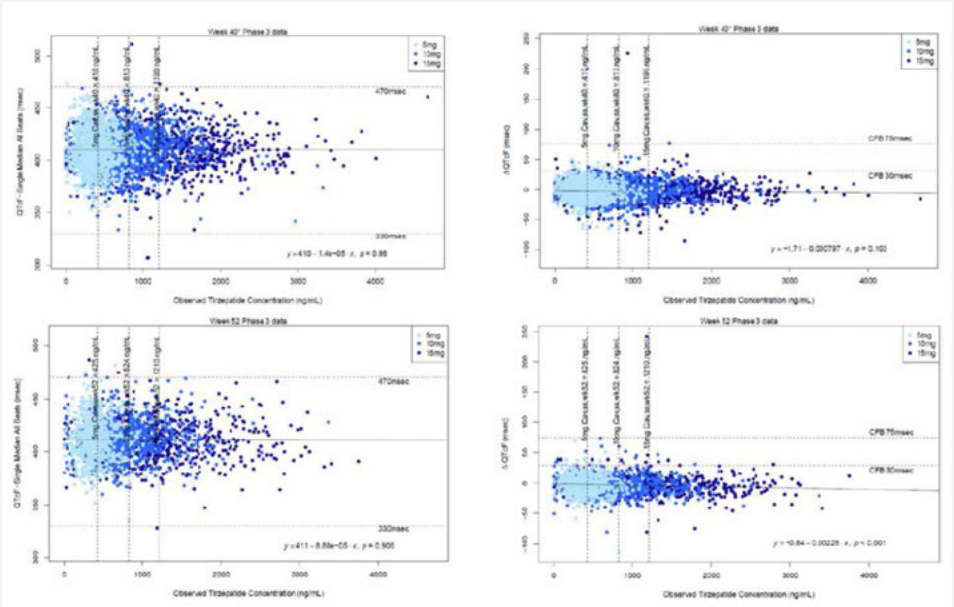
mean baseline QTcF, at time from dose = 24 hours, treatment week = 4 (Study GPGA), 26 (Study GPGB and combined), or 12 (Study GPGF), and for a patient with T2DM. To estimate mean and 90% CI, the models were bootstrapped for 1000 replicates, except for the Study GPGF model, which was bootstrapped for 500 replicates due to convergence issues.

Nonparametric bootstrapping was used to calculate 90% confidence intervals (CIs) of model-predicted mean ΔQTcF and placebo-adjusted ΔQTcF (ΔΔQTcF). To explore possible differences between studies, the prespecified LME model was used to analyze the tirzepatide concentration and ΔQTcF from each individual study. Additionally, the data from Studies GPGA, GPGB, and GPGF were pooled and analyzed with the prespecified LME model.

The LME models were used to predict the ΔQTcF for placebo and for the mean steady-state maximum concentration (Cmax,ss) predicted for tirzepatide 15 mg, the highest dose proposed to be included in Phase 3. For the calculation of model predicted mean ΔQTcF, the PK model predicted mean Cmax,ss of 1560 ng/mL for tirzepatide 15 mg QW was used. The following conditions were also assumed for the model predictions: for influence of time from dose, time is assumed to be 24h, which approximates time of maximum concentration; for influence of time on treatment, time is assumed to be 26 weeks of treatment; and for the influence of disease status, the assumption was patient with T2DM. The placebo ΔQTcF was subtracted from the tirzepatide ΔQTcF to calculate ΔΔQTcF.

Similar graphical exploration of PR interval versus observed tirzepatide concentration was conducted. The positive slopes for PR interval matched to observed tirzepatide concentrations did not reach statistical significance... Additionally, concentration effect analysis was performed for PR interval, based on data from Phase 1 and Phase 2 studies. Tirzepatide did not impact the PR interval.

Figure 9.24 Observed ECG QTcF matched with observed tirzepatide concentration – absolute (left) and change from baseline (right) at Weeks 40 and 52 (rows).



Abbreviations: Cav,ss = average steady-state tirzepatide concentration; Conc = tirzepatide concentration; Δ = change from baseline; ECG = electrocardiogram; QTcF = QTc interval corrected using Fridericia's formula. Note: Vertical dashed lines denote average tirzepatide concentration for each treatment arm (5, 10, or 15 mg) at the study week in the plot. Horizontal dashed lines denote reference values. The solid line is a linear regression. Number of

*QTcF/Conc data pairs 3566 (Week 40) and 1991 (Week 52) Number of ΔQTcF/Conc data pairs 3396 (Week 40) and 1902 (Week 52) Top left: Week 40 QTcF = 410 – 0.000014*Conc (p=0.980); Top right: Week 40 ΔQTcF = -1.71 – 0.000797*Conc (p=0.103); Bottom left: Week 52 QTcF = 411 – 0.000089*Conc (p=0.906); Bottom right: Week 52 ΔQTcF = -0.84 – 0.00226*Conc (p<0.001).*

The QTcF interval values in the Phase 3 studies were generally within clinically acceptable limits. In the analysis of the relationship of QTcF interval matched by date to observed tirzepatide concentration, the Week 52 change from baseline negative slope was statistically significant. The slopes in analyses of QTcF interval (absolute and change from baseline) at Week 40 were also negative but did not reach statistical significance (Figure 9.24).

3.3 Nonclinical Cardiac Safety

Refer to the sponsor's hERG assay report.

LY3298176 inhibited hERG current by (Mean ± SEM; n = 3) 1.5 ± 0.5% at 30 µM and 2.6 ± 0.3% at 300 µM versus 1.9 ± 0.3% (n = 3) in control. hERG inhibition at 30 and 300 µM was not statistically significant (P < 0.05) when compared to vehicle control values. The IC50 for the inhibitory effect of LY3298176 on hERG potassium current was not calculated but was estimated to be greater than 300 µM.

Reviewer's assessment: *The sponsor evaluated the effects of tirzepatide on hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The GLP hERG study report (180917-fmd; link) describes the potential effects of tirzepatide on the hERG current in HEK293 cells. The hERG current was assessed at near-physiological temperature (33 - 35 °C), using a voltage protocol that is similar to the recommended hERG current protocol by the FDA (link). The reviewer does not expect protocol differences to impact hERG current pharmacology. The positive control (60 nM terfenadine) inhibited hERG potassium current by 87.3 ± 2.1% (n=2). Samples of the test article solutions collected from the outflow of the chamber were analyzed for concentration verification. The results from the sample analysis indicated that the measured concentrations of tirzepatide were within ± 10% of nominal concentrations, thereby meeting the acceptance criteria and nominal concentrations were used to describe drug effects.*

Tirzepatide inhibited the hERG currents by 1.5 % and 2.6% at 30 and 300 µM, respectively. The IC50 of tirzepatide inhibit the hERG current is expected to be higher than 300 µM.

The hERG safety margin of tirzepatide on hERG current are summarized below:

Table 1 Safety Margin of tirzepatide on hERG Current

	Cmax (ng/mL)	***Protein Binding***	***Free Cmax (ng/mL)***	***hERG IC50 (µM)***	***Mol Weight (Da.)***	***Safety Margin (Ratio)***
Tirzepatide	*1990*	*99%*	*19.9*	*>300*	*4813*	*>72557x*

The Cmax of Tirzepatide following 15 mg once a week at steady state was ~1990 ng/mL.

The GLP in vivo study (8323700) assessed the potential cardiovascular effects of tirzepatide in instrumented male cynomolgus monkeys when a single dose was administered by subcutaneous injection in a parallel dosing design. Eighteen male cynomolgus monkeys were assigned to three groups (vehicle control group, 0.05 mg/kg group and 0.15 mg/kg group, 6 monkeys/group). The

ECG leads of the transmitter were arranged in an approximate Lead II configuration, with negative ECG lead placement via the jugular vein and positive ECG lead placement on the diaphragm. Telemetry ECG measurements were recorded for at least 2.5 hours prior to dosing and continuously for at least 97 hours after dosing. Blood samples were collected approximately 6 hours ± 15 minutes post-dose on Day 1. The mean (± SD) Cmax were 329 ± 72 and 1335 ± 105 ng/mL, at 0.05 mg/kg and 0.15 mg/kg, respectively. The exposure did not exceed (i.e., 0.67x) the anticipated clinical exposure in humans (1990 ng/mL). Tirzepatide at 0.05 and 0.15 mg/kg produced no test article-related effect on QTc interval. However, administration of tirzepatide was associated with increased mean arterial pressure (+9 mmHg) at dose of 0.15 mg/kg and increased heart rate (+11-19 bpm) and decreased dP/dtmax (- 18 to -19%) in animals given ≥0.05 mg/kg. No positive drugs were used in the study.

Another GLP in vivo study (8325823) assessed the potential toxicity of tirzepatide administered as once a week by subcutaneous injection to monkeys for at least 1 month. Male and female monkeys were assigned to four groups (0, 0.05, 0.15 and 0.5 mg/kg) with six animals (3 males and 3 females) each group. The telemetry ECG measurements were collected from all unanesthetized animals using Jacketed External Telemetry procedures once during the pre-dose phase and on Days 8 and 22 of the dosing phases. Blood samples (approximately 1 mL) were collected via the femoral vein on Days 1, 15, and 29 of the dosing phases. The mean Cmax were 5.23 and 4.6 µg/mL at dose of 0.5 mg/kg, in male and female, respectively. The exposure exceeded (i.e., 2.6x) the anticipated clinical exposure in humans (1.99 µg/mL). No drug-related changes in PR interval, QRS duration, QTc interval were observed on Day 8 or 22 of the dosing phase in animals given 0.05,0.15, or 0.5 mg/kg. However, tirzepatide caused a dose-dependent increase (i.e., heart rates increased by 20, 28 and 44 bpm on day 22, at 0.05,0.15, and 0.5 mg/kg, respectively) in heart rate in male animals. No tirzepatide -related changes in heart rate were observed on Day 8 or 22 of the dosing phase in females namels. No positive drugs were used in the study.

The GLP in vivo study (8336517) assessed the potential toxicity of tirzepatide administered as once a week by subcutaneous injection to monkeys for at least 6 month. Male and female monkeys were assigned to four groups (0, 0.05, 0.15 and 0.5 mg/kg). The telemetry ECG measurements were collected from all unanesthetized animals using Jacketed External Telemetry procedures once during the pre-dose phase, and during Weeks 2, 12, and 25 of the dosing phase. Blood samples (approximately 1.0 mL) were collected via a femoral or saphenous vein on Days 1, 85, and 176 of the dosing phase, and during Weeks 2, 4, 8, 12, and 16 of the recovery phase. The mean Cmax were 4.2 and 4.6 µg/mL at dose of 0.5 mg/kg, in male and female, respectively. The exposure exceeded (i.e., 2.3x) the anticipated clinical exposure in humans (1.99 µg/mL). No drug-related changes in QTc interval were observed on Day 8, 78, or 169 in animals administered 0.05, 0.15, or 0.5 mg/kg. However, higher heart rates were more pronounced during the dark cycle, with respective peak changes in an overall post-dose block mean of 19 (18%) and 31 bpm (30%) in animals administered 0.15 or 0.5 mg/kg. No positive drugs were used in the study.

The in vivo studies were summarized in Table 2.

Table 2. Summaries of in vivo studies of tirzepatide on QTc interval

Study Element	***Study 8323700***	***Study 8325823***	***Study 8336517***
Species Selection	*Monkey (male)*	*Monkey (male, female)*	*Monkey (male, female)*
Study design	*Single dose, 6 animal/group*	*Repeat dose; once per week for 1 month. 6 animals/ group*	*Repeat dose; once per week for 6 months. 8-14 animals/group*
Dose level (mg/kg)	*0, 0.05 and 0.15*	*0, 0.05, 0.15 and 0.5*	*0, 0.05, 0.15 and 0.5*
Exposure Margin	*0.67x*	*2.6x*	*2.3x*
QTc change	*No*	*No*	*No*
Heart Rate Correction	*an individual animal correction factor*	*an individual animal correction factor*	*an individual animal correction factor*
Other findings	*Heart rate ↑; mean arterial pressure ↑; dP/dtmax ↓*	*Heart rate ↑*	*Heart rate ↑; PR ↑*
Positive control	*No*	*No*	*No*

The Cmax of Tirzepatide following 15 mg once a week at steady state was 1990 ng/mL.

In summary, the in vitro hERG study (180917-fmd) met most of the best practice recommendations according to the new draft guidance ICH S7B Q&As 2.1. The results (hERG safety margin: >72557x) suggest that tirzepatide does not directly interact with the hERG channel. Tirzepatide is a synthetic peptide with 39-amino acids (MW: 4813 Da.). Tirzepatide is highly unlikely to inhibit hERG channel activity since it cannot cross plasma membranes and is unable access and block the inner pore of the hERG channel. The hERG assay may not be reliable or appropriate as part of a preclinical strategy for assessing the QT interval prolongation risk of peptides.

The in vivo monkey studies met most of the best practice recommendations according to the new draft guidance ICH S7B Q&As 3.1-3.5. Results showed that tirzepatide caused no QTc prolongation in monkeys at exposure (i.e., 2.6x of clinical exposure) exceeded the anticipated high clinical exposure (1.99 µg/mL), suggesting that tirzepatide has a low risk for prolonging QTc interval at therapeutic exposure.

3.4 Clinical Cardiac Safety

The sponsor did not submit the highlights of clinical pharmacology and clinical safety. Refer to the sponsor's summary of clinical safety (eCTD, Section 2.7.4) and cardiovascular meta-analysis report (eCTD, Section 5.3.5.3).

A comprehensive approach was undertaken to assess CV safety in the tirzepatide clinical development program including a Phase 3 trial (Study GPGM) evaluating patients with an established CV risk. Cardiovascular safety was also assessed using:

- Vital signs (SBP, DBP, and pulse rate) o Sitting vital sign measurements were collected in triplicate in the Phase 2 studies and in duplicate in the Phase 3 studies. Blood pressure measurements were taken using an automated BP machine in the Phase 3 studies.
- Quantitative ECG assessments of heart rate, PR interval, QRS complex, QT interval (including QTcF)
- Events of treatment-emergent arrhythmias and cardiac conduction disorders identified by SMQs
- Major adverse cardiovascular events in Phase 2 and 3 studies adjudicated by a committee of physicians external to Lilly with cardiology expertise. The clinical evaluation of MACE events and the statistical analyses of these are summarized below and included as a separate document in this CTD (Section 5.3.5.3, Cardiovascular Meta-Analysis Report).

No notable differences in treatment-emergent QTc abnormalities between placebo and tirzepatide groups in AS1.. or between tirzepatide doses in AS2.. were observed.

In AS2, 97 patients (2.08%) out of 4665 patients in the tirzepatide ALL group met the threshold of abnormality for QTcF >450 ms (male) or >470 ms (female) and 4 of those patients presented QTcF >500 ms. It is noteworthy that at baseline, 55 (1.18%) of 4666 patients in the tirzepatide ALL group already had a QTcF >450 ms (male) or >470 ms (female). Two patients (1 in the 10-mg group and 1 in the 15-mg group) had ECG QT prolonged reported as an AE. Five patients reported ventricular tachycardia (2 in the 5-mg group, 1 in the 10-mg group and 2 in the 15-mg group); 1 patient in the 5-mg group reported ventricular arrhythmia. All but 1 event were qualified as non-serious. The serious event was a ventricular tachycardia in 15-mg group and the patient recovered. No cases of Torsades de Pointes were reported.

3.5 Summary Results of Prior QTc Assessments

Not available.

3.6 Relevant Details of Planned Phase 3 Study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

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/

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NDA 215866 tirzepatide – Immunogenicity Review 505.b.1

NDA Number:	215866
Product Name	TIRZEPATIDE (LY3298176)
Proposed Proprietary Name	Mounjaro
Pharmacologic Class	TIRZEPATIDE is a dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist.
Proposed Indication(s)	Type 2 diabetes
Route of Administration	Subcutaneous injection
Sponsor	Eli Lilly and Co.
Requested Division/Office	OND/ORO/DRO- Cardiology, Hematology, Endocrinology and Nephrology (CHEN)
Regulatory Project Manager	Lindsey Kelly
Priority Consideration:	Priority review (8-month clock)
Received Date	11/02/2021
Desired Completion Date	02/15/2022
Primary Assessor(s)	Faruk Sheikh, Ph.D., Chemist, OBP, DBRR-II, CDER
Secondary Assessor (s)	Harold Dickensheets, Ph.D., Chemist, OBP, DBRR-II, CDER
Primary Review Goal Date	Feb 15, 2022
Internal Mid-Cycle	Dec 1, 2021
Recommended Regulatory Action	The immunogenicity assessment data submitted in support of the immunogenicity of NDA 215866 suggest that MOUNJARO (tirzapatide) is highly immunogenic. Using a tiered system of appropriately validated immunogenicity assays, the following results were determined. Approximately 51.1% of patients treated with tirzepatide in clinical studies developed treatment-emergent ADAs. Of these ADA-positive patients, 33.9% and 14.2% demonstrated ADAs cross-reactive to native GIP and native GLP-1, respectively. About 1.9% and 2.1% ADA-positive patients were tested positive for neutralizing antibody (NAb) against tirzepatide activity on the GIP and GLP-1 receptors, respectively. In addition, 0.9% and 0.4% of the overall ADA+ population were classified NAb-positive against native GIP and GLP 1, respectively. However, no safety or efficacy concern(s) were correlated with ADA development in patients from current clinical studies under this NDA. I recommend approval of this product from immunogenicity perspective.

Assessor Note: Eli Lilly submitted this New Drug Application (NDA) on 15 September 2021 for tirzepatide (NDA 215866) for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). During the course of the immunogenicity assessment of results submitted in 'Integrated Summary of Immunogenicity,' OBP requested additional information related to immunogenicity results on 15 December 2021 (Mid cycle communication agenda, DARRTS Ref Number: 4904686). The sponsor submitted their responses to immunogenicity information requests on 3 January 2022 (NDA 215866, SDN 27). These responses were reviewed and determined to be acceptable (see Appendix 3).

In addition, OBP sent another set of IR comment (#1 - #6) on Oct 20, 2021 to the sponsor requesting additional information regarding the immunogenicity assay validation reports under IND 12880 (Ref ID: 4858440, 09/16/2021). In a follow-up e-mail on Oct 22, 2021, the sponsor requested for further clarification for IR comment #6. OBP provided a clarification and also sent an additional IR comment to the sponsor on Nov 01, 2021 (EMAIL correspondence by RPM Lindsey Kelly; Nov 1, 2021) ensuring that the neutralizing antibody assay methods were conducted within the validated operational parameters. The sponsor provided response to this comment on Nov 12, 2021 and responses to earlier IR comments were provided on Nov 02, 2021 to NDA 215866 (Letter date: Dec 31, 2021). All responses to IR comments are included in this memo (see Appendix 4) and OBP concludes that the immunogenicity assay methods used in support of this application were adequately validated.

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1. Executive summary:

Tirzepatide (also known as LY3298176) is a 39-amino acid synthetic peptide with a C20 fatty diacid moiety for prolonged duration of action. This peptide, indicated for the treatment of patients with type 2 diabetes mellitus (T2DM), has agonist activities reproducing those of both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) native endogenous peptides. Both peptides are gut hormones that act to potentiate insulin secretion from the pancreas in a glucose-dependent manner. Native GIP (nGIP) acts through binding to its cognate receptor, GIP receptor (GIPR), whereas native GLP-1 (nGLP-1) acts through binding to the GLP-1 receptor (GLP-1R). The tirzepatide peptide was engineered from the nGIP sequence as an agonist for both receptors, to aid in maintenance of post-prandial blood glucose levels.

The anti-drug antibody (ADA) assays to be used in assessing and characterizing the antibodies that may develop in subjects who are treated with the tirzepatide drug in clinical studies were reviewed by the Agency under IND 128801 (DARRTS Reference IDs: 4451422, 06/24/2019; 4858440, 9/16/2021) during clinical development. The multi-tiered immunogenicity assessment strategy was determined to be acceptable by the Agency and includes an ADA screening assay (Tier 1), followed by a confirmatory assay (Tier 2a) and the ADA titering assay (Tier 3). Assays were also developed to assess cross-reactivity of confirmed "binding ADAs" (BAb) to recognize nGIP (Tier 2b), and nGLP-1 (Tier 2c). In Tier 4, the sponsor further characterizes the ability of the Tier 2a confirmed ADAs to neutralize the GIP receptor (Tier 4a) or GLP-1 receptor (Tier 4b) binding activities of tirzepatide using cell-based neutralizing antibody (NAb) assays. The sponsor, after FDA concurrence, also characterizes the cross-reactivity of NAbs against endogenous nGIP (Tier 4c) and nGLP-1 (Tier 4d) peptide hormones using a model in-silico system (DARRTS Reference IDs: 4451422, 06/24/2019) due to poor sensitivity in the cell-based assays developed for assessing NAb cross-reactivity with the native peptides. All assays were determined by the Agency, upon evaluation of additional supporting information, to be adequately validated and suitable for detecting the development of anti-drug antibodies to tirzepatide and to further characterize the antibodies in clinical study samples.

The sponsor implemented clinical immunogenicity assays in seven completed Phase 3 studies, conducted on T2DM subjects (sponsor Table 1, below). The immunogenicity assessment reports from these studies are reported in 'Integrated Summary of Immunogenicity (ISI).

Table 1: Phase 3 Clinical Studies (recreated by the assessor from the ISI submission)

Immunogenicity Assays	Cut Points Implemented	Phase 3 Clinical Studies
Tier 1 (ADA Screening Assay) Tier 2a (ADA Confirmatory Assay) Tier 2b (Cross-reactivity for $nGIP_{1-42}$) Tier 2c (Cross-reactivity for $nGLP\text{-}1_{7-36}$) Tier 3 (ADA Titering Assay) Tier 4a (NAb Assay at GIPR) Tier 4b (NAb Assay at GLP-1R)	T2DM DSCP	18F-MC-GPGK 18F-MC-GPGL 18F-MC-GPGH 18F-MC-GPGM 18F-MC-GPGI 18F-JE-GPGO 18F-JE-GPGP
nGIPR = native GIP Receptor nGLP-1R = native GLP-1 Receptor NAb = Neutralizing Antibody	T2DM = Type 2 Diabetic Mellitus DSCP = disease-state cut point	

The cut points for all ADA binding assays were initially validated by using pre-dose serum samples from healthy subjects and then subsequently verified by using pre-dose serum samples from T2DM subjects during the subsequent portions of the validation studies. These disease-state cut points (DSCP) were determined to be 1.22 (Tier 1), 30.4% (Tier 2a), 14.5% (Tier 2b) and 18.1% (Tier 2c), respectively for the screening (Tier 1), confirmatory (Tier 2a) and cross-reactivity assays for $GIP_{(1-42)}$ (Tier 2b) and $GLP\text{-}1_{(7-36)}$ (Tier 2c). These cut-points were acceptable to use for all seven Phase 3 clinical protocols (source: BAL-20-061-1157-REP).

The serum samples from a total of 5025 T2DM patients from 7 Phase 3 studies receiving tirzepatide doses were evaluated for the development of ADAs. Of those, 2570 (51.1%) tirzepatide-treated patients developed treatment-emergent (TE) ADAs (ADA+ patients who had an ADA titer of at least 2-fold higher than MRD) during the treatment period when DSCP was applied in ADA assays (Table ISI.4.22); 47.8% (2403 of 5025) confirmed TE-ADA+ patients were classified as having treatment-induced ADAs, whereas 3.3% (167 of 5025) patients were classified as having treatment boosted ADAs during the planned treatment period. A small number of patients (353, about 7%) had pre-existing ADAs; nearly half (167, 3.3% of total) of these patients experienced treatment-boosted ADA response in post-baseline samples. Regardless, overall, this data indicates that the majority of ADA detected in patients were treatment-induced rather than treatment-boosted pre-existing ADA.

The ADA data discussed above, however, did not include ADA results from patients at their FU visit. Therefore, we sent a comment in the IR letter dated 15 Dec 2021 to the sponsor to submit this data. In response, the sponsor submitted a revised table including the ADA results generated from follow-up samples tested after four weeks of last dose. This data suggests that the ADA development may continue even after the tirzepatide treatment was stopped (Table.4.1). The ADA development profile in patient cohorts receiving 5mg, 10mg or 15mg tirzepatide for various length of time suggest that the incidence of ADA development was dose-dependent, and the number of ADA+ patients was increased with increasing length of exposure to the study drug. It was observed that the development of anti-tirzepatide ADAs continued during FU period; this is also reflected in the percentage of patients with cross-reactive antibodies to nGIP and nGLP-1 (Tiers 2b & 2c, respectively) and neutralizing antibody results from Tier4a and Tier4b (submission Table APP.2.4).. Therefore, the impact of an increase in ADA or NAb formation that may potentially develop at the later stage of tirzepatide treatment, or after treatment discontinuation, may not be predicted completely from currently available ADA results arising from these studies.

Assessor Note: The sponsor also evaluated the applicability of using in-study cut points (ISCP) determined from pre-treatment samples from their seven clinical studies. ISCP were determined and initially used for assessment of ADA-positive samples (see sponsor Table ISI.4.22). However, it was later determined by the sponsor that although ISCP could be used, the use of the disease state cut point (DSCP), previously determined during assay validation, was a more conservative approach that resulted in a larger number of subjects being classified as ADA-positive. The sponsor was asked to provide an updated table reflecting use of the DSCP, rather than ISCP, for reporting ADA+ subjects. This is discussed further below, in memo Section 4.

To further characterize the ADA responses, patients' samples confirmed as ADA+ during the planned study period were next assessed for their ability to cross-react with native GIP (nGIP) and native GLP-1 (nGLP-1) by using validated cross-reactivity assays (Tier 2b and Tier 2c respectively for nGIP and nGLP-1); 1705 (66.3%) ADA+ patients showed cross-reactivity with nGIP whereas 716 (27.8%) ADA+ patients showed cross-reactivity with nGLP-1. The sponsor further characterized the ADAs that developed during

the treatment period by assessing their ability to neutralize the tirzepatide drug activity by using two fully validated cell based NAb assays. These assays were validated to detect NAb against tirzepatide activity on both the GIP receptor (GIPR) (Tier 4a) and GLP-1 receptor (GLP1R) (Tier 4b) (source: DARRTS Reference - 4858440; 09/16/2021). Among treatment emergent (TE) ADA-evaluable population (N=5025), 94 (1.9%) and 107 (2.1%) had NAb against tirzepatide activity on the GIPR and GLP-1R respectively (Table ISI.4.23).

The sponsor had also developed two additional cell-based NAb assays to detect cross-reactive NAb against nGIP (Tier 4c) and nGLP-1(Tier 4d). However, due to drug tolerance challenges encountered during assay validation, Lilly implemented an 'in silico' method to classify cross-reactive NAb as an alternative approach, to overcome the drug tolerance challenges for Tiers 4c and 4d cell-based assays. The use of 'in silico' determinations of NAb-positivity for nGIP and/or nGLP-1 were assessed previously by the Agency and determined to be acceptable (source: DARRTS Reference - 4451422; 06/24/2019). In the 'in silico' assays, any sample exhibiting NAb+ activity against the GIP or GLP-1 activities of tirzepatide (by Tier 4a or Tier 4b) and showing cross-reactive BAb+ activity against nGIP or nGLP-1 (by Tier 2b or Tier2c) will be considered to have nGIP/nGLP-1 cross-reactive NAb activity. Using this 'in silico' classification, 43 patients (0.9% of 5119 TZP-treated) patients were determined to have 'in silico' cross-reactive neutralizing activity to native GIP, whereas 18 (0.4% of 5119 TZP-treated) patients were determined to have 'in silico' cross-reactive neutralizing activity to native GLP-1 during the planned treatment period (Table ISI.4.23). The effect(s) of these antibodies with cross-reactive activities to native peptides and the neutralizing activities is not clearly understood. A comparison of tirzepatide concentrations from patients with detected NAb and ADAs from Phase 3 studies was provided. This comparison shows no apparent relation between NAb+/ADA+ patients and tirzepatide drug concentrations in patients from Phase 3 studies. The sponsor studied tirzepatide clearance by ADA titer status in Phase 3 studies.

The ADA titer for all TE ADA+ patients was determined using a validated titering assay. These data show that the ADA titers in evaluable TE ADA+ patients ranged from 1:20 to 1:81920 with a median titer of 1:160. Approximately 91 ADA+ samples across all phase 3 studies had an ADA titer ≥1:5120. Although the tirzepatide clearance by ADA+ status in phase 3 studies appears comparable between the ADA-negative and ADA+ groups, the clearance data based on ADA titer indicates that some ADA+ patients, particularly those with a titer ≥ 1:10240, may have an altered tirzepatide clearance status (slower rate of clearance). This concern was communicated to the sponsor via IR letter during the course of this review. To address this issue, the sponsor provided additional data including the numerical values of ADA titer throughout their study visits for all 91 ADA+ patients across all phase 3 studies who had an ADA titer ≥1:5120, along with the change in HbA1c % and body weight for respective visits (Tables submitted with IR response on January 3rd, 2022, not copied in this review). These additional data, evaluated above, suggest that an ADA titer ≥1:5120 at any time during the study did not significantly impact these patients due to reduced efficacy (change in HbA1c decrease or weight loss) of tirzepatide. About 45.4% patients (n=1168 of 2570) had an ADA titer of greater than median titer (>1:160). Neither the ADA titer nor the presence of NAbs were shown to have significant impact on the tirzepatide clearance profile.

The sponsor analyzed the change in HbA1c from baseline and compared the mean change between ADA+ and ADA-negative cohort of each of seven Phase 3 studies; no significant difference was observed in the change in HbA1c profile between ADA+ and ADA-negative patients. The change in mean HbA1c for TZP-treated patients was also analyzed between a cohort with ADA titer <1:5120 vs a cohort with ADA titer ≥1:5120 for each Phase 3 studies. A similar analysis was also performed using ADA-negative

patient and NAb+ patients from each study independently showing no significant difference was observed in mean HbA1c for TZP-treated patients due to ADA titer. *(Assessor Note: This analysis was performed because of our concern (communicated in an information request) that a high titer of ADA, or NAb activity, in a patient from Study GPGK may have had an impact on the change in HbA1c efficacy outcome).* In response to our concern, the sponsor's submitted additional information demonstrating the ADA titer or Nab-positive status for these small group of subjects (2 and 4 tirzepatide-treated patients had either ADA titer ≥1:5120 or NAb+ in the GIPR assay respectively) from Study GPGK did not have any significant impact on drug efficacy. One patient (not included in TE evaluable group since no pre-dose sample was obtained; the first sample was 19 minutes post-injection) achieved the maximum observed ADA titer of 1:327860 seen from all Phase 3 studies (Subject: (b) (6)). The titer of this patient's first ADA sample was reported to be 1:163840, which subsequently fluctuated from 1:40960 at Week 41 to 1:327680 at Week 78. This patient did not experience any hypersensitivity or injection site reaction and showed no reduction in the HbA1c lowering effect of the drug (source: ISI, page 57).

Overall, the immunogenicity ADA assessment results indicate that tirzepatide-treated patients may develop high TE ADA responses during the treatment period. However, no significant impact of ADAs or NAbs was observed on drug efficacies across seven Phase 3 clinical studies.

Hypersensitivity and Injection site reactions
The percentage of TE ADA+ and TE ADA- patients reporting hypersensitivity reactions was generally similar, but slightly skewed towards TE ADA+ (106 TE ADA+ patients with hypersensitivity and 73 TE ADA- patients). A majority of these first onset reactions occurred during the first 16 weeks' treatment with study drug and resolved independently of TE ADA status or titer, and no TE adverse events classified as anaphylactic were observed in study drug treated subjects in the Phase 3 program.

A higher number of TE ADA+ patients (119) than TE ADA- patients (18) reported injection site-related reaction, and the majority of these resolved irrespective of TE ADA status or titer.

2. Background - Sequence of the peptide molecule.

Tirzepatide or LY3298176 is a (b) (4) GIP and GLP-1 receptor co-agonist developed from the nGIP sequence. The peptide consists of 39 amino acid residues conjugated to a C20 fatty acid moiety (for prolonged duration of action) via a linker connected to the lysine residue at position 20 (Figure S.1.2-1). Residues 2 and 13 consist of a non-human amino acid, aminoisobutyric acid. This dual-specificity tirzepatide peptide drug is indicated for the treatment of patients with type 2 diabetes mellitus (T2DM) and the modified amino acid sequence of this product allows it to act through both the GIPR and GLP-1R receptors on pancreatic beta cells, resulting in an increased insulin secretion.

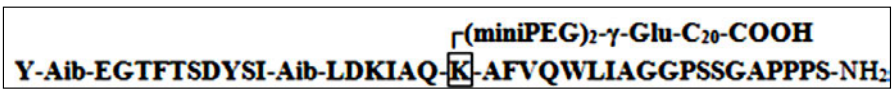


Figure S.1.2-1 Amino acid sequence of tirzepatide with the Standard Single Letter Amino Acid Code and its structure. Aib =Aminoisobutyric Acid (Source: LY3298176 – S.1.2 Structure - v001)

3. Tiered system of Immunogenicity Assays

To characterize the potential immune response of tirzepatide in humans, Lilly used a multi-tiered immunogenicity testing strategy. A ligand-binding method was used for several assays, including those to screen (Tier 1), confirm (Tier 2a), and titer (Tier 3) ADA, and to assess cross-reactive binding of ADA against native GIP (nGIP; Tier 2b) or native GLP-1 (nGLP-1; Tier 2c) peptides. A cell-based method is used for two NAb assays (Tiers 4a and 4b), and in-silico classifications are used to define cross-reactive NAb against nGIP and nGLP-1.

To screen for ADAs to tirzepatide in serum samples from clinical studies, the sponsor used an ACE-ELISA (Affinity Capture and Elution - enzyme-linked immunosorbent assay) ligand-binding method. In this method, serum samples potentially containing ADAs and tirzepatide were incubated on an ELISA plate coated with a mixture of N- and C-terminal biotin-labeled tirzepatide analogs to capture anti-tirzepatide antibodies (front-end). Free tirzepatide drug peptides were washed away, ADAs were eluted off the plate by acid treatment (back-end), and then samples were pH-neutralized on a second ELISA plate, where ADAs were allowed to bind. The bound ADAs were detected by MSD method using a mixture of labeled tirzepatide. The ADAs were further characterized in cell-based assays detecting NAb against tirzepatide activity on the GIPR and GLP-1R (Tiers 4a and 4b, respectively) using same assay principle in reporter cells expressing GIPR and GLP-1R, respectively.

4. Cut Points – Binding Antibody Assays

The sponsor validated a Cut Point Factor (CPF) of 1.25 using 64 normal human serum (NHS) for screening the putatively ADA-positive samples at 5% false positive rate (FPR) in the Tier 1 tirzepatide ADA binding assay. They also validated a disease state CPF using pre-dose serum samples from T2DM subjects (N=302) from a Phase 2 clinical study 18F-MC-GPGB to 1.22. The sensitivity of the assay was determined to be 2.81ng/mL, appropriately interpolated from sensitivity curves.

To analyze the putatively ADA-positive samples in Tier 2a analyses, the sponsor determined a confirmatory cut point (CCP) based on mean %inhibition results in presence of 50µg/mL of unlabeled tirzepatide (or 10.4 µM) for NHS and pre-dose T2DM serum samples. The concentration of competitor drug used in the assay was assessed and determined appropriate. The CCP was statistically calculated at 1% FPR to 27.5% and 30.4% for NHS and T2DM respectively.

i) Screening and Confirmatory ISCP analysis

Once the assay cut point was established using NHS and T2DM serum samples, the sponsor evaluated the need for the in-study cut point (ISCP) for each Phase 3 studies using 100 randomly selected T2DM pre-dose samples from seven Phase 3 trials (I8F-MC-GPGK, I8F-MC-GPGH, I8F-MC-GPGI, I8F-MC-GPGM, I8F-MCGPGL, I8F-JE-GPGP, and I8F-JE-GPGO). The in-study cut-points for all seven Phase 3 studies were then statistically compared with the T2DM disease-state cut points (DSCP) established during assay validation. In addition to each ISCP for 7 Phase 3 studies, a pooled ISCP was also established. The appropriateness of use of the pooled ISCP was then validated against cut-points for the BAb assays determined using disease-state (T2DM) serum samples (Tiers 1, and 2a).

Prior to pooling, the sponsor tested the results from each study for qualification to be included in the pool. The sponsor prepared overlaid density curves for Tier 1 and Tier 2a assay values and assessed qualitatively to support the pooling of the samples together (source: Figures 1 and 2, respectively in page 68 & 69, appendix B, BAL-20-061-1157-REP, which are not copied here). In addition, the sponsor also compared the 95th percentile data of each study to a pool of the other six studies in a percentile

test. A percentile test in both the Tier 1 and Tier 2a comparisons (p-value > 0.005) indicated that the study was acceptable for pooling. The data were provided in the submission supports the pooling of all seven studies (source: Tables 1 and 2, appendix B, BAL-20-061-1157-REP, not copied here).

The pooled study cut point was then statistically and clinically compared to the validated T2DM DSCP. Of 700 pre-dose serum samples (100 samples from each of seven studies), 84 biological outliers were identified using patient-level mean Tier 2a %Inhibition values and Tukey's rule and were removed prior to the pooled CP estimation. A total of 1232 (from 616 patient samples) assay values were used to estimate the cut-point for Tier 1 and Tier 2a. The Tier 1 CPF was estimated using a non-parametric tolerance limit to yield a 5% false-positive rate (FPR), whereas Tier 2a CPF was estimated using a parametric tolerance limit to yield a 1% FPR. The sponsor used non-parametric approach for Tier 1 CPF estimation since the values were not normally distributed and the Tier 1 CPF was determined to 1.30 (Figure 2, BAL-20-061-1157-REP, Nov 11, 2020, not copied in this review memo). For Tier 2a CPF estimation, the %Inhibition response was found to be normally distributed, and a parametric approach was therefore used to estimate the CCP of 34.4% (Figure 3, BAL-20-061-1157-REP, Nov 11, 2020, not copied in this review memo). However, in order to implement a more conservative approach in clinical sample analysis, the sponsor intends to use the DSCP for Tier 1 (CPF=1.22) and Tier 2a (CCP=30.4%) that were determined during assay validation studies using pre-dose samples from T2DM subjects. Use of the DSCP provides a greater number of ADA putative positives and confirmed positives.

Assessor comment: The sponsor validated ADA assays using serum samples from normal human serum and pre-dose serum samples from T2DM subjects from a Phase 2 study (study 18F-MC-GPGB). In order to evaluate whether an individual ISCP is needed for each Phase 3 studies, or an ISCP from pooled pre-dose serum samples will be appropriate for ADA analysis, the sponsor used 100 randomly selected T2DM pre-dose samples from seven Phase 3 trials individually as well as after pooling these samples and determined in-study cut points (ISCP). These cut-points were then compared statistically and clinically with the validated T2DM DSCP. However, the sponsor determined it more appropriate to use DSCP for analyzing immunogenicity in samples from Phase 3 clinical studies, to implement a more conservative approach in clinical sample analysis. The use of these T2DM disease specific cut-points (DSCP) is a more conservative approach and will minimize the risk of false negative results by increasing the number of reported ADA+, and is therefore acceptable.

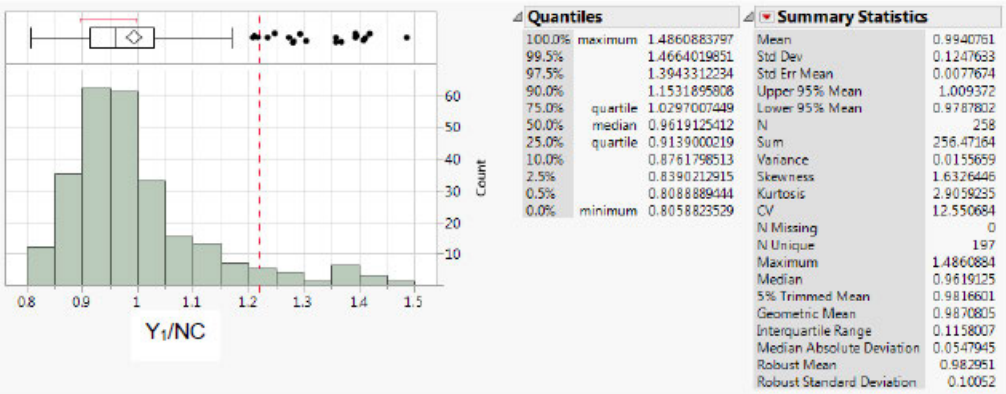


Figure 2. Histogram of normalized Tier 1 screening values (Y_1/NC) following biological outlier removal. The data were not determined to be normally distributed (p<0.0001) so a non-parametric tolerance limit was used to estimate the cut point factor of 1.22 shown in the dashed red line.

Source: BAL 15-061-360 Val addendum 1 amendment 1

ii) Cross reactivity assays for anti-GIP (Tier 2b) and anti-GLP-1 (Tier 2c):

To determine the potential of the anti-tirzepatide antibodies to cross-react with nGIP and nGLP-1 peptide, the sponsor validated cross-reactivity assays for anti-GIP (Tier 2b) and anti-GLP-1 (Tier 2c) using pre-dose serum samples from T2DM subjects. First, they calculated %inhibition in assay signals based on the data obtained in absence or in presence of 52µg/mL (10.4µM) unlabeled GIP (1-42) and 34.3µg/mL (10.4µM) unlabeled GLP-1 (7-36). The cut points for cross-reactivity assays were then determined from %inhibition results at 1% FPR to 14.5% and 18.1%, respectively, for Tier 2b and Tier 2c cross-reactivity assays.

The sponsor evaluated the need for ISCP for cross-reactivity assays for Tier 2b and Tier 2c in T2DM patients enrolled in seven Phase 3 clinical studies (GPGH, GPGI, GPGK, GPGL, GPGM, GPGO, and GPGP). Four replicate assay results were generated for each patient's pre-dose serum sample utilizing multiple analysts (Five analysts), multiple runs, and multiple plates per run resulting in 400 assay results for each of the seven clinical studies.

A pooled study cut point was estimated for Tier 2b and Tier 2c to evaluate if it was applicable for analyzing samples from clinical development program. But the data from seven studies were not considered compatible with a pooled study cut point approach (source: Table 1 page 187 and Table 1 page 189; BAL-20-061-1157-REP; data not copied here). As a result, data from each study was used to estimate individual ISCPs, which were statistically and clinically compared to the previously estimated DSCP of 14.5% and 18.1% respectively for Tier 2b and Tier 2c assay. The bootstrap test of equivalence between the ISCP and DSCP cut points was found to be statistically significant. Therefore, the sponsor decided to use the cut-points determined during assay validation using T2DM serum samples. The sponsor submitted the analyses, which were reviewed but not copied here (source: BAL-20-061-1157-REP).

Assessor comment:
During ADA validation studies, the sponsor determined the cut-points for Tier 2b anti-GIP cross-reactivity assay (DSCP =14.5%) and for Tier 2c anti-GLP-1 cross-reactivity assay (18.1% DSCP) respectively, using pre-dose serum samples from T2DM subjects from a Phase 2 clinical study (18F-MC-GPGB). The sponsor evaluated the ISCP for anti-GIP$_{(1-42)}$ and for anti-GLP-1$_{(7-36)}$ cross-reactivity assays for each of seven Phase 3 studies to determine if a pooled CP can be generated. The statistical analysis suggested that all seven studies were not compatible for pooling. As a result, data from each study was used to estimate individual ISCPs, which were statistically and clinically compared to the established DSCP. All seven trial-specific ISCP were found to be statistically different from the DSCP. Therefore, the sponsor decided to use the DSCP for anti-GIP and for anti GLP-1 that were determined during assay validation studies using pre-dose samples from T2DM subjects (14.5% and 18.1% for Tier 2b and Tier 2c respectively). The use of these validated disease-state cut-points is a more conservative approach, resulting in a larger set of potential cross-reactive ADA-positive samples and will minimize the risk of false negative results. Therefore, the approach is acceptable.

The sponsor plans to use the validated DSCP for Tiers 1, 2a, 2b, and 2c established using pre-dose T2DM serum samples from phase 2 study to analyze clinical immunogenicity samples from Phase 3 studies, therefore, the reestablishment of the sensitivity and drug tolerance is not needed.

5. Cut Points – Neutralizing Antibody Assays

In order to further characterize the confirmed anti-tirzepatide antibodies, the sponsor validated two cell-based neutralizing antibody (NAb) assays to evaluate the ability of ADAs to neutralize the tirzepatide activities through the GIPR (Tier 4a) and the GLP-1R (Tier 4b) cellular receptors (Reference ID: 4858440, 09/16/2021) using cAMP readout, rather than a traditional luciferase-based assay that might be less sensitive due to accumulation of relatively long-lived luciferase reporter. The NAb assays met validation acceptance criteria for all parameters tested to ensure robust, reproducible detection and characterization of neutralizing ADA activity against tirzepatide on both the GIP and GLP-1 receptors. To determine the cut-points for anti-tirzepatide NAb assays for GIPR and GLP-1R, they used pre-dose serum samples from 122 T2DM subjects from Phase 2 study I8F-MC-GPGB (GPGB). Shapiro-Wilk test of Normality indicates a non-normal distribution ($p<0.001$) for both assays, so a nonparametric approach was used to yield a 1% FPR for the neutralization cut point of 10.8% for NAb assay on the GIPR and for NAb assay on GLP-1R (Tier 4b) the CP was determined to 6.6%.

The sponsor also evaluated the need for ISCP for NAb assays for Tier 4a and Tier 4b, in T2DM patients enrolled in all Phase 3 clinical studies (GPGH, GPGI, GPGK, GPGL, GPGM, GPGO, and GPGP). The use of pooled in-study cut point was also evaluated using pre-dose clinical samples from all 7 Phase 3 studies. The appropriateness of use of the pooled ISCP was evaluated against the validated cut-points for the NAb assays determined using T2DM serum samples (Tiers 4a, and 4b). The assessments were performed by analyzing at least 100 randomly selected baseline serum samples from each of seven Phase 3 clinical protocols (I8F-MC-GPGH, I8FMC- GPGI, I8F-MC-GPGK, I8F-MC-GPGL, I8F-MC-GPGM, I8F-JE-GPGO and I8F-JE-GPGP).

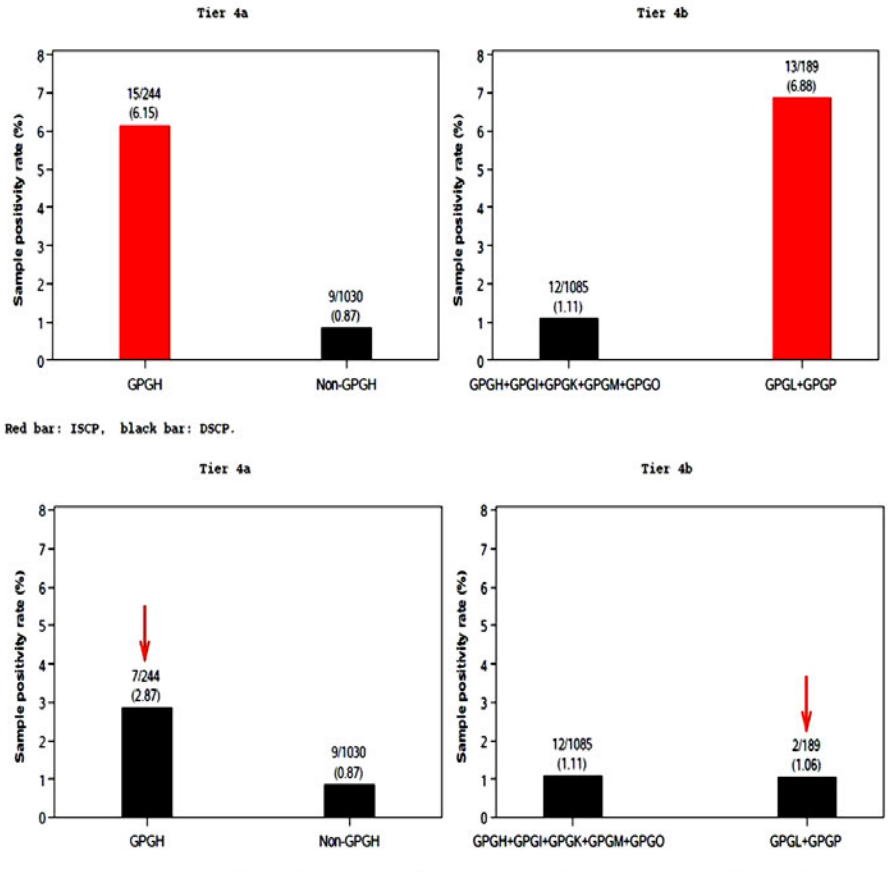
The anti-tirzepatide GIP-R NAb assay (Tier 4a) and anti- tirzepatide GLP-1 R NAb assay (Tier 4b) ISCP were statistically calculated for all seven Phase 3 studies and analyzed. It was found that all 7 studies were not compatible for pooling for either NAb assays. As a result, data from each study was used to estimate individual ISCPs, which were then statistically compared to the established DSCP (for Tier 4a DSCP = 10.8% and for Tier 4a DSCP = 6.6%). The comparability results suggest that with the exception of study GPGH, *all ISCPs were statistically different from the DSCP (higher than the DSCP) for Tier 4a*. For Tier 4b with the exception of studies GPGL and GPGP, all ISCPs were not statistically different from the DSCP.

To minimize the risk of false negative results, the sponsor decided to use the DSCP (10.8%) for clinical protocols GPGK, GPGI, GPGM, GPGL, GPGP and GPGO for characterization of confirmed ADA by Tier 4a evaluation and for 4b the existing DSCP of 6.6% was accepted for use in characterizing ADA-positive samples under clinical protocols GPGK, GPGI, GPGM, GPGO and GPGH.

For clinical protocol GPGH (Tier 4a assay), they established an GPGH study specific ISCP of 7.5%, using pre-dose samples from this clinical study. Similarly, to the ADA+ samples from clinical protocols GPGP and GPGL by Tier 4b assay, the sponsor pooled the data from these study samples for estimation of a pooled ISCP to 3.7%. The sponsor determined the appropriateness of use of these ICSP values for studies GPGH, GPGP and GPGL by comparing the FPR for these assays in comparison to FPR obtained from rest of studies grouped together (Figure APP.2.5, below). For study GPGH, the red bar shows that when ISCP (7.5%) was used for analyzing samples from study GPGH, the FPR was 6.15% (in comparison to 0.87%, for the rest six studies together when DSCP for Tier 4a GIP-R NAb assay was used). However, using DSCP for GPGH, the FPR was reduced to 2.87% (red arrow), suggesting lower false negative results.

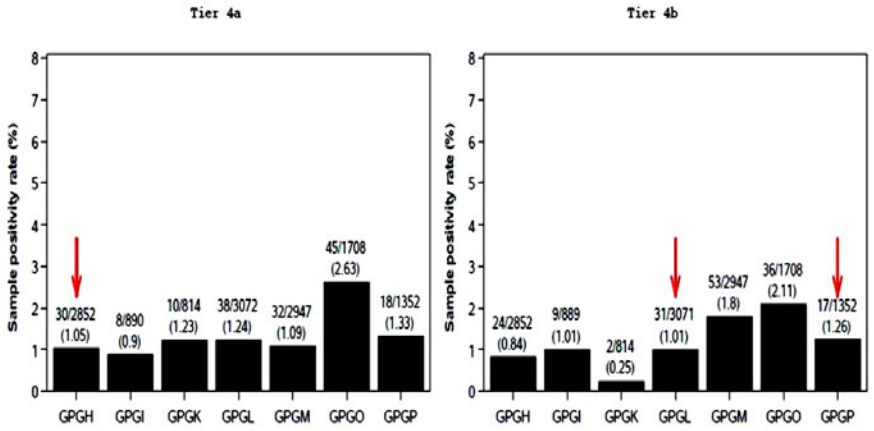
Similarly, for studies GPGP and GPGL, the red bar (Figure APP.2.5, below) showed that when ISCP (3.7%) was used for analyzing samples from studies GPGP and GPGL, the FPR was 6.88% (in comparison to 1.11%, for the rest five studies together when used DSCP for Tier 4b GLP1-R NAb assay). However, using DSCP, the FPR was reduced to 1.06% (red arrow) for both studies, GPGP and GPGL, suggesting lower false negative results.

Figure APP.2.6 (excerpt copied below) shows the FPR individually for each of seven Phase 3 studies were between 0.9% to 2.63% when DSCP was used to analyze clinical samples in anti-tirzepatide GIP-R NAb assay (Tier 4a) and the FPR for all seven Phase 3 studies were between 0.25% to 2.11% when analyzed the clinical samples in anti- tirzepatide GLP-1 R NAb assay (Tier 4b). Based on the FPR results, use of DSCP was appropriate to analyze clinical samples from all seven Phase 3 studies.



Abbreviations: DSCP = disease-state cut point; GLP = glucagon-like peptide; ISCP = in-study cut point; NAb = neutralizing antibody.

Figure APP.2.5. Tier 4a and 4b sample positivity rates. *Analysis includes baseline samples from all patients and postbaseline samples from non-GLP- and non-tirzepatide-treated patients*. Red bars indicate results with ISCPs applied; black bars indicate results with DSCPs applied. Red arrows indicate the change in sample positivity rate per study after using DSCP to analyze clinical samples for those studies.



Abbreviations: DSCP = disease-state cut point; GLP = glucagon-like peptide; ISCP = in-study cut point; NAb = neutralizing antibody.

Figure APP.2.6. Tier 4a and 4b sample positivity rates*. Includes baseline samples from all patients and postbaseline samples from non-GLP-treated patients.* Red bars indicate results with ISCPs applied; black bars indicate results with DSCPs applied. Red arrows indicate the change in sample FPR using DSCP to analyze clinical samples for those studies.

Assessor Comment:
The sponsor compared the baseline sample distributions for these 3 studies (specifically GPGH, GPGL & GPGP) showing that the baseline sample distributions from ISCP validation experiments are qualitatively similar to the respective baseline sample distributions from DSCP validation experiments (histograms in Pages 11-13 of ISI-app data not copied here). These data suggest that the ISCP distributions were more compact in comparison to DSCP distributions, suggesting less variable baseline results in ISCP distributions. This was possibly due to less inherent assay variation during experiments performed during ISCP evaluation that may have had a significant impact on the calculated ISCPs. Nevertheless, the sponsor compared the sample positivity rates for drug-naïve samples (baseline samples from all patients and postbaseline samples from non-glucagon-like peptide (GLP)- and non-tirzepatide- treated patients) across all Phase 3 studies using ISCP versus DSCP.

The sample positivity rates for pre-dose samples for all studies seem acceptable for all studies but were found considerably higher for study GPGH (Tier 4a) and for studies GPGL and GPGP (Tier 4b) when ISCPs were applied (6.15% in Tier 4a for GPGH; 6.88% for GPGL and GPGP respectively in Tier 4b) than studies with DSCPs applied (2.87% in Tier 4a for GPGH; 1.11% for GPGL and GPGP respectively in Tier 4b). The sample positivity rates for drug-naïve pre-dose samples were closer to the expected FPR of 1%, when the established DSCPs are applied to each study.

The sponsor also compared the sample positivity rates across all Phase 3 studies using the ISCP and the established DSCP. This analysis indicates that the sample positivity rates for all samples were similar across studies and within acceptable range of 0.9% to 2.63% for Tier 4a and 0.25% to 2.11% for Tier 4b when the established DSCPs are applied to each study (Figure APP.2.6).

Therefore, the sponsor stated that they selected and applied DSCP for all assay Tiers (Tiers 1, 2a, 2b, 2c, 4a, and 4b) for all Phase 3 studies (table below). The DSCPs for all assays were fully validated using serum samples from T2DM subjects and the use of these cut-points is the more conservative approach

and may be expected to minimize the risk of false negative results. Based on my evaluation of these data, the use of the DSCP is acceptable.

Table. ADA and NAb Assay Cut Points for Each Phase 3 Study

Phase 3 Study	ADA Assay Cut Points (%)				NAb Assay Cut Points (%)	
	Screening	Confirmatory	Cross-reactivity to nGIP	Cross-reactivity to nGLP-1	for GIPR	for GLP-1R
	Tier 1	Tier 2a	Tier 2b	Tier 2c	Tier 4a	Tier 4b
GPGK	1.22	30.4	14.5	18.1	10.8	6.6
GPGL	1.22	30.4	14.5	18.1	10.8	6.6
GPGH	1.22	30.4	14.5	18.1	10.8	6.6
GPGM	1.22	30.4	14.5	18.1	10.8	6.6
GPGI	1.22	30.4	14.5	18.1	10.8	6.6
GPGO	1.22	30.4	14.5	18.1	10.8	6.6
GPGP	1.22	30.4	14.5	18.1	10.8	6.6

* created by the Assessor based on available information in the submission

6. In Silico Classification for Cross-Reactive NAbs

The sponsor also developed two additional cell-based assays to determine the cross-reactive neutralizing against nGIP and nGLP-1 for Tier 4c and Tier 4d respectively using anti-tirzepatide antibodies. However, the drug tolerances for these two assays determined during assay validation indicated that the implementation of these assays may not allow identification of all ADAs that may be cross-reactive neutralizing against nGIP and nGLP-1. Therefore, the sponsor proposed classification of the cross-reactive NAb based on an *in-silico* approach, allowing conservative interpretation of the immunogenicity data for cross-reactive nGIP NAb and nGLP-1 NAb in patient samples This proposal was evaluated and accepted by the Agency previously (source: DARRTS Reference - 4451422; 06/19/2019).

Assessor comment: In this approach, any patient sample detected positive for cross-reactive binding ADA to nGIP in Tier 2b and also detected positive for NAb against tirzepatide on the GIPR in Tier 4a assay will be interpreted as positive for cross-reactive NAb against nGIP. Likewise, any samples detected positive for cross-reactive binding ADA to nGLP-1 in Tier 2c and for NAb against tirzepatide on the GLP-1R in Tier 4b will be interpreted as positive for cross-reactive NAb against nGLP-1. This approach may be more sensitive than relying on the study drug-intolerant cell-based assays that were developed, and therefore potentially reduces the risk of false-negative cross-reactive NAb reporting.

7. Immunogenicity Sampling Schedule (Phase 3 studies):

The ADA sampling times for the seven Phase 3 clinical trials were designed with follow up periods for at least 3-4 weeks after dosing in order to adequately assess immunogenicity. The sponsor collected all samples on dosing days before dosing. An overview of the antibody collection time points is presented in the following Table (source: ISI – Table ISI.4.15).

Table ISI.4.15. Overview of Immunogenicity Sampling Schedule for Tirzepatide Phase 3 Studies in patients with T2DM

Study Alias	Sampling Time Points (Weeks)											
	0	4	12	24	40	42	44	52	56	78	104	108
GPGK	X	X	X	X	X		X (SFU)					
GPGL	X	X	X	X	X		X (SFU)					
GPGH	X	X	X	X	X			X	X (SFU)			
GPGM	X	X	X	X		X		X		X[a]	X[a]	X[a] (SFU)
GPGI	X	X	X	X	X		X (SFU)					
GPGO	X	X	X	X	X			X	X (SFU)			
GPGP	X	X	X	X	X			X	X (SFU)			

Abbreviations: SFU = safety follow-up; T2DM = type 2 diabetes mellitus.

[a] For patients that continued past the primary endpoint at 52 weeks in GPGM, SFU visits occurred 4 weeks after the last treatment visit that could have occurred between 52 to 104 weeks

All Phase 3 studies included a 4-week SFU visit, to be conducted after the last scheduled treatment visit or early discontinuation visit.

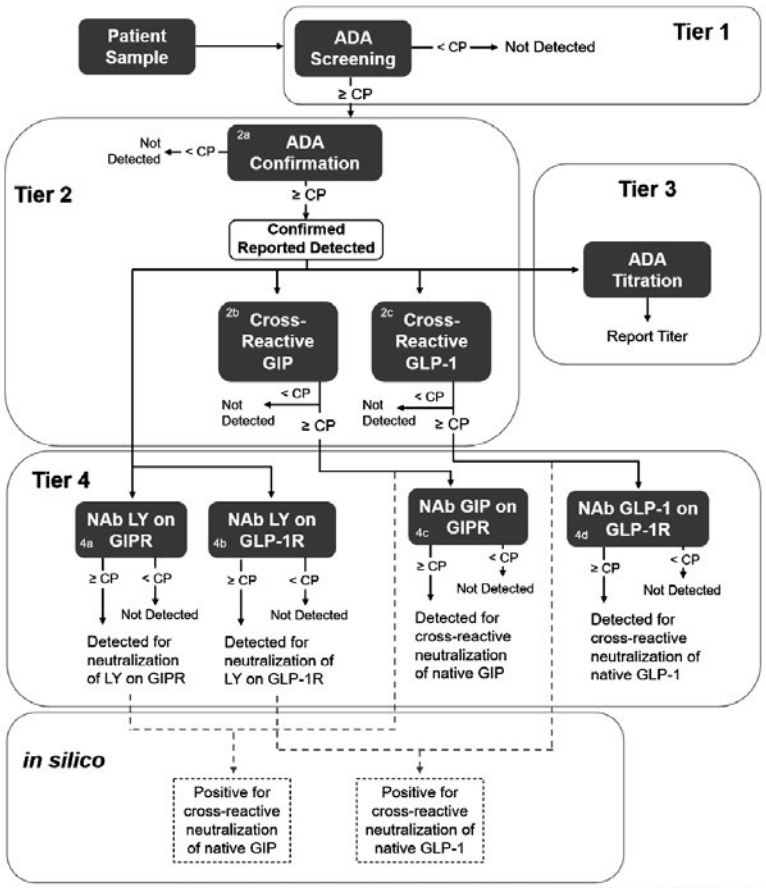
Assessor comment: The immunogenicity evaluation data were generated from seven Phase 3 studies. All these studies were conducted in T2DM subjects and the ADA evaluation was performed using DSCP. DSCP was determined based on pre-dose serum samples from T2DM subjects from a Phase 2 study during assay validation. The sampling time for testing the development of anti-drug antibodies is adequately designed.

8. Immunogenicity testing strategy:

Participant samples were analyzed using a 4-tiered approach (Figure 1). The ADA assay implementation strategy includes the use of validated ADA screening assay followed by a confirmatory assay. The confirmed ADA-positive samples are then planned to analyze by ADA titering assay, and to assess cross-reactivity of confirmed binding ADAs against endogenous GIP, and GLP-1 (referred to as assay Tiers 1-3; Figure 1). In Tier 4, the sponsor plans to further characterize the confirmed ADAs for their ability to neutralize the GIP or GLP-1 receptor-activating activities of tirzepatide (Tier 4a and Tier 4b) using cell-based NAb assays, or the endogenous GIP and GLP-1 peptide hormone counterparts (Tier 4c and Tier 4d) using *in silico* methods. The *in silico* NAb assays for GIP & GLP-1 are discussed below with additional background information regarding the cell-based assays they replaced.

Regarding the Tier 4c and 4d cell-based assays that were developed, but not implemented, the sponsor stated earlier (DARRTS Reference ID: 4451422; 06/24/2019) that they were unable to identify ADA that possess cross-reactive neutralizing activity against native GIP (Tier 4c) or native GLP-1(Tier 4d) due to poor neutralizing ability of their respective positive control neutralizing antibodies against the GIP and the GLP-1 moiety of tirzepatide. To overcome these potential issues, Lilly proposed to employ a more conservative “in silico” approach for determination of NAb against native GIP (Tier 4c) or native GLP-1 (Tier 4d). Per Figure 1, below, in this “in silico” approach they plan to use the NAb-positivity data from samples tested against the tirzepatide drug GIP moiety (Tier 4a) or GLP-1 moiety (Tier 4b), combined with the respective cross-reactive ADA-positivity results for endogenous GIP (Tier 2b) or endogenous GLP-1 (Tier 2c) to assign a patient as positive for NAb recognizing native GIP (Tier 4c) and/or native GLP-1 (Tier 4d). This approach was discussed earlier and accepted by OBP (DARRTS Reference ID: 4451422; 06/24/2019).

Figure 1: Immunogenicity testing strategy (copied from the submission)



Abbreviations: ADA = anti-drug antibodies; CP = cut point; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; LY = LY3298176 (tirzepatide); NAb = neutralizing antibody; R = receptor.

9. Immunogenicity Results from Phase 3 studies:

The immunogenicity of tirzepatide is supported in this application by 5 global (pivotal) and 2 regional (Japan) Phase 3 studies. All these studies were conducted in T2DM subjects. The global Phase 3 studies (GPGK, GPGL, GPGH, GPGM, and GPGI) were designed to assess the efficacy and safety of tirzepatide drug at 5, 10, and 15 mg once-weekly doses (for 40- or 52-week) versus placebo or active comparators in adults. The treatment exposure in Study GPGM lasted for up to 104 weeks.

The 2 regional Phase 3 studies (GPGO and GPGP) were 52-week, conducted in Japan to meet registration requirements of the 'Pharmaceuticals and Medical Devices Agency (PMDA)', Japan. The sponsor used the same FDA validated immunogenicity assays to assess the immune responses in patients from these studies, therefore, the immunogenicity assessment results are used in analyzing overall immunogenicity from all seven Phase 3 studies.

Treatment emergent ADA-positive (TE ADA+) patients are defined by the sponsor as those having baseline ADA-negative and at least one post-baseline status of ADA present with titer ≥2× MRD of the ADA assay. Alternatively, if a patient is baseline ADA+, the postbaseline titer should be 2 dilutions (4-fold) greater than the baseline titer in order to be considered ADA+.

The immunogenicity incidence is discussed for two placebo-controlled phase 3 studies (GPGK and GPGI) followed by five other clinical studies (GPGL, GPGH, GPGM, GPGO, and GPGP). The studies are each briefly described below.

9.1. Placebo-controlled studies (GPGK and GPGI)

a. I8F-MC-GPGK - 40-week, placebo-controlled study

Dosage:
(1) 5 mg - 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg; 4 weeks each, then 10 mg maintenance dose.
(3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg; each dose for 4 weeks, followed by 15 mg maintenance dose.

A total of 478 T2DM patients received tirzepatide (121 patients in each group received 5mg, or 10mg or 15mg TZP) and 115 patients received placebo (QW SC). ADA results are summarized in table GPGK.1, copied below, and the effect ADA on HbA1c change is shown in Figure GPGK.5.6 below (source: current submission).

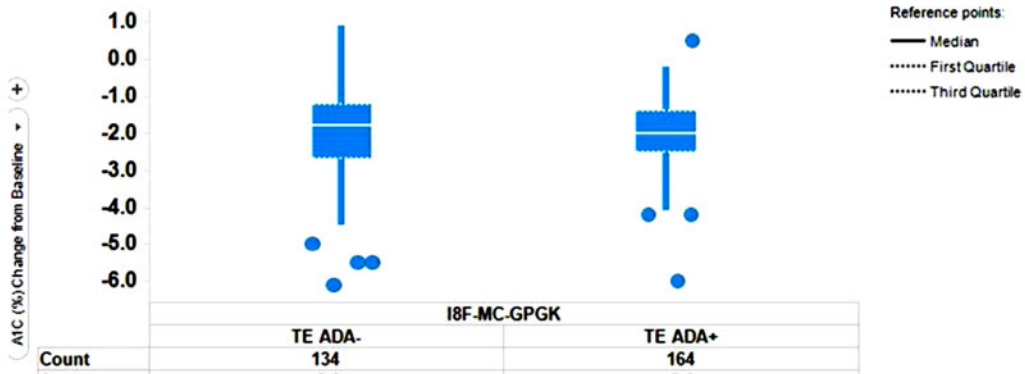
Table GPGK.1. Summary of TE Tirzepatide ADA Status during the Entire Postbaseline Period, Including the Safety Follow-up Safety Population

Summary of TE Tirzepatide Anti-Drug Antibody Status — Page 1 of 1
During the Entire Postbaseline Period including Safety Follow-up — 13:16 26FEB2021
Safety Population — PDPM
I8F-MC-GPGK

Category	TZP 5mg (N=121) n (%)	TZP 10mg (N=121) n (%)	TZP 15mg (N=121) n (%)	TZP All (N=363) n (%)	Placebo (N=115) n (%)
Patients Evaluable for TE ADA *a	119 [98.3]	115 [95.0]	117 [96.7]	351 [96.7]	114 [99.1]
Evaluable Patients with ADA Present at Baseline	9 (7.6)	4 (3.5)	13 (11.1)	26 (7.4)	15 (13.2)
Patients Postbaseline TE ADA+ *b	64 (53.8)	64 (55.7)	54 (46.2)	182 (51.9)	5 (4.4)
Treatment-Induced TE ADA+	59 (49.6)	62 (53.9)	51 (43.6)	172 (49.0)	3 (2.6)
Treatment-Boosted TE ADA+	5 (4.2)	2 (1.7)	3 (2.6)	10 (2.8)	2 (1.8)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	55 (46.2)	51 (44.3)	63 (53.8)	169 (48.1)	109 (95.6)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide

ADA status and HbA1c change from baseline (%):



	I8F-MC-GPGK	
	TE ADA-	TE ADA+
Count	134	164
Avg	-2.0	-2.0
StdDev	1.24	0.90
Min	-6.10	-6.00
Median	-1.8	-2.0
Max	0.9	0.5
Outliers	4	4

Abbreviations: Avg = average; HbA1c = glycosylated hemoglobin A1c; Max = maximum; Min = minimum; StdDev = standard deviation; TE-ADA = treatment-emergent anti-drug antibody.
Note: blue circles are outlier observed HbA1c.

Figure GPGK.5.36. Change from baseline in HbA1c versus TE-ADA status for tirzepatide-treated patients.

Assessor comments:

- *ADA incidence during the entire postbaseline period, including the FU period shows that out of 351 tirzepatide-treated patients, 182 patients (51.9%) were TE ADA positive. Of these TE ADA+, 172 patients (49.0%) were classified as treatment-induced ADA, and 10 patients (2.8%) were classified as treatment boosted.*
- *Percent of ADA+ patients increased from a cohort treated with 5mg (53.8%) to 10mg (55.7%) tirzepatide but then decreased in patient cohort treated with 15 mg tirzepatide (46.2%). The dose dependent ADA-positivity is not conclusive.*
- *7.4% of all patients receiving tirzepatide were tested positive for pre-existing ADAs, whereas 13.2% patients from placebo-controlled group were tested positive for pre-existing ADAs.*
- *Visual comparison in HbA1c change from baseline (%) showed no apparent difference between ADA+ (N=164) and ADA- (N=134) patients (source: Figure GPGK.5.36 and Table GPGK 5.1, gpgk-04-body). Therefore, no loss of efficacy is expected in patients from this study that could be related to ADA status of the patient.*

- *Assessments for cross-reactive binding ADAs and NAbs were presented in the ISI report (Table APP2.4 below.*

b. I8F-MC-GPGI - 40-week, placebo-controlled study

Dosage:
(1) 5 mg - 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg; 4 weeks each, then 10 mg maintenance dose.
(3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg; each dose for 4 weeks, followed by 15 mg maintenance dose.

A total of 475 T2DM patients received tirzepatide (116 patients received 5 mg, 119 patients received 10 mg and 120 patients received 15 mg TZP) and 120 patients received placebo. ADA results are summarized in Table GPGI.1, and the effect ADA on HbA1c change is shown in Figure GPGI.5.47, copied below (source: current submission).

Table GPGI. 1. Summary of Postbaseline Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA During the Entire Postbaseline Period, including the Safety Follow-up Safety Population

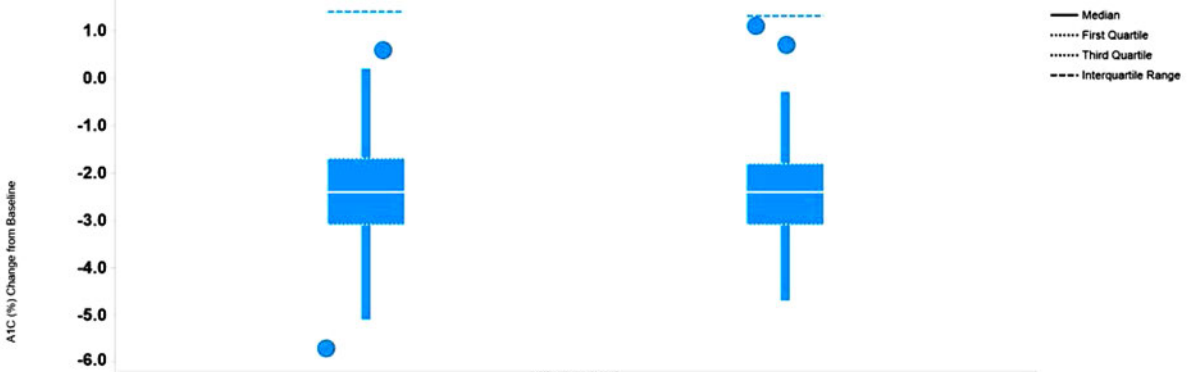
Summary of TE Tirzepatide Anti-Drug Antibody Status
During the Entire Postbaseline Period including Safety Follow-up
Safety Population
I8F-MC-GPGI

Page 1 of 1
13:40 29MAR2021
PDPM

Category	TZP 5mg (N=116) n (%)	TZP 10mg (N=119) n (%)	TZP 15mg (N=120) n (%)	TZP_All (N=355) n (%)	Placebo (N=120) n (%)
Patients Evaluable for TE ADA *a	113 [97.4]	114 [95.8]	117 [97.5]	344 [96.9]	116 [96.7]
Evaluable Patients with ADA Present at Baseline	9 (8.0)	6 (5.3)	10 (8.5)	25 (7.3)	11 (9.5)
Patients Postbaseline TE ADA+ *b	56 (49.6)	67 (58.8)	60 (51.3)	183 (53.2)	7 (6.0)
Treatment-Induced TE ADA+	53 (46.9)	63 (55.3)	52 (44.4)	168 (48.8)	3 (2.6)
Treatment-Boosted TE ADA+	3 (2.7)	4 (3.5)	8 (6.8)	15 (4.4)	4 (3.4)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	57 (50.4)	47 (41.2)	57 (48.7)	161 (46.8)	109 (94.0)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide

ADA status and HbA1c change from baseline (%):



I8F-MC-GPGI

	TE ADA-	TE ADA+
Count	129	169
Avg	-2.5	-2.5
StdDev	1.10	0.93
Min	-5.70	-4.70
Median	-2.4	-2.4
Max	0.6	1.1
Outliers	2	2

Abbreviations: A1C = glycosylated hemoglobin A1c; Avg = average; HbA1c = glycosylated hemoglobin A1c; Max = maximum; Min = minimum; StdDev = standard deviation; TE ADA = treatment-emergent antidrug antibody; TZP = tirzepatide.
Figure GPGI.5.47 Change from baseline in HbA1c versus TE ADA status for tirzepatide-treated patients.

Assessor comment:

- *A total of 344 tirzepatide-treated patients were evaluated for TE ADA.*
- *Of these, 183 patients (53.2%) were TE ADA+; including 168 patients (48.8%) that were classified as treatment induced ADA+ and 15 patients (4.4%) that were classified as treatment boosted (pre-existing) ADA+. This suggests that the incidence of ADA+ patients was slightly higher in*

placebo-controlled studies than overall from all seven Phase 3 studies (51.1% reported to be ADA+ from all seven phase 3 studies). Nevertheless, the sponsor reported total ADA+ patients in the product label, from all seven phase 3 studies.

- *An increase in dose-dependent ADA development could be observed in patients treated with 5mg (49.6%) to 10mg (58.8%) but then the incidence reduced to 51.3% in the cohort receiving 15mg tirzepatide.*
- *7.3% patients were tested positive for pre-existing ADAs in patients treated with tirzepatide, whereas 9.5% patients receiving placebo had pre-existing ADAs.*
- *Visual comparison of ADA status (129 ADA- versus 169 ADA+ patients) and HbA1c change from baseline (%) showed no apparent difference in HbA1c relative to TE-ADA status (Figure GPGI.5.47; GPGI Body). Therefore, no loss of efficacy is expected in patients from this study that could be related to TE-ADA status of the patient.*
- *Assessments for cross-reactive binding ADA and NAb are presented as overall summary from all seven Phase 3 studies together (Table APP.2.4).*

9.2. Pivotal Phase 3 studies:

c. Study I8F-MC-GPGH - effects of treatment with TZP versus insulin degludec

Dosage (52-week treatment):
(1) 5 mg - 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg for 4 weeks each, then 10 mg maintenance dose.
(3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg; each for 4 weeks, followed by 15 mg maintenance dose.

A total of 1444 T2DM patients received terzepatide (359 patients received 5mg, 361 patients received 10 mg, 359 patients received 15mg TZP) and 365 patients received insulin degludec. ADA results are summarized in Table GPGH.1 and the effect ADA on HbA1c change is shown in Figure GPGH.5.44 below (source: current submission).

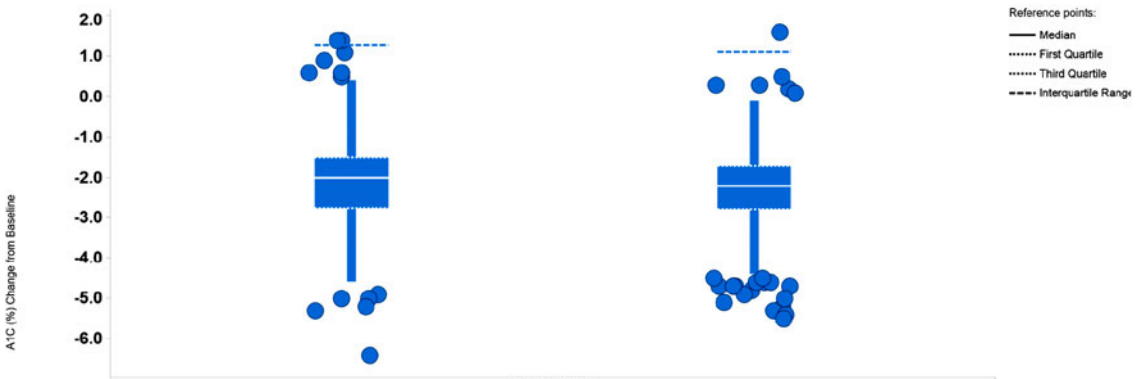
Table GPGH.1. Summary of TE Tirzepatide ADA Status during the Entire Postbaseline Period, Including the Safety Follow-up
Safety Population

Summary of TE Tirzepatide Anti-Drug Antibody Status — Page 1 of 1
During the Entire Postbaseline Period including Safety Follow-up — 14:20 25MAR2021
Safety Population — PDPM
I8F-MC-GPGH

Category	TZP 5mg (N=358) n (%)	TZP 10mg (N=360) n (%)	TZP 15mg (N=359) n (%)	TZP_All (N=1077) n (%)	Insulin Degludec (N=360) n (%)
Patients Evaluable for TE ADA *a	356 [99.4]	356 [98.9]	351 [97.8]	1063 [98.7]	351 [97.5]
Evaluable Patients with ADA Present at Baseline	26 (7.3)	26 (7.3)	23 (6.6)	75 (7.1)	22 (6.3)
Patients Postbaseline TE ADA+ *b	176 (49.4)	179 (50.3)	194 (55.3)	549 (51.6)	14 (4.0)
Treatment-Induced TE ADA+	164 (46.1)	167 (46.9)	182 (51.9)	513 (48.3)	13 (3.7)
Treatment-Boosted TE ADA+	12 (3.4)	12 (3.4)	12 (3.4)	36 (3.4)	1 (0.3)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	180 (50.6)	177 (49.7)	157 (44.7)	514 (48.4)	337 (96.0)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide

ADA status and HbA1c change from baseline (%):



	I8F-MC-GPGH	
	TE ADA-	TE ADA+
Count	398	486
Avg	-2.1	-2.3
StdDev	1.08	1.01
Min	-6.40	-5.50
Median	-2.0	-2.2
Max	1.4	1.6
Outliers	13	23

Abbreviations: A1C = glycosylated hemoglobin A1c; Avg = average; HbA1c = glycosylated hemoglobin A1c; Max = maximum; Min = minimum; StdDev = standard deviation; TE ADA = treatment-emergent antidrug antibody; TZP = tirzepatide.

Figure GPGH.5.44 Change from baseline in HbA1c versus TE ADA status for tirzepatide-treated patients.

Assessor comment:

- *A total of 1063 tirzepatide-treated patients were evaluated for TE ADAs during the postbaseline period. Of these, 549 patients (51.6%; 549/1063) were confirmed for TE-ADA+ by anti-tirzepatide antibody assay.*
- *Seventy-five of 1063 (7%) patients had pre-existing antibodies to tirzepatide and 22 of 351 patients (6.3%) receiving insulin degludec had pre-existing ADAs to tirzepatide.*
- *A total of 513 patients (48.3%) were classified as treatment-induced, and 36 patients (3.4%) were classified as treatment-boosted.*
- *The mean change in HbA1c based on ADA status was assessed (396 ADA- versus 486 ADA+ patients). Visual comparison of ADA status and the mean HbA1c change from baseline (%) showed no apparent difference in HbA1c relative to TE-ADA status (Figure GPGH.5.44; GPGH-Body, page 381).*
- *Assessments for cross-reactive binding ADA and NAb are presented as overall summary from all seven Phase 3 studies together (Table APP.2.4).*

d. Study I8F-MC-GPGM – safety and efficacy of TZP versus insulin glargine.

Dosage (104-week treatment):
(1) 5 mg - 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg; 4 weeks each, followed by 10 mg maintenance dose. (3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg; each dose for 4 weeks, followed by 15 mg maintenance dose.

A total of 2002 T2DM patients received tirzepatide (329 patients received 5mg, 330 patients received 10 mg, 338 patients received 15mg TZP) and 1005 patients received insulin glargine. ADA results are

summarized in Table GPGM.1 and the effect ADA on HbA1c change is shown in Figure GPGM.5.50 below (source: current submission).

Table GPGM.1. Summary of TE Tirzepatide ADA Status during the Entire Postbaseline Period, Including the Safety Follow-up
Safety Population

Summary of TE Tirzepatide Anti-Drug Antibody Status
During the Entire Postbaseline Period including Safety Follow-up
Safety Population
I8F-MC-GPGM

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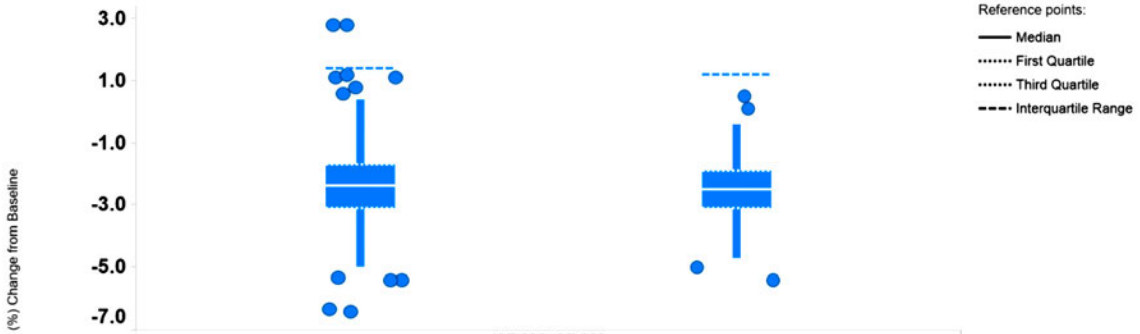
Category	TZP 5mg (N=329) n (%)	TZP 10mg (N=328) n (%)	TZP 15mg (N=338) n (%)	TZP_All (N=995) n (%)	Insulin Glargine (N=1000) n (%)
Patients Evaluable for TE ADA *a	316 [96.0]	315 [96.0]	325 [96.2]	956 [96.1]	960 [96.0]
Evaluable Patients with ADA Present at Baseline	15 (4.7)	17 (5.4)	18 (5.5)	50 (5.2)	61 (6.4)
Patients Postbaseline TE ADA+ *b	123 (38.9)	141 (44.8)	144 (44.3)	408 (42.7)	47 (4.9)
Treatment-Induced TE ADA+	114 (36.1)	132 (41.9)	135 (41.5)	381 (39.9)	33 (3.4)
Treatment-Boosted TE ADA+	9 (2.8)	9 (2.9)	9 (2.8)	27 (2.8)	14 (1.5)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	193 (61.1)	174 (55.2)	181 (55.7)	548 (57.3)	913 (95.1)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide

ADA status and HbA1c change from baseline (%):



	I8F-MC-GPGM	
	TE ADA-	TE ADA+
Count	461	368
Avg	-2.4	-2.5
StdDev	1.16	0.90
Min	-6.40	-5.40
Median	-2.4	-2.5
Max	2.8	0.5
Outliers	12	4

Abbreviations: A1C/HbA1c = glycosylated hemoglobin A1c; Avg = mean; Min = minimum; Max = maximum; StdDev = standard deviation; TE-ADA = treatment-emergent antidrug antibody; TZP = tirzepatide. Note: outliers were marked by closed circles.

Figure GPGM.5.50. Change from baseline in HbA1c versus TE-ADA status for tirzepatide-treated patients.

Assessor comment:

- *There were 956 tirzepatide-treated patients evaluable for TE-ADA during the treatment including FU period. Of these, 408 patients (42.6 %) were TE-ADA positive.*
- *A total of 111 patients (5.8%) treated with tirzepatide had ADAs at baseline, whereas 61 of 960 patients (6.4%) were tirzepatide ADA+ at baseline in the insulin glargine treated arm.*

- *Of 408 ADA+ patients treated with tirzepatide, 381 patients (39.9%) were classified as treatment-induced, and 27 patients (2.8%) were classified as treatment-boosted.*
- *The ADA-positivity appears to increase dose dependently in cohort treated with 5mg (38.9%) and 10mg (44.8%) tirzepatide but remains similar in cohort treated with 15mg tirzepatide (44.3%).*
- *The sponsor used 461 ADA-negative and 368 ADA+ patients who received tirzepatide to analyze the effect of ADA on primary endpoint (%change in HbA1c from baseline). Visual comparison of group's ADA status and the mean HbA1c change from baseline (%) showed no apparent difference in HbA1c relative to TE-ADA status (Figure GPGM.5.50, source: GPGM-04-Body, page 443).*
- *Assessments for cross-reactive binding ADA and NAb are presented as overall summary from all seven Phase 3 studies together (Table APP.2.4).*

e. Study I8F-MC-GPGL- safety and efficacy of TZP versus Semaglutide treatment.

Dosage (40-week treatment):
(1) 5 mg - SC QW 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg QW; 4 weeks each, then 10 mg maintenance dose.
(3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg QW; each dose for 4 weeks, followed by 15 mg maintenance dose.
(4) Semaglutide 1 mg - dose escalation: 0.25, 0.5 mg QW; each dose for 4 weeks followed by 1 mg maintenance dose.

A total of 1879 T2DM patients received tirzepatide - 471 patients received 5 mg, 469 patients received 10 mg, 470 patients received 15 mg, and 469 patients received 1mg semaglutide. ADA results are summarized in table GPGL.1 and the effect ADA on HbA1c change is shown in Figure GPGL 5.49 below (source: current submission).

Table GPGL.1. Summary of Patients with Treatment-Emergent Tirzepatide Antidrug Antibodies During the Entire Postbaseline Period, including the Safety Follow-up
Safety Population

Summary of TE Tirzepatide Anti-Drug Antibody Status
During the Entire Postbaseline Period including Safety Follow-up
Safety Population
I8F-MC-GPGL

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Category	TZP 5mg (N=470) n (%)	TZP 10mg (N=469) n (%)	TZP 15mg (N=470) n (%)	TZP_All (N=1409) n (%)	SEMA 1mg (N=469) n (%)
Patients Evaluable for TE ADA *a	462 [98.3]	465 [99.1]	467 [99.4]	1394 [98.9]	460 [98.1]
Evaluable Patients with ADA Present at Baseline	34 (7.4)	48 (10.3)	35 (7.5)	117 (8.4)	39 (8.5)
Patients Postbaseline TE ADA+ *b	236 (51.1)	241 (51.8)	261 (55.9)	738 (52.9)	20 (4.3)
Treatment-Induced TE ADA+	221 (47.8)	223 (48.0)	242 (51.8)	686 (49.2)	19 (4.1)
Treatment-Boosted TE ADA+	15 (3.2)	18 (3.9)	19 (4.1)	52 (3.7)	1 (0.2)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	226 (48.9)	224 (48.2)	206 (44.1)	656 (47.1)	440 (95.7)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; SEMA = semaglutide; TE = treatment-emergent; TZP = tirzepatide

ADA status and HbA1c change from baseline (%):

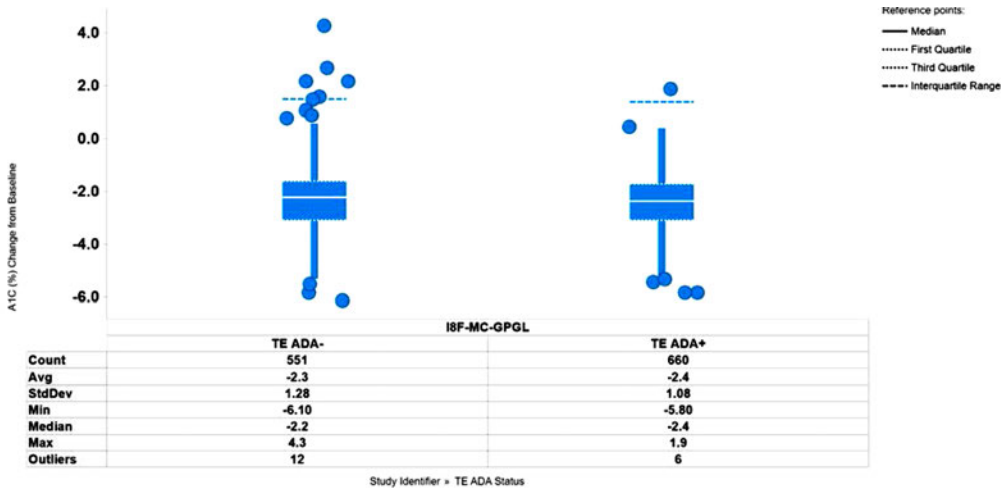


Figure GPGL.5.49. Change from baseline in HbA1c versus TE ADA status for tirzepatide-treated patients.

Assessor comment:

- *The sponsor reported that there were 1394 tirzepatide-treated patients' serum samples assessed for the development of TE ADA during the planned treatment period.*
- *Of these, 708 patients were TE ADA+ (52.9%); 686 patients (49.2%) were classified as treatment induced and 52 patients (3.7%) were classified as treatment boosted.*
- *8.4% patients receiving tirzepatide had pre-existing ADAs, while only 3.7% patients were determined to be treatment-boosted, therefore, it appears that pre-existing ADAs may not have any effect on boosting the ADA incidence in these patients.*
- *A dose-dependent ADA positivity exists in patient's cohort receiving tirzepatide from 5mg (51.1%), 10mg (51.8%) and 15mg (55.8%).*
- *The sponsor used 551 ADA-negative and 660 ADA+ patients who received tirzepatide to analyze the effect of ADA on primary endpoint (%change in HbA1c from baseline). Visual comparison of group's ADA status and the mean HbA1c change from baseline (%) showed no apparent difference in HbA1c relative to TE-ADA status (Figure GPGL.5.49, source: GPGL-04-Body, page 409).*
- *Assessments for cross-reactive binding ADA and NAb are presented as overall summary from all seven Phase 3 studies together (Table APP.2.4).*

f. Study I8F-JE-GPGP- safety and efficacy of TZP in patients with T2DM taking therapeutic doses of various oral antihyperglycemic medications.

Dosage (52-week treatment):
(1) 5 mg - 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg QW; 4 weeks each, then 10 mg maintenance dose.
(3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg QW; each dose for 4 weeks, followed by 15 mg maintenance dose.

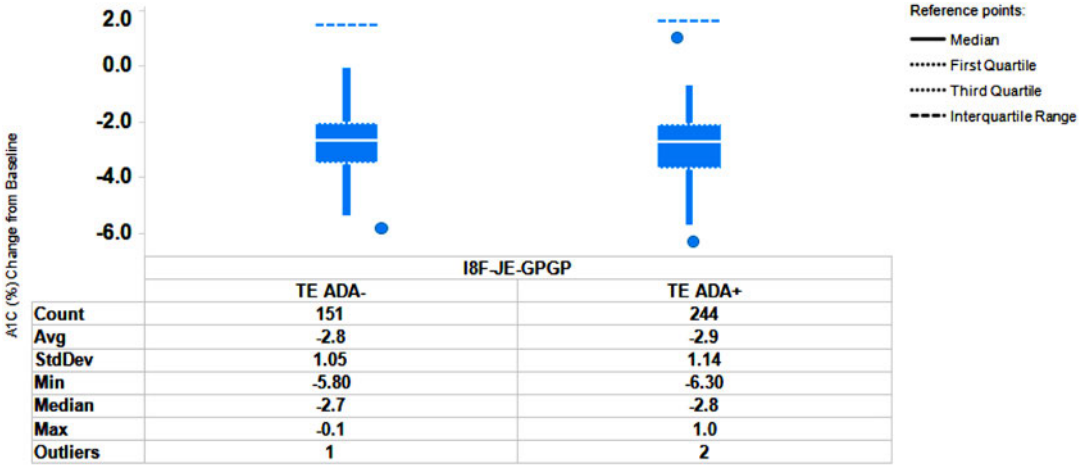
Number of subjects (N = 443/636 T2DM patients): 148 patients received 5 mg TZP, 147 patients received 10mg TZP, and 148 patients received 15mg TZP. ADA results are summarized in table GPGP.1 and the effect ADA on HbA1c change is shown in Figure GPGP.5.20 below (source: current submission).

Table GPGP.1. Summary of Treatment-Emergent Tirzepatide ADA Status During the Entire Postbaseline Period, Including the Safety Follow-up
Safety Analysis Set

Category	TZP 5mg (N=148) n (%)	TZP 10mg (N=147) n (%)	TZP 15mg (N=148) n (%)	TZP_All (N=443) n (%)
Patients Evaluable for TE ADA *a	148 [100.0]	147 [100.0]	148 [100.0]	443 [100.0]
Evaluable Patients with ADA Present at Baseline	13 (8.8)	9 (6.1)	8 (5.4)	30 (6.8)
Patients Postbaseline TE ADA+ *b	88 (59.5)	91 (61.9)	92 (62.2)	271 (61.2)
Treatment-Induced TE ADA+	81 (54.7)	86 (58.5)	88 (59.5)	255 (57.6)
Treatment-Boosted TE ADA+	7 (4.7)	5 (3.4)	4 (2.7)	16 (3.6)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0
Patients Postbaseline TE ADA- *b	60 (40.5)	56 (38.1)	56 (37.8)	172 (38.8)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; SEMA = semaglutide; TE = treatment-emergent; TZP = tirzepatide.

ADA status and HbA1c change from baseline (%):



	I8F-JE-GPGP	
	TE ADA-	TE ADA+
Count	151	244
Avg	-2.8	-2.9
StdDev	1.05	1.14
Min	-5.80	-6.30
Median	-2.7	-2.8
Max	-0.1	1.0
Outliers	1	2

Figure GPGP.5.20. Change from baseline in HbA1c versus TE ADA status for tirzepatide-treated patients.

Assessor comment:

- *ADA incidence was assessed in 443 tirzepatide-treated patients; 30 patients (6.8%) had pre-existing antibodies.*
- *Of these 443, 271 patients (61.2%) were TE ADA-positive, 255 patients (57.6%) were classified as treatment-induced, and 16 patients (3.6%) were classified as treatment-boosted.*
- *Percent of ADA-positivity increased dose-dependently from 59.5% to 61.9% to 62.2% in patient cohorts receiving 5 mg, 10mg and 15mg tirzepatide respectively.*
- *The sponsor used 151 ADA-negative and 244 ADA+ patients who received tirzepatide to analyze the effect of ADA on primary endpoint (%change in HbA1c from baseline), visual comparison of ADA status and the mean HbA1c change from baseline (%) showed no apparent difference in HbA1c relative to TE-ADA status (Figure GPGP.5.20., above; from GPGP-04-Body, page 183).*

- *Assessments for cross-reactive binding ADA and NAb are presented as overall summary from all seven Phase 3 studies together (Table APP.2.4).*

g. Study I8F-JE-GPGO - safety and efficacy study of TZP versus dulaglutide

Dosage (52-week treatment):
(1) 5 mg - 2.5 mg for 4 weeks, followed by 5 mg maintenance dose.
(2) 10 mg - dose escalation: 2.5, 5, 7.5 mg; 4 weeks each, then 10 mg maintenance dose.
(3) 15 mg - dose escalation: 2.5, 5, 7.5, 10, 12.5 mg QW; each dose for 4 weeks, followed by 15 mg maintenance dose.

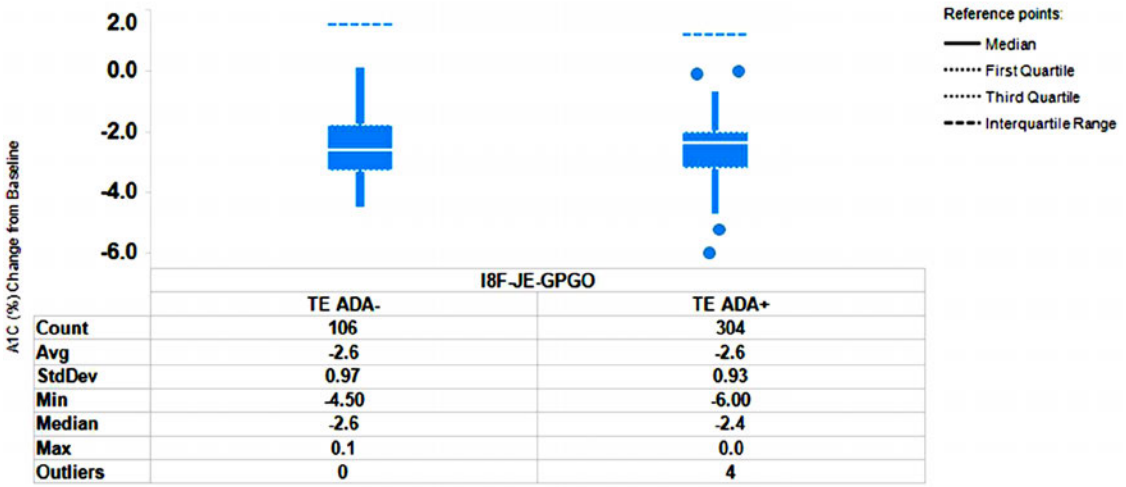
A total of 636 T2DM patients received tirzepatide (159 patients received 5mg, 158 patients received 10mg, 160 patients 15mg) and 159 patients received 0.75 mg dulaglutide. ADA results are summarized in table GPGO.1 and the effect ADA on HbA1c change is shown in Figure GPGO.5.23 below (source: current submission).

Table GPGO.1. Summary of Treatment-Emergent Tirzepatide ADA Status During the Entire Postbaseline Period, Including the Safety Follow-up
Safety Analysis Set

Category	TZP 5mg (N=159) n (%)	TZP 10mg (N=158) n (%)	TZP 15mg (N=160) n (%)	TZP_All (N=477) n (%)	Dulaglutide 0.75mg (N=159) n (%)
Patients Evaluable for TE ADA *a	158 [99.4]	158 [100.0]	160 [100.0]	476 [99.8]	159 [100.0]
Evaluable Patients with ADA Present at Baseline	9 (5.7)	10 (6.3)	11 (6.9)	30 (6.3)	10 (6.3)
Patients Postbaseline TE ADA+ *b	100 (63.3)	102 (64.6)	125 (78.1)	327 (68.7)	8 (5.0)
Treatment-Induced TE ADA+	94 (59.5)	98 (62.0)	117 (73.1)	309 (64.9)	7 (4.4)
Treatment-Boosted TE ADA+	6 (3.8)	4 (2.5)	8 (5.0)	18 (3.8)	1 (0.6)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	58 (36.7)	56 (35.4)	35 (21.9)	149 (31.3)	151 (95.0)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; SEMA = semaglutide; TE = treatment-emergent; TZP = tirzepatide.

ADA status and HbA1c change from baseline (%):



I8F-JE-GPGO

	TE ADA-	TE ADA+
Count	106	304
Avg	-2.6	-2.6
StdDev	0.97	0.93
Min	-4.50	-6.00
Median	-2.6	-2.4
Max	0.1	0.0
Outliers	0	4

Figure GPGO.5.23. Change from baseline to Week 52 in HbA1c versus TE ADA status for tirzepatide-treated patients.

Assessor comment:

- *The serum samples for a total of 476 tirzepatide-treated patients were assessed for TE ADAs during the entire postbaseline period including the FU period. Thirty (30) patients (6.3%) were tested positive for pre-existing ADAs.*
- *Of 476, 327 patients (68.7%) were tested ADA-positive; 309 patients (64.9%) were classified as treatment-induced, and 18 patients (3.8%) were classified as treatment boosted.*
- *None of the control subjects treated with dulaglutide were detected positive by anti-tirzepatide antibody assay, suggesting good sensitivity of the assay.*
- *Percent of ADA-positivity increased dose-dependently from 63.3% to 64.6% to 68.7% in patient cohorts receiving 5 mg, 10mg and 15mg tirzepatide respectively.*
- *The sponsor used 106 ADA-negative and 304 ADA+ patients from this study who received tirzepatide to analyze the effect of ADA on primary endpoint (%change in HbA1c from baseline).*
- *Visual comparison of ADA status and the mean HbA1c change from baseline (%) showed no apparent significant difference in average HbA1c change relative to ADA status (Figure GPGO.5.23.; GPGO-04-Body, page 206).*
- *Assessments for cross-reactive binding ADA and NAb are presented as overall summary from all seven Phase 3 studies together (Table APP.2.4).*

10. Summary of Immunogenicity results:

The sponsor summarized all immunogenicity data assessed from seven Phase 3 studies in Table ISI.4.22. below that indicates that a total of 5027 T2DM patients (including FU period) were assessed for ADA status from all seven studies together who received tirzepatide at various drug dosages. The immunogenicity results based on sampling time are presented in sponsor's Tables ISI.4.22- 23 (treatment period) and APP.2.4 (treatment period plus the FU studies) which are copied below (source: ISI and ISI-APP).

Binding antibody status during treatment period of Phase 3 studies:

Table ISI.4.22. Summary of Treatment-Emergent Antidrug Antibody Status (Phase 3 Dose-Effect Analysis)

Summary of TE Tirzepatide Anti-Drug Antibody Status — Page 1 of 1
During the Planned Treatment Period — 10:06 03JUN2021
Safety Population — PDPM
Phase 3 Dose Effect Analysis Set
I8F-MC-GPGH, I8F-MC-GPGI, I8F-MC-GPGK, I8F-MC-GPGL, I8F-MC-GPGM, I8F-JE-GPGO, I8F-JE-GPGP

Category	TZP 5mg (N=1701) n (%)	TZP 10mg (N=1702) n (%)	TZP 15mg (N=1716) n (%)	TZP_All (N=5119) n (%)
Patients Evaluable for TE ADA *a	1670 [98.2]	1670 [98.1]	1685 [98.2]	5025 [98.2]
Evaluable Patients with ADA Present at Baseline	115 (6.9)	120 (7.2)	118 (7.0)	353 (7.0)
Patients Postbaseline TE ADA+ *b	815 (48.8)	858 (51.4)	897 (53.2)	2570 (51.1)
Treatment-Induced TE ADA+	759 (45.4)	809 (48.4)	835 (49.6)	2403 (47.8)
Treatment Boosted TE ADA+	56 (3.4)	49 (2.9)	62 (3.7)	167 (3.3)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0	0
Patients Postbaseline TE ADA- *b	855 (51.2)	812 (48.6)	788 (46.8)	2455 (48.9)

Table ISI.4.23. Summary of Cross-Reactive and Neutralizing Antibodies from Patients with Treatment-Emergen Tirzepatide Antidrug Antibodies (Phase 3 Dose-Effect Analysis)

Summary of Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA Page 1
During the Planned Treatment Period Using Disease-State Cut Points 10:06 03JUI
Safety Population
Phase 3 Dose Effect Analysis Set 4
I8F-MC-GPGH, I8F-MC-GPGI, I8F-MC-GPGK, I8F-MC-GPGL, I8F-MC-GPGM, I8F-JE-GPGO, I8F-JE-GPGP

Category	TZP 5mg (N=1701) n (%)	TZP 10mg (N=1702) n (%)	TZP 15mg (N=1716) n (%)	TZP_All (N=5119) n (%)
Patients Evaluable for TE ADA *a	1670 [98.2]	1670 [98.1]	1685 [98.2]	5025 [98.2]
Evaluable Patients with ADA Present at Baseline	115 (6.9)	120 (7.2)	118 (7.0)	353 (7.0)
Neutralizing TZP for GIPR at Baseline	0	2 (0.1)	0	2 (0.0)
Neutralizing TZP for GLP-1R at Baseline	1 (0.1)	0	1 (0.1)	2 (0.0)
GIP Cross-Reactive at Baseline	29 (1.7)	34 (2.0)	34 (2.0)	97 (1.9)
In Silico Neutralizing to Native GIP at Baseline	0	0	0	0
GLP-1 Cross-Reactive at Baseline	11 (0.7)	10 (0.6)	13 (0.8)	34 (0.7)
In Silico Neutralizing to Native GLP-1 at Baseline	0	0	0	0
Patients Postbaseline TE ADA+ *b	815 (48.8)	858 (51.4)	897 (53.2)	2570 (51.1)
Neutralizing TZP for GIPR	33 (2.0)	25 (1.5)	36 (2.1)	94 (1.9)
Neutralizing TZP for GLP-1R	32 (1.9)	36 (2.2)	39 (2.3)	107 (2.1)
GIP Cross-Reactive	533 (31.9)	577 (34.6)	595 (35.3)	1705 (33.9)
In Silico Neutralizing to Native GIP	14 (0.8)	5 (0.3)	24 (1.4)	43 (0.9)
GLP-1 Cross-Reactive	223 (13.4)	250 (15.0)	243 (14.4)	716 (14.2)
In Silico Neutralizing to Native GLP-1	7 (0.4)	6 (0.4)	5 (0.3)	18 (0.4)

Abbreviations: ADA = anti-drug antibodies; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; N = total number of patients in specified treatment group; n = number of patients in specified category; R = receptor; TE = treatment-emergent; TZP = tirzepatide

Note: Denominator for percent (%) is the number of patients who are TE ADA Evaluable in each treatment group, except the [%] of which the denominator is the number of the patients who are from the safety population.

*a - A patient is TE ADA Evaluable if there is at least one non-missing test result for TZP ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA Evaluable patients in each treatment group.
*b - A TE ADA Evaluable patient is considered to be TE ADA+ if the patient has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA Not Present, the patient is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 1:20 (treatment-induced). A TE ADA Evaluable patient is TE ADA Inconclusive if >=20% of the patient's postbaseline samples, drawn pre-dose, are ADA Inconclusive and the patient is not otherwise TE ADA+. A TE ADA Evaluable patient is TE ADA- if not TE ADA+ and not TE ADA Inconclusive.

Note: Table ISI.4.22 (ISI) indicates that number of ADA+ patients was 2570, during the planned treatment period, whereas the total ADA+ patients were 2658 (Table APP.2.4, ISI-APP) when FU period was included. The change in total ADA+ patients in Table APP.2.4, may also potentially change the number of treatment- induced and treatment boosted ADA+ patients' data, which was not presented in the table (Table APP.2.4 below). A request for clarification of these data was sent to the sponsor. The sponsor provided a new revised table to include these data (Table 4.1).

Cross-reactive and Neutralizing antibody status during treatment in phase 3 studies:

Table APP.2.4. Summary of Cross-reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA

Summary of Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA — Page 1 of 2
During the Entire Postbaseline Period including Safety Follow-up Using Disease-State Cut Points — 10:06 03JUN2021
Safety Population — PDPM
Phase 3 Dose Effect Analysis Set
I8F-MC-GPGH, I8F-MC-GPGI, I8F-MC-GPGK, I8F-MC-GPGL, I8F-MC-GPGM, I8F-JE-GPGO, I8F-JE-GPGP

Category	TZP 5mg (N=1701) n (%)	TZP 10mg (N=1702) n (%)	TZP 15mg (N=1716) n (%)	TZP_All (N=5119) n (%)
Patients Evaluable for TE ADA *a	1672 [98.3]	1670 [98.1]	1685 [98.2]	5027 [98.2]
Evaluable Patients with ADA Present at Baseline	115 (6.9)	120 (7.2)	118 (7.0)	353 (7.0)
Neutralizing TZP for GIPR at Baseline	0	2 (0.1)	0	2 (0.0)
Neutralizing TZP for GLP-1R at Baseline	1 (0.1)	0	1 (0.1)	2 (0.0)
GIP Cross-Reactive at Baseline	29 (1.7)	34 (2.0)	34 (2.0)	97 (1.9)
In Silico Neutralizing to Native GIP at Baseline	0	0	0	0
GLP-1 Cross-Reactive at Baseline	11 (0.7)	10 (0.6)	13 (0.8)	34 (0.7)
In Silico Neutralizing to Native GLP-1 at Baseline	0	0	0	0
Patients Postbaseline TE ADA+ *b	843 (50.4)	885 (53.0)	930 (55.2)	2658 (52.9)
Neutralizing TZP for GIPR	44 (2.6)	44 (2.6)	49 (2.9)	137 (2.7)
Neutralizing TZP for GIPR Inconclusive	81 (4.8)	93 (5.6)	115 (6.8)	289 (5.7)
Neutralizing TZP for GLP-1R	38 (2.3)	45 (2.7)	43 (2.6)	126 (2.5)
Neutralizing TZP for GLP-1R Inconclusive	9 (0.5)	43 (2.6)	46 (2.7)	98 (1.9)
GIP Cross-Reactive	607 (36.3)	646 (38.7)	674 (40.0)	1927 (38.3)
In Silico Neutralizing to Native GIP	19 (1.1)	18 (1.1)	30 (1.8)	67 (1.3)
In Silico Neutralizing to Native GIP Inconclusive	10 (0.6)	10 (0.6)	10 (0.6)	30 (0.6)
GLP-1 Cross-Reactive	271 (16.2)	305 (18.3)	302 (17.9)	878 (17.5)
In Silico Neutralizing to Native GLP-1	7 (0.4)	6 (0.4)	5 (0.3)	18 (0.4)
In Silico Neutralizing to Native GLP-1 Inconclusive	0	0	0	0

Abbreviations: ADA = anti-drug antibodies; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; N = total number of patients in specified treatment group; n = number of patients in specified category; R = receptor; TE = treatment-emergent; TZP = tirzepatide

*a - A patient is TE ADA Evaluable if there is at least one non-missing test result for TZP ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA Evaluable patients in each treatment group.

*b - A TE ADA Evaluable patient is considered to be TE ADA+ if the patient has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA Not Present, the patient is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 1:20 (treatment-induced). A TE ADA Evaluable patient is TE ADA Inconclusive if >=20% of the patient's postbaseline samples, drawn pre-dose, are ADA Inconclusive and the patient is not otherwise TE ADA+. A TE ADA Evaluable patient is TE ADA- if not TE ADA+ and not TE ADA Inconclusive.

Assessor comment (Overall immunogenicity):

1) *Binding antibody status:*

A total of 5025 patients' samples were evaluated for the presence of anti-drug antibodies during the planned treatment period (Table ISI.4.22) while 5027 patients were reported to have evaluable serum samples from entire studies including the FU period (Table APP.2.4).

- *Of 5025, 353 (7%) patients had pre-existing antibodies to tirzepatide, whereas 2750 (51.1%) patients developed ADAs during the treatment period. (Table ISI.4.22; source: ISI-APP). The number of ADA+ reported to be higher (2658 of 5027 patients = 52.9%) when results from FU period was included, where total number of evaluable samples for TE-ADA was also more than the samples during the planned treatment period. The reason of this change is not understood but the sponsor may have evaluated all patient's samples together and reported later who were detected ADA+. Nevertheless, this observation suggests that the development of ADAs may continue at later stage of the treatment. The sponsor plans to report the number of ADA+ patients (b) (4) who were detected ADA+ during the treatment period minus the ADA results obtained from FU period.*

- *The overall ADA results from Phase 3 studies suggest that the incidence of ADA+ patients increased in a dose-dependent manner from 5mg, 10mg and 15mg TZP to 48.4%, 51.4% and*

53.2%, respectively, during the course of the treatment. This is also reflected in the incidence of treatment-induced ADA+ patients (45.4%, 48.4% and 49.6% respectively for 5, 10 and 15mg tirzepatide).

- *Table 4.22 suggests that out of 2570 ADA+ patients during planned treatment period, 2403 (47.8% of 5025) patients were categorized as positive for treatment-induced ADA+ (who were ADA-negative at baseline but became seroconverted or ADA+ after treatment with an ADA titer of >1:20), whereas 167 (3.3%) patients had treatment boosted ADA. When considering the ADA incidence inclusive of the FU period, the change in the number of TE-ADA evaluable samples during the follow-up period was considered. The resulting incidence of treatment-induced and treatment-boosted ADA+ patients was reported to be 2484 (49.4%) and 174 (3.5%) of 2658 ADA+ patients, respectively (Table 4.1, sponsor response to FDA comments). The reason for this observation is unclear; some potential explanations may be that the sponsor may have assessed all evaluable samples including the samples collected at FU period from all patients at the same time and then analyzed the ADA results, or some patients who lacked pre-dose samples were assessed and ADA+ samples were included in the revised table. Nevertheless, this result suggests that the incidence of the development of ADAs may increase at later stage of the treatment as well.*

- *This indicates that a majority of TE-ADA+ is treatment-induced rather than treatment-boosted (47.8% versus 3.3%, respectively). Therefore, pre-existing ADAs may not have a substantial role in leading the development of TE ADAs.*

  The sponsor reported 2403 (47.8%) patients had treatment-induced ADA, whereas 167 (3.3%) patients had treatment-boosted ADA where 7% patients had pre-existing antibodies suggesting that pre-existing ADAs may not have impact on boosting the ADA incidence rate in these studies.

Assessor Note: The sponsor categorized ADA+ samples of a patient as treatment-induced if a patient has at least one postbaseline result of ADA with a titer ≥2xMRD (1:20) and tested ADA-negative for pre-existing antibodies. Any sample with %inhibition greater than or equal to the CCP were reported as ADA 'detected' and were then tested for ADA titer since titer is expected when ADA assay result is 'detected'. Also, the titer above the MRD was used as a method to determine the ADA status, which seems rational to define treatment-induced ADAs. It appears that the sponsor did not report patients who were tested ADA+ with ADA titer at MRD in Table APP.2.4. This report includes ADA+ patients who had an ADA titer of at least 2-fold greater than MRD (referred to as 'Treatment Emergent ADA or (TE-ADA).

The treatment-boosted ADA+ samples were categorized based on the FDA guidance for immunogenicity[1] as the sample which is ADA+ at the baseline and with the postbaseline titer being 2 dilutions (4-fold) greater than the baseline titer.

1) Cross-Reactive (Tier 2b and 2c) and Neutralizing Antibodies (Tier 4a and 4b)

The ADA+ patients were further evaluated by validated cross-reactivity and NAb assays.

[1] Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection- Guidance for Industry (2019). . *https://www.fda.gov/media/119788/download.*

- *The results from the planned treatment period showed that 1705 patients (33.9%) and 716 (14.2%) patients had cross-reactive anti-tirzepatide antibodies respectively, to native GIP and native GLP-1 (Table ISI.4.23). However, the number of patients with cross-reactive antibody results increased to a total of 1927 (38.3%) and 878 (17.5%) ADA+ patients to native GIP and native GLP-1 respectively when ADA+ patients from FU period was included (Table APP.2.4). This suggests that more ADA+ patients serum samples may become cross-reactive to native peptides over the length of the treatment even after the treatment is stopped.*

- *31.9% patients receiving 5mg, 34.6% receiving 10mg and 35.3% patients receiving 15mg tirzepatide were tested positive by anti-GIP cross-reactivity assay (Tier 2b). Similarly, 13.4% patients receiving 5mg, 15% receiving 10mg and 14.4% patients receiving 15mg tirzepatide were tested positive by anti-GLP-1 cross-reactivity assay (Tier 2c). The cross-reactivity results indicate that a dose dependent correlation may exist with the development of cross-reactive antibodies to either nGIP or nGLP-1.*

- *A total of 94 (1.9% of 5025) patients were reported to be positive for NAb antibodies (NAb+) for GIPR (Tier 4a) and 107 (2.1%; 107/5025) patients were reported to be positive for NAb+ for GLP-1R (Tier 4b) during planned treatment period (Table ISI.4.23). This demonstrates that a similar level of NAb was detected by Tier 4a and Tier 4b assay. However, when the NAb characterization of ADAs include ADA+ patients from FU period, a total of 137 (2.7% of 5027) patients were reported to be positive for NAb antibodies for GIPR and 126 (2.5%; 107/5025) patients were reported to be positive for NAb+ for GLP-1R (Table APP.2.4).*

- *This observation suggests that the development of cross-reactive antibodies as well as the NAb antibodies to terazapatide continues to increase even after the administration of last dose of the drug. Nevertheless, no impact of these antibodies on safety or efficacies were noticed during the trial period.*

- *The sponsor reported that a total of 289 (5.7% of 5025) patients NAb assay results by Tier 4a (for GIPR) and a total of 98 (1.9% of 5025) patients NAB assay results by Tier 4b (for GLP-1R) from post-baseline period including the FU period were inconclusive (see footnote of Table APP.2.4) suggesting majority of ADA+ samples resulted a decisive result by Tier 4a and Tier 4b assays, therefore, the assays performed good and were tolerant.*

- *A patient's data was considered inconclusive, when ≥ 20% of the patient's postbaseline samples were inconclusive for ADA results, in addition to the pre-dose samples. Also, if the ADA assay result was not detectable due to drug concentration higher than the assay's drug tolerance level in the sample that may cause interference in the ADA detection method, these samples were also designated inconclusive.*

2) In-silico Neutralizing Antibodies (Tier 4c and 4d)

The sponsor implemented an in-silico classification for cross-reactive NAb to identify ADA neutralizing against nGIP and nGLP-1, due to the lower-than-desired drug tolerance in the in vitro, cell-based cross-reactive NAb assays (Tier 4c and 4d, respectively). The results are provided in tables ISI.4.23 and APP.2.4. (Source: ISI and ISI-APP) copied below.

- *Of 2570, 43 patients (0.9%) were considered to be positive for ADA neutralizing to nGIP (nGIP NAb+; Tier 4c) and 18 (0.4%) patients were considered to be positive for ADA neutralizing to nGLP-1 (nGLP-1 NAb+; Tier 4d) (Table ISI.4.23). These patients were cross-reactive to corresponding native peptides and also neutralizing in nature. The clinical effects for these subjects are not analyzed separately in the submission. An information request was included in a letter sent to the sponsor. The response to this comment was received on 3 January 2022 and reviewed below (appendix-2).*

- *A total of 30 patients (0.6%; 30 of 5027) Tier 4c assay results using in-silico approach was inconclusive, in contrast to in-silico neutralizing to nGLP-1 (Tier 4d) where none of the assay results were inconclusive, therefore the assay was well tolerant, and the risk of false negative results may have avoided by these assays.*

11. Antidrug Antibody Dynamics:

1. ADA development based on exposure time

The frequency of ADA development in tirzepatide-treated patients from each of the Phase 3 studies is summarized in the following Table ISI.4.24, showing a cumulative ADA frequency at each assessment time. (Each study used 3-4 different doses of the drug, and the results reported are cumulative for all dose levels in TZP-treated patients).

Table ISI.4.24. Cumulative Frequency of Time-to-First TE ADA+ Titer (Phase 3 Dose-Effect Analysis)

Study	N	Time-to-First TE ADA+ Titer, Cumulative Categories, n (%)						
		<=4 Weeks	<=12 Weeks	<=24 Weeks	<=40 Weeks	<=52 Weeks	<=78 Weeks	<=104 Weeks
GPGH	1062	12 (1.1)	80 (7.5)	266 (25.0)	466 (43.9)	518 (48.8)	536 (50.5)*	
GPGI	344	3 (0.9)	26 (7.6)	89 (25.9)	160 (46.5)	178 (51.7)*	-	
GPGK	351	0	16 (4.6)	90 (25.6)	155 (44.2)	174 (49.6)*	-	
GPGL	1393	6 (0.4)	91 (6.5)	352 (25.3)	639 (45.9)	704 (50.5)*	-	
GPGM	956	7 (0.7)	62 (6.5)	190 (19.9)	300 (31.4)	367 (38.4)	389 (40.7)	399 (41.7)
GPGO	476	4 (0.8)	51 (10.7)	182 (38.2)	278 (58.4)	312 (65.5)	322 (67.6)*	
GPGP	443	1 (0.2)	32 (7.2)	119 (26.9)	209 (47.2)	244 (55.1)	257 (58.0)*	

Abbreviations: ADA = antidrug antibody; N = number of patients who are evaluable for TE ADA during the Planned Treatment Period; n = number of TE ADA+ patients; TE = treatment-emergent
*Represents flexibility of visit windows as per schedule of activities.

[GPGI, GPGK and GPGL = 40 weeks treatment; GPGH, GPGO and GPGP = 52 weeks treatment and GPGM = 104 weeks treatment]

Assessor comment:
The ADA results based on the length of exposure time was as follows:

- *0 to 1.1% (median 0.7%) developed TE ADA by 4 weeks*
- *4.6 to 10.7% (median 7.2%) developed TE ADA by 12 weeks,*
- *19.9 to 38.2% (median 25.6%) developed TE ADA by 24 weeks,*
- *31.4 to 58.4% (median 45.9%) developed TE ADA by 40 weeks,*
- *38.4 to 65.5% (median 50.5%) developed TE ADA by 52 weeks, and*

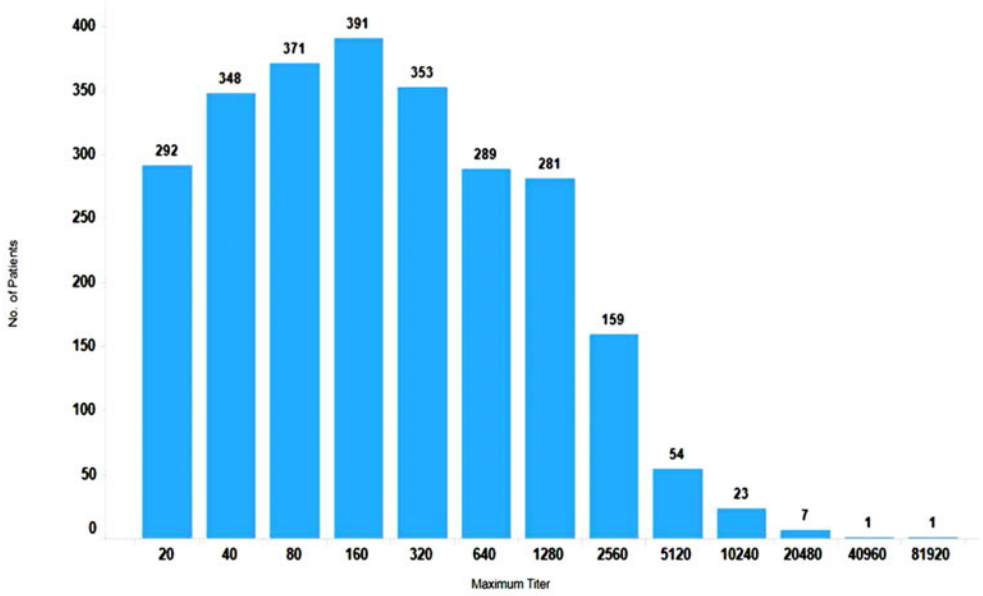
- *40.7 to 67.6% (median 54.2%) up to 78 weeks (includes GPGH, GPGM, GPGO, and GPGP studies only).*

➢ *These results suggest the possibility of a linear relationship of the incidence of ADA development and the length of exposure of the drug; similar trends could be seen across all Phase 3 studies.*

2. Antidrug Antibody Titers

Maximum ADA titer distribution in 2658 tirzepatide-treated TE ADA+ patients (from 5207 total tirzepatide-treated) from all seven Phase3 studies was presented in Figure APP.2.4 (copied below from ISI-APP). The ADA titers for all ADA+ participants reported in these studies ranged from 1:20 to 1:81920 (median 1:160) during the planned treatment period.

The sponsor stated that one patient (b) (6) from the 5-mg tirzepatide group was ADA+ in first samples that was taken 19 minutes after the first dose of 2.5 mg. *This patient did not have a baseline sample*. The ADA titer of this patient's first ADA sample was 1:163840, and the titer subsequently fluctuated from 1:40960 at Week 41 to 1:327680 at Week 78. This patient had high ADA titer consistently; however, the sponsor stated that this patient did not experience any hypersensitivity or injection site reaction and showed HbA1c lowering similar to other tirzepatide-treated patients. The ADA titer of this patient was not included in the analysis below.



Abbreviations: ADA = antidrug antibody; TE = treatment emergent.

Figure ISI.4.2. Maximum titer distribution of tirzepatide TE ADA+ patients during the planned treatment period.

Assessor comment:

- *The peak titer data from each of 2570 ADA+ patients was used to evaluate titer distribution in ADA+ patients. The graphical titer distribution data appears to peak at the median titer 1:160 (with 391 patients having this peak titer during their planned treatment period), and then declines gradually to a single patient showing an ADA titer of 1:81920.*

- *One patient (Subject (b) (6)) had a maximum ADA titer of 1:327680, was not included in this analysis. The sponsor noted that this patient may have had pre-existing ADA, but this was not confirmed since the pre-dose sample was not taken. Rather, sampling 19 minutes after the first dosing at 2.5mg revealed a titer of 1:163840. The tirzapatide clearance in this subject did not show any significant difference when compared to ADA-negative subjects (Fig ISI.4.5 below).*

- *Out of a total of 2570 patients' titers reported, 1168 (45.4%) had a titer greater than the median titer. The ADA titers for all ADA+ participants reported in these studies ranged from 1:20 to 1:81920 (median 1:160) during the planned treatment period.*

- *The ADA titer data also indicates that more patients' ADA titers peaked before reaching the median ADA titer.*

Assessor Note: The number of ADA+ patients with titer from 1:20 to 1:81920 was 2570, which is reported to be total number of ADA+ patients from Phase 3 studies (ISI.4.23). The sponsor however did not include patients with ADA titer 1:10, which is indicated below in Figure ISI.4.5 to be 547. Therefore, the total number of ADA-positives was reported higher in Figure ISI.4.5 and PK analysis.

3. Changes in ADA Titers over Time

The sponsor determined the median titer from tirzepatide-treated TE ADA+ patient and plotted against weeks 4, 12, 24, 40, 42, 52, 78 and 104 including at FU period.

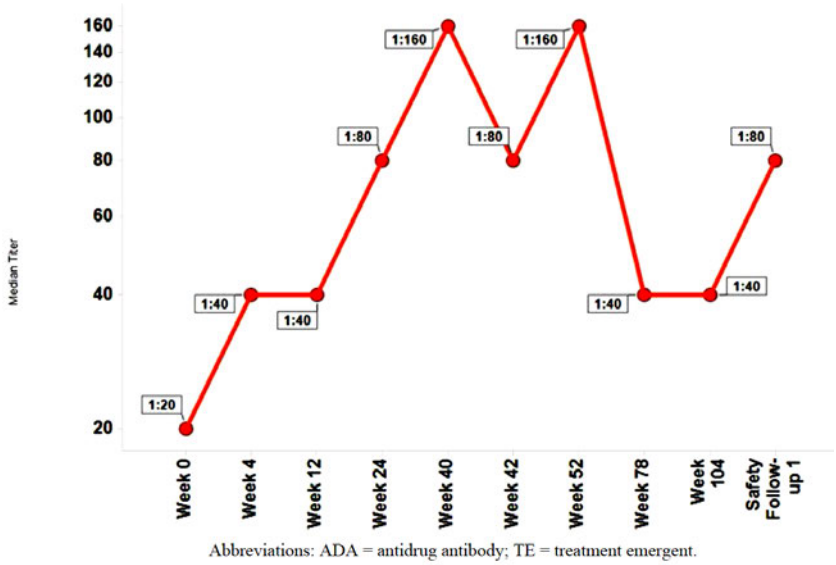


Figure ISI.4.3. Median ADA titer profile of TE ADA+ patients at scheduled visits during planned treatment period.

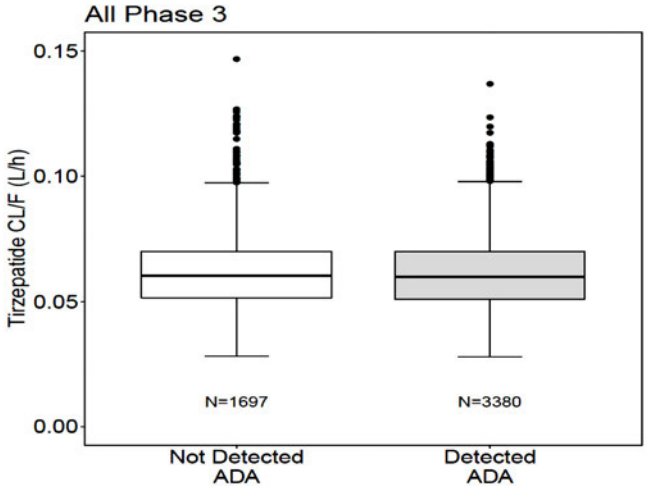
Assessor comment:
The plot of the median ADA titer versus the visit weeks during the treatment period indicates that the median titer (1:160) from Phase 3 studies peaked at week 40, plateaued between median 1:90 at Week 42 and Week 52 (median of 1:160) and then generally declined to lower levels. The effect of the median titer on PK is not directly applicable in patient's safety analysis, but it may provide an idea about the

strength of the ADAs that are developing during the tirzepatide treatment phase in patients with T2DM, in general.

12. Effect of Immunogenicity on Pharmacokinetics

The tirzepatide clearance profile was compared between 1) patients with ADA+ and ADA-negative, 2) ADA titer and 3) NAb-positive patients from all Phase 3 studies.

1) Tirzepatide clearance profile: ADA+ and ADA-negative patients from all Phase 3 studies



Abbreviations: ADA = antidrug antibody; CL/F = apparent clearance; N= number of patients.

(Note: Solid circles denote individual values for each group; the top and bottom margins of the boxplot represent the 75th and 25th percentiles; the whiskers extend to ±1.5x interquartile range).

Figure ISI.4.4. Tirzepatide apparent clearance (CL/F) by ADA status in Phase 3 studies.

Assessor Note: The data presented in Figure ISI.4.4. indicates that the total of 3380 ADA+ sample data was used from all 2658 ADA+ patients reported in Table APP.2.4. The sponsor included all samples starting with an ADA titer of 1:10 (MRD) and since each ADA+ patient reported in Table APP.2.4 potentially may have more than one titer values included in Figure ISI.4.5 below, the number of ADA+ samples used in Figures ISI.4.4 and ISI.4.5 seems apparently different. Overall, the analysis demonstrates that the mean tirzepatide clearance does not differ in ADA+ samples compared to ADA- samples.

Tirzepatide clearance profile based on ADA titer (all Phase 3 studies)

Tirzepatide clearance was measured in ADA+ samples from all patients in Phase 3 studies and analyzed based on ADA titer. The results are provided below.

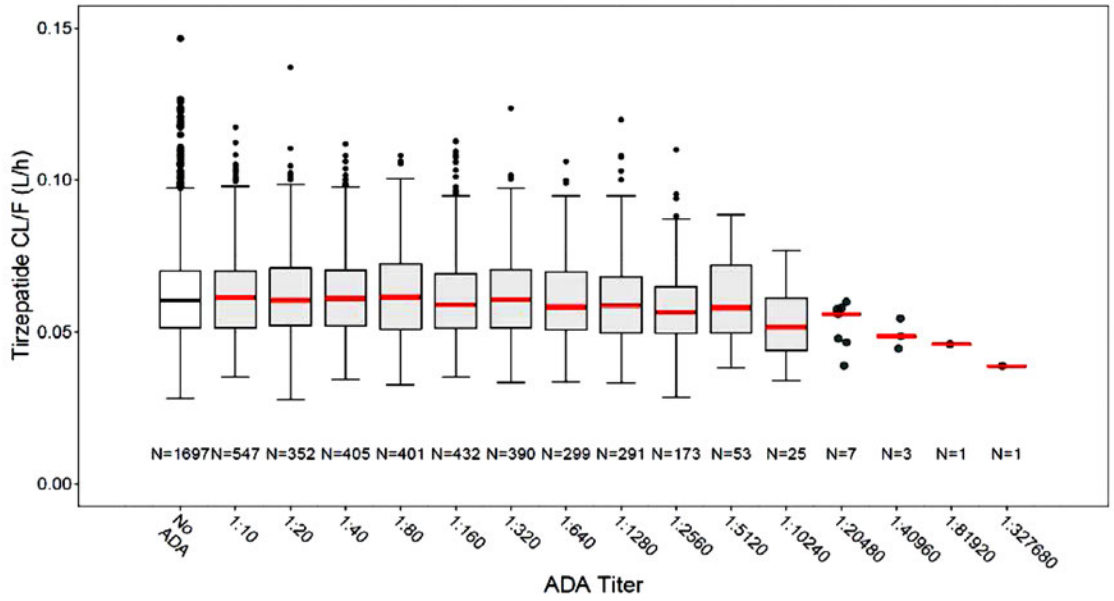
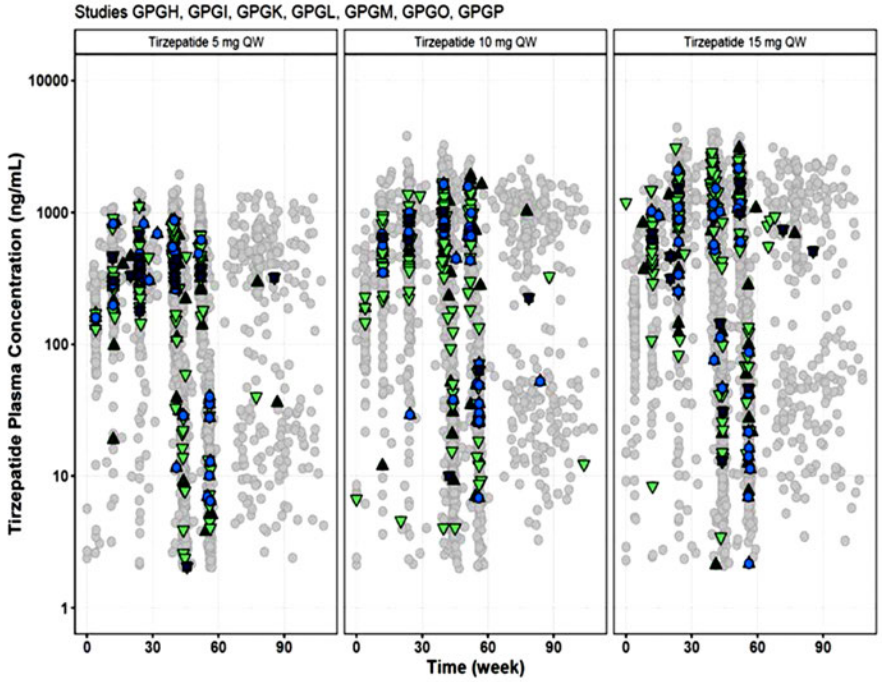


Figure ISI.4.5. Tirzepatide apparent clearance (CL/F) across ADA titer in Phase 3 studies.

Assessor comment: The sponsor included all samples with measurable ADA titer in this analysis. No significant difference in tirzepatide clearance profile was observed.

2) Tirzepatide clearance profile in NAb-positive patients from all Phase 3 studies

Tirzepatide plasma concentration (ng/mL) was measured for all ADA+ patients' samples and plotted with patients showing positive in all NAb assays from phase 3 studies against weeks of treatment for each tirzepatide treatment group. The data is copied from the original below.



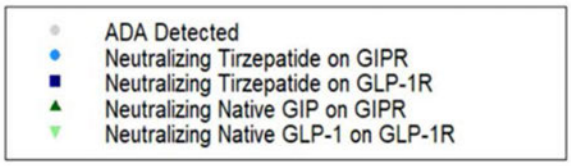


Figure ISI.4.6. Comparison of observed tirzepatide concentrations from patients with detected tirzepatide neutralizing antibodies in Phase 3 studies.

Assessor comment on PK analysis:

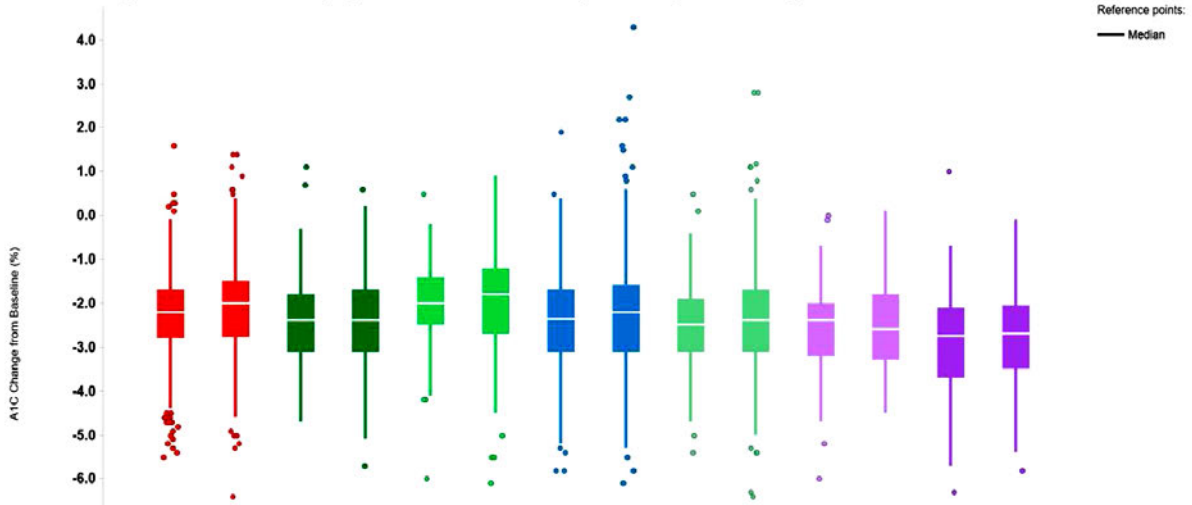
- *No apparent relation was obvious in the graphical comparison of tirzepatide clearance profile between ADA+ and ADA-negative patients.*
- *Although the ADA titer suggests about 45.4% patients had ADA titer above the median titer of 1:160 and 2.95% ADA+ patients ADA titers ≥1:5120 across all Phase 3 studies, no apparent relationship between ADA titer and tirzepatide clearance was observed (Figure ISI.4.4).*
- *No relationship between NAb and tirzepatide clearance could be detected.*

13. Effects of Immunogenicity on Efficacy

%HbA1c change from baseline compared to TE ADA status:

The sponsor evaluated the HbA1c change from baseline (%) induced by tirzepatide by TE ADA status (Figure ISI.4.7) for each Phase 3 studies. The data is provided as boxplot analysis below.

A1C change from baseline (%) vs TE ADA status (on treat): TZP Only



	GPGH		GPGI		GPGK		GPGL		GPGM		GPGO		GPGP	
	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-	TE ADA+	TE ADA-
Count	486	398	169	129	164	134	660	551	368	461	304	106	244	151
Avg	-2.3	-2.1	-2.5	-2.5	-2.0	-2.0	-2.4	-2.3	-2.5	-2.4	-2.6	-2.6	-2.9	-2.8
StdDev	1.01	1.08	0.93	1.10	0.90	1.24	1.08	1.28	0.90	1.16	0.93	0.97	1.14	1.05
Min	-5.50	-6.40	-4.70	-5.70	-6.00	-6.10	-5.80	-6.10	-5.40	-6.40	-6.00	-4.50	-6.30	-5.80
Median	-2.2	-2.0	-2.4	-2.4	-2.0	-1.8	-2.4	-2.2	-2.5	-2.4	-2.4	-2.6	-2.8	-2.7
Max	1.6	1.4	1.1	0.6	0.5	0.9	1.9	4.3	0.5	2.8	0.0	0.1	1.0	-0.1

Abbreviations: Avg = average; A1C = glycated hemoglobin (HbA1c); Max = maximum; Min = minimum; StdDev = standard deviation; TE ADA = treatment-emergent antidrug antibody; TZP = tirzepatide.

Figure ISI.4.7. Change from baseline in HbA1c versus TE ADA status for tirzepatide-treated patients.

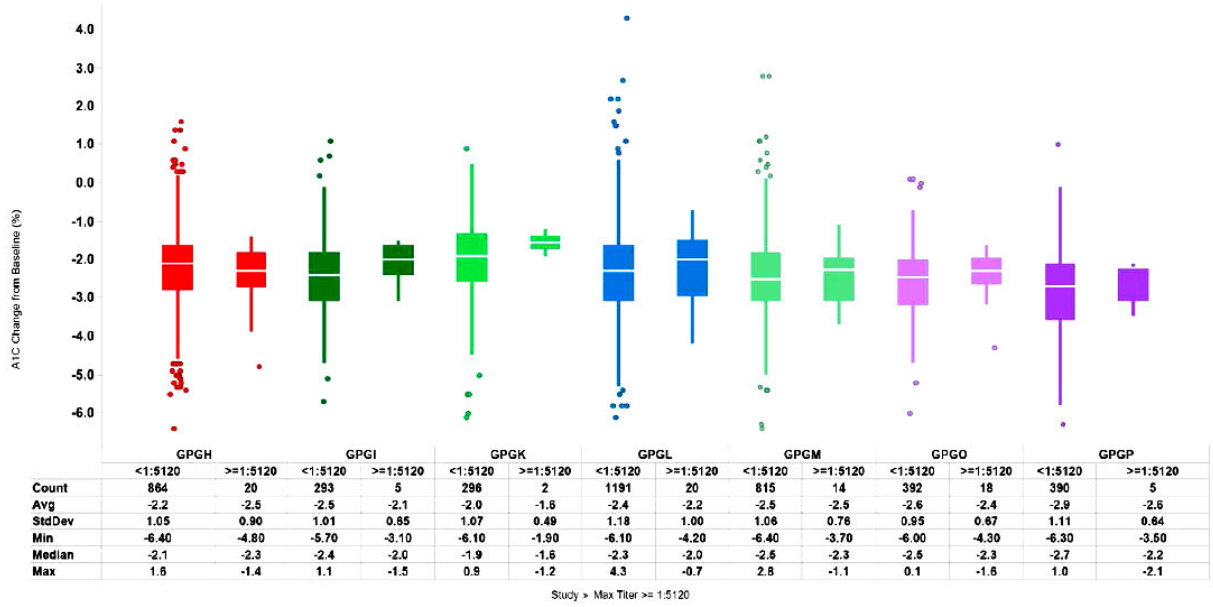
Assessor comment:

- *A total of 2395 ADA+ samples with titer was used in this analysis.*
- *The boxplot data compares the mean %HbA1c change from baseline between the ADA+ and ADA-negative patients for each of seven Phase 3 studies separately.*
- *No significant change in mean %HbA1c change from baseline between ADA+ and ADA-negative cohorts for each study was apparent.*
- *Visual assessment of %HbA1c change from baseline also did not show significantly different mean/median %HbA1c change difference between ADA- and ADA+ patients, suggesting that the presence of ADA was not associated with loss of efficacy (reduction in %HbA1c) of tirzepatide.*

%HbA1c change from baseline compared to TE ADA TITER status:

The sponsor evaluated whether %HbA1c change from baseline induced by tirzepatide was impacted by ADA titer for each Phase 3 studies. The impact evaluation was categorized for ADA titer ≥1:5120 vs <1:5120 and the results are provided in Figure ISI.4.8.

A1C change from baseline (%) vs max titer (on treat) (1:5120): TZP Only



	GPGH		GPGI		GPGK		GPGL		GPGM		GPGO		GPGP	
	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120	<1:5120	>=1:5120
Count	864	20	293	5	296	2	1191	20	815	14	392	18	390	5
Avg	-2.2	-2.5	-2.5	-2.1	-2.0	-1.6	-2.4	-2.2	-2.5	-2.5	-2.6	-2.4	-2.9	-2.6
StdDev	1.05	0.90	1.01	0.65	1.07	0.49	1.18	1.00	1.06	0.76	0.95	0.67	1.11	0.64
Min	-6.40	-4.80	-5.70	-3.10	-6.10	-1.90	-6.10	-4.20	-6.40	-3.70	-6.00	-4.30	-6.30	-3.50
Median	-2.1	-2.3	-2.4	-2.0	-1.9	-1.6	-2.3	-2.0	-2.5	-2.3	-2.5	-2.3	-2.7	-2.2
Max	1.6	-1.4	1.1	-1.5	0.9	-1.2	4.3	-0.7	2.8	-1.1	0.1	-1.6	1.0	-2.1

Study » Max Titer >= 1:5120

Abbreviations: ADA = antidrug antibody; Avg = average; A1C = glycated hemoglobin (HbA1c); Max = maximum; Min = minimum; StdDev = standard deviation; TZP = tirzepatide.

Figure ISI.4.8. Change from baseline in HbA1c for tirzepatide-treated patients with ADA titer <1:5120 vs ≥1:5120.

Assessor comment:

The sponsor used the samples with an ADA titer of 1:5120 as "high ADA titer" to evaluate whether high titer might affect the %HbA1c change from baseline in patients from all Phase 3 studies. The boxplot data showed a comparison in the mean %HbA1c change from baseline between ADA titer <1:5120 vs ≥1:5120 for each of seven Phase 3 studies.

Visual assessment of graphical data for HbA1c change from baseline suggests that the presence of ADA was not consistently associated with loss of efficacy of tirzepatide in patient from Phase 3 studies.

In Figure ISI.4.8 the mean change in HbA1c from baseline for tirzepatide-treated patients in Study GPGK with ADA titer ≥1:5120 was (-)1.6 in comparison to (-)2.1 for patients with an ADA titer of <1:5120. Similarly, in that study the average change in HbA1c from baseline was (-)1.4 for patients who were

NAb+ in the GIPR assay, in comparison to (-)2.0 for NAb-negative patients. In my opinion, these differences may suggest that a higher titer of ADA, or NAb activity, in a patient from Study GPGK may have had an impact on the change in HbA1c efficacy outcome. In order to understand whether there is any correlation between the ADA titer and efficacy of the drug, we sent an IR comment to provide a summary listing of the patients from this study.

%HbA1c change from baseline compared to neutralizing antibody status:
The sponsor evaluated whether the HbA1c change from baseline induced by tirzepatide was impacted by NAb against tirzepatide activity on GIPR and GLP-1R status for each Phase 3 studies. The results are presented in Table ISI.4.25 below.

Table ISI.4.25. Change from Baseline in HbA1c for Tirzepatide-Treated Patients with or without NAb+ against Tirzepatide Activity to GIPR and/or GLP-1R

Statistic	GPGH			GPGI			GPGK			GPGL			GPGM			GPGO			GPGP		
	TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+		TE ADA-	TE ADA+	
		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R		NAb + TZP GIPR	NAb + TZP GLP-1R
N	398	12	11	129	2	5	134	4	1	551	21	20	461	16	26	106	23	25	151	9	11
Mean	-2.1	-2.3	-2.4	-2.5	-2.2	-3.2	-2.0	-1.4	-1.9	-2.3	-2.5	-2.1	-2.4	-2.4	-2.2	-2.6	-2.7	-2.6	-2.8	-3.8	-2.9
SD	1.08	0.58	0.67	1.10	0.28	1.17	1.24	0.98	-	1.28	1.48	0.89	1.16	0.74	0.87	0.97	0.90	0.82	1.05	0.62	1.42
Min	-6.40	-3.30	-3.50	-5.70	-2.40	-4.50	-6.10	-2.70	-1.90	-6.10	-4.60	-3.60	-6.40	-4.00	-4.70	-4.50	-4.70	-4.70	-5.80	-5.00	-5.70
Median	-2.0	-2.3	-2.2	-2.4	-2.2	-3.6	-1.8	-1.3	-1.9	-2.2	-2.9	-2.2	-2.4	-2.3	-2.1	-2.6	-2.5	-2.4	-2.7	-3.5	-2.2
Max	1.4	-1.2	-1.5	0.6	-2.0	-1.4	0.9	-0.4	-1.9	4.3	1.9	-0.4	2.8	-1.1	-0.6	0.1	-1.5	-1.5	-0.1	-3.1	-1.0

Abbreviations: GIPR = glucose-dependent insulinotropic polypeptide receptor; GLP-1R = glucagon-like peptide-1 receptor; HbA1c = glycated hemoglobin; Max = maximum; Mean = arithmetic mean; Min = minimum; N = number of patients; NAb = neutralizing antibody; SD = standard deviation; TE ADA = treatment-emergent antidrug antibody; TZP = tirzepatide.

Assessor comment:

- *Comparison of the HbA1c change from baseline showed no significant difference in mean %HbA1c change for patients with NAb+ at GIP1R or at GLP-1R for any studies.*

- *For study GPGK, the mean %HbA1c was changed from -2.0% for ADA-negative to -1.4% for ADA+ NAb+ patients at GIPR, suggesting that NAb may be have influenced in efficacy of tirzepatide in 4 NAb+ patients, but the change does not appear to be significant.*

These data suggest that the development of NAb antibodies was not associated with the change in efficacy of tirzepatide.

14. Effect of Immunogenicity on Hypersensitivity Reactions

The hypersensitivity reactions by TE ADA status is provided in the table below (source: Table 2.7.4.99. – Clinical safety summary, page 235).

Table 2.7.4.99. Summary of Hypersensitivity Reactions by TE ADA Status During the Planned Treatment Period Safety Population Phase 3 Dose Effect Analysis Set (AS2)

	n (%)			
TE ADA status	TZP 5 mg (N=1701)	TZP 10 mg (N=1702)	TZP 15 mg (N=1716)	TZP_ALL (N=5119)
TE ADA+	32 (1.88)	31 (1.82)	43 (2.51)	106 (2.07)
TE ADA-	26 (1.53)	26 (1.53)	21 (1.22)	73 (1.43)

Abbreviations: ADA = anti-drug antibodies; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide.

Assessor comment:

- *A total of 179 of 5119 tirzepatide-treated patients experienced hypersensitivity reactions during the planned treatment period; 106 (2.07%) of them were TE ADA+ and 73 (1.43%) were ADA-negative indicating a higher proportion of TE ADA+ patients reported to have hypersensitivity than ADA-negative patients.*

- *The sponsor stated that the events reported in TE ADA+ patients were mostly mild to moderate in severity. Of the 106 TE ADA+ patients that experienced 1 or more hypersensitivity reactions, the ADA titer range was 1:10 to 1:10240 during the treatment period.*

- *11 of 86 patients with a maximum ADA titer of ≥1:5120 experienced mild or moderate potential hypersensitivity reactions; while no hypersensitivity events were reported for all other 75 patients with the same titer or higher (up to 1:81920).*

- *Majority of hypersensitivity reactions occurred at first onset within 16 weeks of receiving tirzepatide and resolved independent of TE ADA status or titer. No TEAE of anaphylactic reaction in tirzepatide-treated patients was observed in the Phase 3 program (Source: ISS - Table 2.7.4.99).*

Of note is a patient (GPGO-104-14603) who was reported to experience throat tightness and decreased blood pressure. This patient was TE ADA+ at Week 24 and titer peaked (1:320) at Week 40 which was 7 weeks prior to the event. The throat tightness resolved later, and the ADA titer remained 1:160 throughout the duration of the study.

15. Effect of Immunogenicity on injection Site Reactions

The incidence of injection site reactions (ISR) by TE ADA status is provided in the table below (Source: ISS - Table 2.7.4.100).

Table 2.7.4.100. Summary of Injection site Reactions by TE ADA Status During the Planned Treatment Period
Safety Population
Phase 3 Dose Effect Analysis Set (AS2)

	n (%)			
TE ADA status	**TZP 5 mg (N=1701)**	**TZP 10 mg (N=1702)**	**TZP 15 mg (N=1716)**	**TZP_ALL (N=5119)**
TE ADA+	25 (1.47)	38 (2.23)	56 (3.26)	119 (2.32)
TE ADA-	7 (0.41)	7 (0.41)	4 (0.23)	18 (0.35)
Not evaluable	1 (0.06)	1 (0.06)	0	2 (0.04)

Abbreviations: ADA = anti-drug antibodies; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide.

Assessor Note:

- *A total of 137 (of 5119) tirzepatide-treated patients experienced ISR during the planned treatment period; 119 were TE ADA+ and 18 were TE ADA-negative indicating a higher proportion of TE ADA+ patients reported injection-site-related reactions than AD-negative patients.*

- *Eighteen of 86 patients with a maximum ADA titer of ≥1:5120 experienced an ISR, with the highest titer being 1:81920. The sponsor stated that all of these reactions were mild and no ISR reactions were reported for the other 68 patients with titers ≥1:5120.*

- *Although the incidence of injection site reactions was numerically higher among TE ADA+ patients, there was no pattern detected between the time of the event reporting and antidrug antibody status or titer level in the individual patient-level data.*

16. Impact of Prior GLP-1 Receptor Agonist Exposure

The sponsor stated that they included some patients in clinical studies who were known for prior exposure to a GLP-1 receptor agonist. They analyzed 351 such patients' samples, who were exposed to a GLP-1 receptor agonist previously. The ADA results and the ADA titer distribution in ADA+ samples are provided in table ISI.4.30 and in figure ISI.4.10 respectively.

Table ISI.4.30. Summary of Cross-reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA (Phase 3 Dose-Effect Analysis Set for Patients with Prior Therapy of GLP-1 Agonist)

Summary of Cross-Reactive and Neutralizing Antibodies from Patients with TE Tirzepatide ADA
During the Planned Treatment Period Using Disease-State Cut Points
Safety Population
Phase 3 Dose Effect Analysis Set for Patients with Prior Therapy of GLP-1 Agonist
I8F-MC-GPGH, I8F-MC-GPGI, I8F-MC-GPGK, I8F-MC-GPGL, I8F-MC-GPGM, I8F-JE-GPGO, I8F-JE-GPGP

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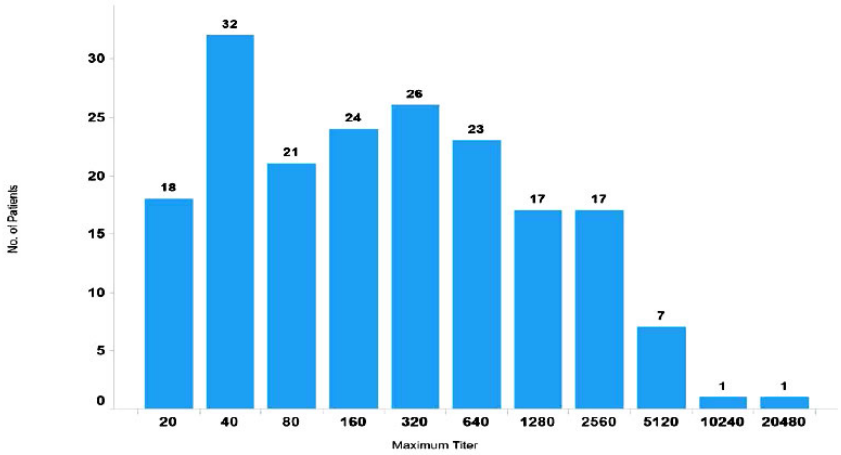
Category	TZP 5mg (N=114) n (%)	TZP 10mg (N=126) n (%)	TZP 15 mg (N=120) n (%)	TZP_All (N=360) n (%)
Patients Evaluable for TE ADA *a	109 [95.6]	126 [100]	116 [96.7]	351 [97.5]
Evaluable Patients with ADA Present at Baseline	10 (9.2)	9 (7.1)	10 (8.6)	29 (8.3)
Neutralizing TZP for GIPR at Baseline	0	0	0	0
Neutralizing TZP for GLP-1R at Baseline	0	0	0	0
GIP Cross-Reactive at Baseline	2 (1.8)	1 (0.8)	3 (2.6)	6 (1.7)
In Silico Neutralizing to Native GIP at Baseline	0	0	0	0
GLP-1 Cross-Reactive at Baseline	1 (0.9)	2 (1.6)	1 (0.9)	4 (1.1)
In Silico Neutralizing to Native GLP-1 at Baseline	0	0	0	0
Patients Postbaseline TE ADA+ *b	58 (53.2)	69 (54.8)	60 (51.7)	187 (53.3)
Neutralizing TZP for GIPR	0	1 (0.8)	4 (3.4)	5 (1.4)
Neutralizing TZP for GLP-1R	6 (5.5)	3 (2.4)	3 (2.6)	12 (3.4)
GIP Cross-Reactive	42 (38.5)	35 (27.8)	31 (26.7)	108 (30.8)
In Silico Neutralizing to Native GIP	0	0	2 (1.7)	2 (0.6)
GLP-1 Cross-Reactive	20 (18.3)	20 (15.9)	13 (11.2)	53 (15.1)
In Silico Neutralizing to Native GLP-1	2 (1.8)	0	2 (1.7)	4 (1.1)

Abbreviations: ADA = anti-drug antibodies; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; N = total number of patients in specified treatment group; n = number of patients in specified category; R = receptor; TE = treatment-emergent; TZP = tirzepatide



Abbreviations: GLP-1RA = glucagon-like peptide-1 receptor antagonist; TE ADA = treatment-emergent antidrug antibody.

Figure ISI.4.10. Maximum titer distribution during the planned treatment period of tirzepatide-treated TE ADA+ patients with prior therapy of GLP–1 RA.

Assessor Comments:
Binding ADAs:

- *Patients with preexisting ADA = 29 of 351 (8.3%) patients.*
- *TE ADA+ patients = 187 of 351 (53.2%) patients.*
  - *Treatment induced ADA+ = 171 (48.7%) patients.*
  - *Treatment Boosted ADA+ = 16 (4.6%) patients.*
- *Cross-reactive binding ADA to nGIP = 108 (30.8%) patients.*
- *Cross-reactive binding ADA to nGLP-1 = 53 (15.1%) patients.*

Neutralizing ADAs:

- *NAb against tirzepatide activity on GIPR = 5 (1.4%) patients*
- *NAb against tirzepatide activity on GLP-1R = 12 (3.4%) patients*
- *Cross-reactive NAb against nGIP = 2 (0.6%) patients*
- *Cross-reactive NAb against nGLP-1R = 4 (1.1%) patients*

The rates of preexisting ADA, TE ADA, cross-reactive antibodies (GIP, GLP-1), and NAb against tirzepatide activity on GIPR and on GLP1R in patients with prior exposure to GLP-1 receptor agonist are comparable to the corresponding counterpart in the overall tirzepatide-treated population during the planned treatment period (7.0%, 51.1%, 33.9%, 14.2%, 1.9%, 2.1% respectively).

The data indicates that 2.1% patients had NAb against tirzepatide activity on GLP-1R in TZP-treated population during the planned treatment period, while 3.4% patients had NAb against tirzepatide activity on GLP-1R who were exposed to GLP-1R agonist previously. This difference (2.1% versus 3.4%) suggests that more patients may have developed NAb against tirzepatide activity on GLP-1R due to prior exposure to GLP-1 receptor agonist. But the overall trend of TE-ADA, cross-reactive antibodies, and NAb development are comparable to the corresponding counterpart in the overall tirzepatide-treated population during the planned treatment period.

The ADA titer distribution for tirzepatide-treated TE ADA+ patients who had prior GLP-1 receptor agonist as shown in Figure ISI.4.10 (above), ranging from 1:20 to 1:20480 (median 1:160), is comparable to the entire tirzepatide-treated TE ADA+ population (median 1:160).

The sponsor also stated that out of the 187 TE ADA+ patients with known exposure to GLP-1 receptor agonist, 9 patients (4.8%) experienced injection site reactions and 4 patients (2.1%) experienced hypersensitivity reactions.

17. Conclusions

1) Across seven Phase 3 clinical studies, 2570 (51.1% of 5025 evaluable patients) tirzepatide-treated patients developed TE ADA during the planned treatment period.

2) Of 2570, 2403 (93.5%) confirmed TE-ADA+ patients were classified as having treatment-induced ADAs, whereas 167 of 2570 (6.5%) ADA+ patients were classified as having treatment boosted ADAs during the planned treatment period.

3) The ADA results suggest that the incidence of ADA+ patients increased in a dose dependent manner from 5mg, 10mg and 15mg as well as with the length of the treatment.

4) 1705 of 2403 ADA+ patients (66.3%) showed cross-reactivity with native GIP and 716 of 2403 ADA+ patients (27.8%) showed cross-reactivity with native GLP-1.

5) Among TE ADA-evaluable population, 1.9% (94 of 5025 patients) and 2.1% (107 of 5025 patients) had NAb against tirzepatide activity on the GIPR and GLP-1R, and 0.9% (43 of 5025 patients) and 0.4% (18 of 5025 patients) had cross-reactive NAb against nGIP and nGLP-1, respectively.

6) The ADA titers in TE ADA+ patients ranged from 1:20 to 1:327860 (median 1:160). About 45.4% patients (N=1168 of 2570) had a titer of > median titer (1:160). No significant impact between ADA titer or NAb on the PK profile of tirzepatide was observed.

7) The percentage of TE ADA+ and TE ADA- patients reporting hypersensitivity reactions was similar, and a higher number of TE ADA+ patients than TE ADA- patients reported injection site-related reaction.

8) The data presented from 7 Phase 3 studies showed that development of antidrug antibody was not associated with an altered PK profile or an impact on efficacy of the drug.

Appendix 1:

Table 4.1. Summary of Treatment-Emergent Antidrug Antibody Status (Phase 3 Dose–Effect Analysis) during the Entire Postbaseline Period Using Disease-State Cut Points

Summary of TE Tirzepatide Anti-Drug Antibody Status — Page 1 of 1
During the Entire Postbaseline Period including Safety Follow-up — 10:06 03JUN2021
Safety Population — PDPM
Phase 3 Dose Effect Analysis Set
I8F-MC-GPGH, I8F-MC-GPGI, I8F-MC-GPGK, I8F-MC-GPGL, I8F-MC-GPGM, I8F-JE-GPGO, I8F-JE-GPGP

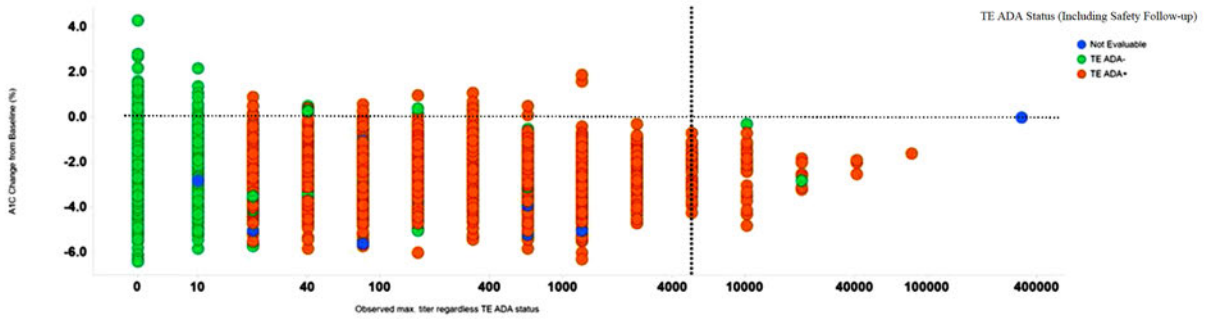
Category	TZP 5mg (N=1701) n (%)	TZP 10mg (N=1702) n (%)	TZP 15mg (N=1716) n (%)	TZP_All (N=5119) n (%)
Patients Evaluable for TE ADA *a	1672 [98.3]	1670 [98.1]	1685 [98.2]	5027 [98.2]
Evaluable Patients with ADA Present at Baseline	115 (6.9)	120 (7.2)	118 (7.0)	353 (7.0)
Patients Postbaseline TE ADA+ *b	843 (50.4)	885 (53.0)	930 (55.2)	2658 (52.9)
Treatment-Induced TE ADA+	786 (47.0)	831 (49.8)	867 (51.5)	2484 (49.4)
Treatment-Boosted TE ADA+	57 (3.4)	54 (3.2)	63 (3.7)	174 (3.5)
Patients Postbaseline TE ADA Inconclusive *b	0	0	0	0
Patients Postbaseline TE ADA- *b	829 (49.6)	785 (47.0)	755 (44.8)	2369 (47.1)

Abbreviations: ADA = anti-drug antibody; N = total number of patients in specified treatment group; n = number of patients in specified category; TE = treatment-emergent; TZP = tirzepatide

Note: Denominator for percent (%) is the number of patients who are TE ADA Evaluable in each treatment group, except the [%] of which the denominator is the number of the patients who are from the safety population.

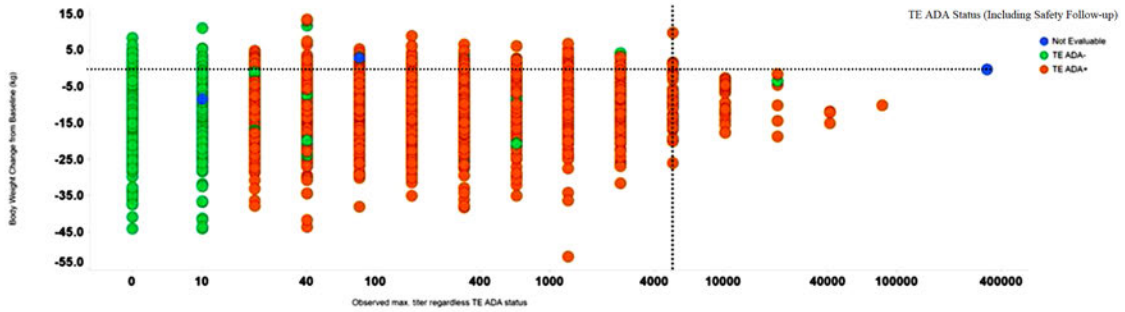
*a - A patient is TE ADA Evaluable if there is at least one non-missing test result for TZP ADA for each of the baseline period and the postbaseline period. All percentages are relative to the total number of TE ADA Evaluable patients in each treatment group.
*b - A TE ADA Evaluable patient is considered to be TE ADA+ if the patient has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA Not Present, then the patient is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 1:20 (treatment-induced). A TE ADA Evaluable patient is TE ADA Inconclusive if >=20% of the patient's postbaseline samples, drawn pre-dose, are ADA Inconclusive and the patient is not otherwise TE ADA+. A TE ADA Evaluable patient is TE ADA- if not TE ADA+ and not TE ADA Inconclusive.

Appendix 2:



Abbreviations: A1C = hemoglobin A1C; TE ADA= treatment-emergent antidrug antibody.
Dashed line along the x-axis indicates titer of 1:5120; dashed line along the y-axis indicates 0 of A1C change from baseline.

Figure 4.1. **Scatter plot of endpoint HbA1c (%) change from baseline (on-treatment and without rescue) and observed maximum titer including safety follow-up regardless of TE ADA status.**



Abbreviation: TE ADA= treatment-emergent antidrug antibody.
Dashed line along the x-axis indicates titer of 1:5120; dashed line along the y-axis indicates 0 of body weight change from baseline.

Figure 4.2. **Scatter plot of endpoint body weight change from baseline (on-treatment and without rescue) and observed maximum titer including safety follow-up regardless of TE ADA status.**

Table 4.2. Listing of TE-ADA+ Patients with NAb+ for GIPR during the Planned Treatment Period Study I8F-MC-GPGK

Listing of TE ADA+ Patients with NAb+ for GIPR during the Planned Treatment Period and with Valid A1C and Body Weight Data at Week 40
From Baseline through the Planned Treatment Period
Safety Population
I8F-MC-GPGK

Unique Subject ID	Treatment	TE ADA Category	Visit (Weeks)	Collection Date (Day)	TZP Conc. (ng/mL)	ADA Titer	A1C [Change from baseline] (%)	Body Weight [Change from baseline] (kg)
I8F-MC-GPGK (b) (6)	TZP 5mg	TE ADA+	3 (0)	2019-07-11 (1)	<2.00	NP	8.2	142.4
			4 (4)	2019-08-08 (29)	131.81	NP	7.5 [-0.7]	135.3 [-7.1]
			7 (12)	2019-10-03 (85)	231.73	NP	5.6 [-2.6]	132.1 [-10.3]
			12 (24)	2019-12-27 (170)	185.24	1:10*	5.6 [-2.6]	131.7 [-10.7]
			14 (40)	2020-04-16 (281)	305.73	1:320	5.5 [-2.7]	128.3 [-14.1]
I8F-MC-GPGK (b) (6)	TZP 5mg	TE ADA+	3 (0)	2019-11-06 (1)	<2.00	NP	8	131.8
			4 (4)	2019-12-04 (29)	79.34	NP	7.2 [-0.8]	128.5 [-3.3]
			7 (12)	2020-01-29 (85)	197.12	1:10*	6.3 [-1.7]	125.9 [-5.9]
			12 (24)	2020-04-20 (167)	294.48	1:40	5.7 [-2.3]	124.3 [-7.5]
			14 (40)	2020-08-07 (276)	96.7	1:80	6.4 [-1.6]	129.3 [-2.5]
I8F-MC-GPGK (b) (6)	TZP 5mg	TE ADA+	3 (0)	2019-12-17 (1)	<2.00	NP	8.1	106.3
			4 (4)	2020-01-13 (28)	56.02	NP	7.4 [-0.7]	106.3 [0]
			7 (12)	2020-03-11 (86)	212.09	1:20*	6.5 [-1.6]	102.1 [-4.2]
			12 (24)	2020-05-29 (165)	<2.00	1:10	7.2 [-0.9]	99.3 [-7]
			14 (40)	2020-09-24 (283)	20.35	NP	7.7 [-0.4]	95.4 [-10.9]
I8F-MC-GPGK (b) (6)	TZP 15mg	TE ADA+	3 (0)	2019-11-12 (1)	<2.00	NP	8	85.2
I8F-MC-GPGK (b) (6)	TZP 15mg	TE ADA+	4 (4)	2019-12-10 (29)	176.98	NP	7 [-1]	83.7 [-1.5]
			7 (12)	2020-02-04 (85)	554.04	NP	5.9 [-2.1]	81 [-4.2]
			12 (24)	2020-04-28 (169)	121.59	1:20*	6.7 [-1.3]	83.4 [-1.8]
			14 (40)	2020-08-25 (288)	86.63	NP	7 [-1]	84.1 [-1.1]

Abbreviations: ADA = anti-drug antibodies; ID = identification; NP = not present; TE = treatment-emergent; TZP = tirzepatide

Note1: TE ADA Category:
TE ADA+: If the patient has at least one postbaseline titer that is a 4-fold or greater increase in titer from baseline measurement (treatment boosted). If baseline result is ADA Not Present, then the patient is TE ADA+ if there is at least one postbaseline result of ADA Present with titer >= 1:20 (treatment-induced).
Note2: Day is relative to the first dosing date.
Note3: ADA Titer value followed by a * indicates the patient has NAb to TZP GIPR presents at this visit.

Appendix 3: Evaluation of Sponsor responses to Immunogenicity information requests

Non-hold comments sent to the sponsor on 15 December 2021 and Lilly's Responses to FDA Information Request received on 3 January 2022 are reviewed below:

We are evaluating your immunogenicity assessment results, submitted in the 'Integrated Summary of Immunogenicity' for NDA 215866. In order to complete our evaluation, address the following requests for additional information. Provide your response within two weeks of receiving this request.

Immunogenicity comment 1:

Immunogenicity data from seven phase 3 clinical studies in patients with T2DM suggest that 52.9% of patients (Table APP.2.4, ISI-APP) receiving tirzepatide developed anti-drug antibodies (ADA) at any time during the study when the disease-state cut-point (DSCP) was applied. You reported the number of treatment-induced and treatment boosted ADA-positive (ADA+) patients in Table ISI.4.22 (ISI report). Those data were based on the ADA+ patients identified using an in-study cut point (ISCP), rather than DSCP (Table APP.2.4, ISI-APP). The change to use of DSCP resulted in additional patients being classified as ADA+. Since you used DSCP for Tiers 1 and 2a in assessing clinical samples for immunogenicity, provide a table (similar to your Table ISI.4.22) updating the number of treatment-induced and treatment boosted ADA+ patients detected from all phase 3 studies, determined using the DSCP.

Summary of sponsor's Response to IR comment 1 (labeled "FDA Request 6"):

The sponsor stated that Table APP.2.4 in the ISI Appendix presents immunogenicity results from the entire post-baseline period for the seven Phase 3 studies, which includes ADA results from FU visits (collected 4-weeks after the last dose), whereas Table ISI.4.22 in the ISI presents immunogenicity results from the planned treatment period for the seven Phase 3 studies, which do not include ADA data from the FU visits. They used DSCP for all assay tiers for identifying ADA+ patients presented in Table APP.2.4 (ISI Appendix) and Table ISI.4.22.

In response to OBP comment, the sponsor submitted a revised Table (Table 4.1, appendix 1) that summarizes the number of treatment-induced and treatment-boosted ADA+ patients using ADA results from all seven Phase 3 studies, determined using the DSCPs. The Table 4.1 showed that the incidence of treatment-induced and treatment-boosted ADA+ patients were 49.4% and 3.5% respectively when ADA data from the FU period was included. The incidences of treatment-induced and treatment-boosted ADA+ patients were previously reported to be 47.8% and 3.3%, respectively when ADA+ patients' samples from FU period were not included. The sponsor stated that compared to results reported in the ISI (Table ISI.4.22) for the planned treatment period, when including patient's post-treatment FU visit assessments, there were 88 more TE-ADA+ patients, however, the incidence of TE ADA+ as well as the incidence of treatment-induced and treatment-boosted TE-ADA+ results were similar with and without ADA data from the FU period.

Reviewer comment:
The sponsor provided a revised Table that presents summarized immunogenicity results from the entire post-baseline period for all seven Phase 3 studies including the FU study period as requested. The revised table shows that the incidences of treatment-induced and treatment-boosted ADA+ patients were 49.4% (2484 of 5027 ADA+ subjects) and 3.5% (174 of 5027 ADA+ patients) respectively. The overall incidence of TE-ADA+ patients increased from 51.1% (2570 ADA+ patients of 5027 total evaluable) to 52.9% (2658 ADA+ of 5027 total evaluable patients) as a result of inclusion of FU samples ADA data analysis in this table suggesting that some patients receiving tirzepatide may develop antibodies at later stage of the treatment

The sponsor's response is adequate. No additional comment is needed.

Immunogenicity comment 2:

Figure ISI.4.5 indicates that about 90 ADA+ samples across all Phase 3 studies had an ADA titer **≥1:5120.** The tirzepatide clearance by ADA status in phase 3 studies appears comparable between the ADA-negative and ADA+ groups (Figure ISI.4.4). However, the clearance data based on ADA titer indicates that some ADA+ patients, particularly those with a titer **≥** 1:10240 may have an altered tirzepatide clearance status (Figure ISI.4.5).

a. Provide a list of subjects per study who were ADA+ with a titer of **≥1:5120** at any time and include their titer profiles throughout their respective study.
b. Describe any correlation between efficacy (e.g., change in HbA1c or other appropriate efficacy endpoint) and ADA titer in these patients from their baseline through follow-up.

Summary of sponsor's Response to IR comment 2a (labeled "FDA Request 7a"):

Lily stated that there were 91 patients from all seven Phase 3 studies who were ADA+ with a titer of ≥1:5120 at any time and submitted a listing (Table APP.5.1, a multi-page table, is not reproduced in this

review memo) of 91 tirzepatide-treated patients, by study, with an ADA titer ≥1:5120 sampled at any time during the study, including the FU period. The listing includes ADA titer profiles, patient treatment dose group, TE ADA category, efficacy parameters, and tirzepatide concentrations over time.

Reviewer comment:
In response to our IR comment, the sponsor submitted a tabular list of data from 91 patients from all seven Phase 3 studies who were ADA+ with a titer of ≥1:5120 at any time, and the data presents their titer profiles throughout their respective study visits (Table APP.5.1, which is not copied here but my evaluation is summarized below).

My evaluation of the data presented in Table APP.5.1 indicates:

- *Of 91 TE-ADA, 59 (64.8%) patients who experienced an ADA titer ≥1:5120 at any time during the study, including the FU assessment (approximately four weeks after study completion, or after "washout" period), tend to demonstrate a reduction of their ADA titer to less than 1:5120 at the FU assessment.*
- *28.6% (26 of 91) of patients who experienced an ADA titer ≥1:5120 at any time during the study, including the FU period had an ADA titer <1:640.*
- *37.4% (34 of 91) of patients who experienced an ADA titer ≥1:5120 at any time during the study had reduced the ADA titer to 1:2560 or 1:1280 at the last FU period test (after approximately 4 weeks since last dose).*
- *However, 30.8% (28 of 91) of ADA+ patients remained ADA+ with relatively high ADA titers ≥1:5120 at their last FU period test. Of those, 2 patients had a FU sample ADA titer of 1:81920, 2 patients had a titer of 1:40960, 1 patient had a titer of 1:20480, 8 patients had titer of 1:10240 and 15 patients had an ADA titer of 1:5120 at their FU visit. This indicates that nearly a third of ADA+ patients may have developed a durable ADA response against tirzepatide.*

The sponsor's response is adequate. No additional comment is needed.

Summary of sponsor's Response to IR comment 2b (labeled "FDA Request 7b"):

In response to FDA's immunogenicity comment 2b, the sponsor submitted two figures (scatter plots) providing visual assessments of endpoint changes in HbA1c % (Figure 4.1, appendix 2) and body weight in kilograms (Figure 4.2, appendix 2) from baseline, by observed maximum patient ADA titer. The sponsor reported that these analyses did not show an apparent relationship between efficacy indicators/endpoints and ADA titers ≥1:5120. The efficacy observed from the ADA+ patients with titer ≥1:5120 overlapped with the range of efficacy results observed for ADA-negative and ADA+ patients with titer <1:5120. Therefore, according to the sponsor, high ADA titer (≥1:5120) was not associated with loss of efficacy of tirzepatide.

Reviewer comment:

The sponsor submitted a listing of 91 subjects who had an ADA titer of ≥1:5120 at any time from all seven Phase 3 studies. The data also included the numerical values of ADA titer throughout their study visits along with the change in HbA1c % and body weight from baseline levels for respective visits. These data were also plotted as scatter plots of maximum titer per patient versus change in HbA1c or weight in Figures 4.1 and 4.2; all these data suggest that the ADA titer in subjects with an ADA titer ≥1:5120 at any

time during the study, did not have significant impact on the loss of efficacy of tirzepatide. Visual inspection of the data in Table APP.5.1 for trends in change in HbA1c (percent change from baseline) and change in weight from baseline versus ADA titer at each timepoint revealed that most of the 91 patients, generally corroborated the sponsor's evaluation of no apparent impact of ADA titer on these efficacy readouts.

The sponsor's response is adequate. No additional comment is needed.

Immunogenicity comment 3:

In Figure ISI.4.8 the mean change in HbA1c from baseline for tirzepatide-treated patients in Study GPGK with ADA titer **≥1:5120** was (-)1.6 in comparison to (-)2.1 for patients with an ADA titer of <1:5120. Similarly, in that study the average change in HbA1c from baseline was (-)1.4 for patients who were positive for neutralizing antibody (NAb) in the glucose-dependent insulinotropic polypeptide receptor (GIPR) assay, in comparison to (-)2.0 for NAb-negative patients (Table ISI.4.25). These differences suggest that a higher titer of ADA, or NAb activity, in a patient from Study GPGK may have had an impact on the change in HbA1c efficacy outcome. Provide a summary listing of patients where efficacy data may have correlated with higher titer **(≥1:5120)** ADA and/or NAb+ status. Explain the significance of these data with respect to any efficacy changes potentially impacted by ADA.

Summary of sponsor's Response to IR comment 3 (labeled "FDA Request 8"):

In response to comment 3, the sponsor stated that there were only two tirzepatide-treated patients in Study GPGK (Table APP.5.1, Page 44 of 67: ID GPGK-129- 01541, GPGK-805-01016; Regulatory Response: Request for Information on Immunogenicity) with an ADA titer ≥1:5120 (titer 1:40960 and 1:10240 respectively). This small group of two patients had a mean change in HbA1c (%) from baseline of -1.6 (-1.9 and -1.2, respectively, for titers 1:40960 and 1:10240). In comparison, there were 296 tirzepatide-treated patients in Study GPGK who were either ADA-negative, or ADA+ with ADA titer <1:5120, who had a mean change in HbA1c (%) from baseline of -2.0 (Figure ISI.4.8) ranging from -6.1 to 0.9. The efficacy response from these two patients with ≥1:5120 ADA titers were within the range of response for both ADA-negative and ADA+ patients with titer <1:5120. Therefore, these patient data do not show a relationship between efficacy and ADA titer ≥1:5120.

There were four tirzepatide-treated patients in Study GPGK who were NAb+ against tirzepatide in the GIPR assay during the planned treatment period; this group had a mean change in HbA1c (%) from baseline of -1.4 (individual HbA1c% of -0.4, -1, -1.6, and -2.7 at Week 40; see Response Table 4.2). In comparison, there were 134 tirzepatide-treated patients in Study GPGK who were ADA-negative and NAb negative, who had a mean change in HbA1c (%) from baseline of -2.0 (Table ISI.4.25 in the ISI); actual values ranged from -6.1 to 0.9. The efficacy responses from these four Nab+ patients are within the range of responses for ADA-negative and ADA+ patients with titer <1:5120. Therefore, these patient data do not show a relationship between efficacy and NAb results.

Based on these data, the sponsor stated that the immunogenicity data from seven Phase 3 clinical studies do not suggest that either ADA titer or Nab-positive status has any discernable impact on the efficacy of tirzepatide.

Reviewer comment:

The efficacy results of patients who had high titer ADA (≥1:5120) and NAb positive results were very small (2 and 4 patients respectively) from study GPGK in comparison to 246 and 134 tirzepatide-treated patients who were ADA-negative and with titer <1:5120 or NAb negative respectively. The efficacy response from these small numbers of patients were within the range of response for corresponding ADA-negative and ADA+ patients. Therefore, the reviewer agrees with the sponsor that the neither the ADA titer nor the Nab-positive status for these small groups of subjects have any significant impact on efficacy. However, interpretation of an impact on efficacy using data from such a small sample size may be incorrect due to increase in the margin of error. The sponsor's response is adequate. No additional comment is needed.

Assessor conclusion:
The sponsor's responses received on Jan 3, 2022 to OBP IR requests on Dec 15, 2021 are adequate. No further comments are needed.

Appendix 4:

FDA IR comments (Oct 20, 2021) regarding the assay validation reports and the responses to the corresponding comments from the sponsor (Nov 2, 2021 and Nov 12, 2021) are reviewed below to complete the evaluation of the adequacy of the assay methods used in support of the application.

1. FDA IR comments sent on Oct 20, 2021 and Lilly's responses are reviewed below:

FDA Comment 1:
You used an Affinity Capture and Elution (ACE) assay for the validation of screening, confirmatory, and ADA titer assays and to assess ADA cross-reactivity with native GIP (nGIP) and native GLP-1 (nGLP-1). The ACE step mitigates many of the concerns for drug tolerance by removal of excess drug and other inhibitory components that may be present within patient serum samples. However, this ACE method does not dissociate ADA complexes with drug, nGLP-1 or nGIP antigens in clinical patient sera prior to antibody capture. We are concerned that this method may not be able to capture the antibodies bound in complexes quantitatively, which could possibly lead to a reduced apparent ADA incidence, particularly in drug-treated subjects. Provide additional data from studies addressing this concern.

Lilly Response to Request 1: In response to our concern, Lilly stated that the pretreatment of clinical samples with heat or acid may induce dissociation of such complexes and enhance ADA detection, however, they do not consider that inclusion of a pretreatment step in their ACE-format method would be necessary for the following reasons (Bourdage et al. 2007[2]);

1) the exceptional drug tolerance (DT) of the validated ACE-format ADA assay,
2) the extremely low physiological concentrations of nGIP and nGLP-1, and
3) the potential risks associated with pretreating clinical samples.

[2] Bourdage JS, Cook CA, Farrington DL, et al. An Affinity Capture Elution (ACE) assay for detection of anti-drug antibody to monoclonal antibody therapeutics in the presence of high levels of drug. J Immunol Methods. 2007;327(1-2):10-17.

Lilly states that the DT indicates how effectively ADA complexed with drug can be detected and, in their experiments, performed in the ACE assay validation were designed (Butterfield et al. 2010[3]) to recreate drug/ADA complexes via a 30-minute incubation of tirzepatide with positive control (PC) antibody in serum prior to capture that established a DT of >250 µg/mL tirzepatide at 25, 50, 100, 250, 375, and 500 ng/mL of PC representing up to 500-10,000-fold excess of tirzepatide compared with ADA. Since the DT is >100-fold higher than expected trough concentration of tirzepatide (<2 µg/mL), Lilly justifies that the antibodies bound in complexes can be reliably measured without pretreating clinical samples. Secondly, the physiological concentration of nGIP (native) and nGLP-1 (native) are extremely low (<100 pg/mL; Sumithran et al. 2011[4]) relative to both tirzepatide concentrations and levels of detectable ADA. Therefore, the risk is minimal that these native hormones can complex with ADA in a way that impairs effective detection of clinically significant ADA.

Lilly also stated that although they recognize that pretreating clinical samples with acid or heat can be performed to dissociate ADA complexes prior to capture, these treatments may also cause antibody denaturation and subsequently prevent effective ADA capture and detection (Le Basle et al. 2020[5]). For this reason, the addition of a pretreatment step to dissociate ADA complexes is only considered when DT is not sufficient for clinical use. Therefore, Lilly believes that the pretreatment is not necessary or preferred with this ACE-format ADA assay.

Reviewer comment:
Many current immunogenicity assays use bridging assays to assess ADAs. These assays often encounter significant interference from even low levels of free drug. Free drug in this type of assay can prevent bridge formation by blocking one of the physicochemical determinants of antibody-protein interactions, making this format particularly sensitive to interference. However, if free drug is present in significant quantities it can complex with ADAs directly interfering with the assay. The ACE–Bridge format provides a superior option as a screening method to monitor patient ADA responses, with ability to measure ADA in the presence of high circulating drug while demonstrating very high drug tolerance (Chen et al, 2016[6]). The trough level of tirzepatide concentration was <2µg/mL, while the drug tolerance was established (after recreating the drug/ADA complexes) to about >250 µg/mL tirzepatide suggesting a high drug tolerance level of this assay. Based on satisfactory validation results for drug tolerance, it appears that the assay performed adequately even without an acid dissociation step. Therefore, the sponsor's response is adequate to our concern. No further comment is needed.

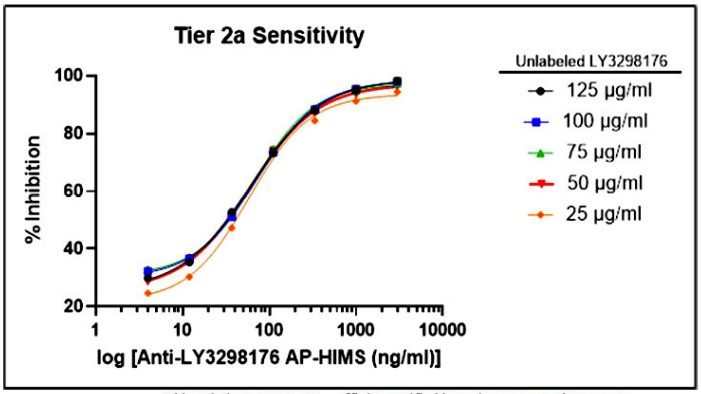
FDA comment 2:
You stated that during the Tier 1 screening assay development various concentrations of unlabeled tirzepatide (25, 50, 100, and 125 µg/mL) were evaluated for their ability to inhibit the positive control anti-LY3298176 antisera (AP-HIMS) in order to determine the appropriate concentrations of unlabeled tirzepatide, GIP (1-42) or GLP-1 (7-36), in Tier 2a, Tier 2b or Tier 2c assays, respectively, that are needed for the validation of inhibition assays. Specifically, data supporting and clarifying the following issues could not be located in the submission.
a. Submit the developmental dose titration data supporting selection of **50µg/mL** unlabeled tirzepatide, **52µg/mL (10.4µM)** unlabeled nGIP (1-42) and 34.3/mL **(10.4µM)** unlabeled nGLP-1 (7-36)

[3] Butterfield AM, Chain JS, Ackermann BL, Konrad RJ. Comparison of assay formats for drug tolerant immunogenicity testing. Bioanalysis. 2010;2(12):1961-1969.
[4] Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. N Engl J Med. 2011;365(17):1597-1604.
[5] Le Basle Y, Chennell P, Tokhadze N, et al. Physicochemical stability of monoclonal antibodies: a review. J Pharm Sci. 2020;109(1):169-190.
[6] Chen YQ, Pottanat TG, Carter QL et al. Affinity capture elution bridging assay: A novel immunoassay format for detection of anti-therapeutic protein antibodies. Journal of Immunological Methods 431 (2016) 45–51.

as appropriate concentrations for the Tier 2a, Tier 2b and Tier 2c inhibition assays, respectively. These data will allow evaluation of whether the competitor concentrations selected for use in inhibition assays are appropriate.

Lilly Response to Request 2: Lily submitted a dose titration data supporting the selection of 50 µg/mL of unlabeled tirzepatide for Tier 2a (Figure 1). The Tier 2a sensitivity curves were individually generated using AP-HIMS and varying concentrations of 25 to 125 µg/mL of unlabeled-tirzepatide in the presence of a fixed concentration (0.1 µg/mL) of each of 2 labeled tirzepatide peptide analogs. The sponsor stated that the curves demonstrated that near maximal inhibition was achieved with 50 µg/mL of unlabeled tirzepatide, and higher concentrations did not provide additional signal reduction (Figure 1). The selected concentration of 50 µg/mL unlabeled-tirzepatide produced a reasonable Tier 2a cut point inhibition and is approximately 250 X molar excess over each of the two 0.1 µg/mL labeled tirzepatide peptide analogs.

Lily stated that GIP(1-42) concentration of 52.0 µg/mL and a GLP-1(7-36) concentration of 34.3 µg/mL were selected for use in Tiers 2b and 2c, respectively. These concentrations represent the molar equivalent of the 50 µg/mL of unlabeled-tirzepatide used in Tier 2a and also represent a 250x molar excess over the 0.1 µg/mL of each labeled peptide used for detection. The selection of 52.0 µg/mL of GIP(1-42) produced a reasonable Tier 2b cut point of 14.5% inhibition, and the use of 34.3 µg/mL of GLP-1(7-36) produced a reasonable Tier 2c cut point of 18.1% inhibition.



Abbreviation: AP-HIMS = affinity-purified hyperimmune monkey serum.
Note: Tier 2a (confirmatory) analysis of AP-HIMS sensitivity curves using 25 to 125 µg/mL of unlabeled tirzepatide in the presence of fixed concentration (0.1 µg/mL) of each of 2 labeled tirzepatide peptide analogs.

Figure 1. Tier 2a sensitivity curves of unlabeled tirzepatide at different concentrations.

Reviewer comment:
The sponsor submitted a sensitivity curve generated using 25, 50, 75, 100 and 125µg/mL of unlabeled tirzepatide. All curves appear to achieve similar inhibition pattern in presence of 25-125µg/mL of unlabeled tirzepatide and the selection of any higher than 50 µg/mL of unlabeled tirzepatide concentrations in this assay would not have additional signal reduction effect. Therefore, the use of 50 µg/mL of unlabeled tirzepatide for Tier 2a assay is acceptable. Based on this determination, they used equimolar of unlabeled nGIP and nGLP-1 for Tier 2b and Tier 2c inhibition assays. The sponsor did not provide any additional data for using unlabeled nGIP and nGLP-1 for Tier 2b and Tier 2c inhibition assays, but the validation data indicates that the selection of 52µg/mL of unlabeled GIP and 34.3µg/mL of unlabeled GLP-1 in Tier 2b and Tier 2c assays respectively produced reasonable 14.5% and 18.1% CP inhibition. Therefore, the sponsor response is adequate to our concern. No further comments are needed.

FDA comment 3:

For the validation of Tiers 4a and 4b NAb assays, you used 0.61ng/mL and 5.6ng/mL of tirzepatide for stimulation of the GIPR and the GLP-1R reporter cells, respectively. These concentrations were determined during assay development as optimum stimulation conditions for these assays. However, the data demonstrating that 0.61ng/mL and 5.6ng/mL LY3298176, respectively were the optimum LY3298176 concentrations for NAb assay validation using the GIPR and GLP-1R cell lines, were not found. Submit the developmental data that supports the use of these concentrations of LY3298176 for NAb assays on the GIPR and GLP-1R cell lines as appropriate concentrations for the inhibition assays to allow complete evaluation of the validation of your NAb assays.

Lilly Response to Request 3
Lily stated that the stimulation concentrations were selected using the potency and stimulation curve data and based on the following criteria 1) a signal window >3x to maximize the dynamic range of the assays, 2) sufficient neutralizing ability, preferably >80% neutralization, to ensure adequate levels of positive controls for monitoring assay performance and for optimized assay sensitivity and drug tolerance, and 3) minimal assay variability (CV%).

The potency curves were generated by using serially diluted tirzepatide into serum and then analyzed in the cell-based assay method, in the absence of any added surrogate ADA. The signal response was measured in ECLU. The sponsor stated that they determined EC_{50}, EC_{60} , EC_{70} EC_{80} and EC_{90} of tirzepatide from the potency curves (Tables 2 and 3). Stimulation curves were subsequently generated by serially diluting the PC antibody and stimulating with a fixed concentration of tirzepatide (in the EC_{60-90} range) and measured %neutralization.

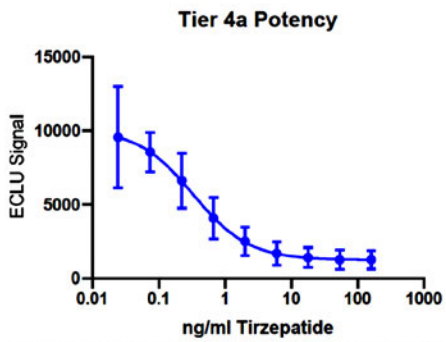
For Tier 4a, the EC_{70} stimulation concentration of 0.61 ng/mL was selected as it had a signal window >3x, minimal assay variability (18%), and sufficient % neutralization (89%) (Tables 1 and 2, Figures 2 and 3).

For Tier 4b, the EC_{60} stimulation concentration of 5.6 ng/ml was selected as it had a signal window >3x, minimal assay variability (13%), and sufficient %neutralization (87%) (Tables 1 and 2, Figure 4 and 5).

- For Tier 4a NAb - stimulation concentration

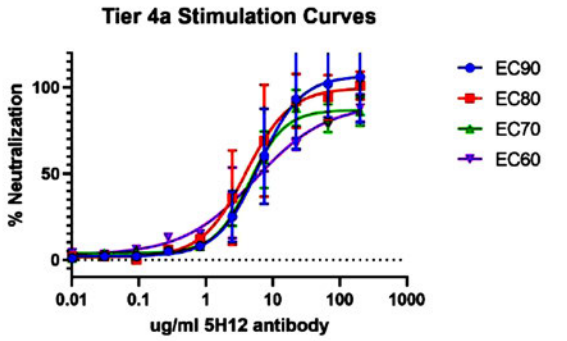
Table 1. Stimulation Concentrations for Tier 4a and Tier 4b NAb Assays

Stimulation Concentration (ng/mL)		
Tier	**Preparation**	**On Cells**
4a	0.61	0.11
4b	5.6	1.04



Abbreviations: ECLU = electrochemiluminescence units; GIPR = glucose-dependent insulinotropic polypeptide receptor.

Figure 2. Tier 4a (GIPR) potency.



Abbreviations: EC_{60} = effective concentration at 60% response; EC_{70} = effective concentration at 70% response; EC_{80} = effective concentration at 80% response; EC_{90} = effective concentration at 90% response.
Note: The selected stimulation was EC70 = 0.61 ng/mL.

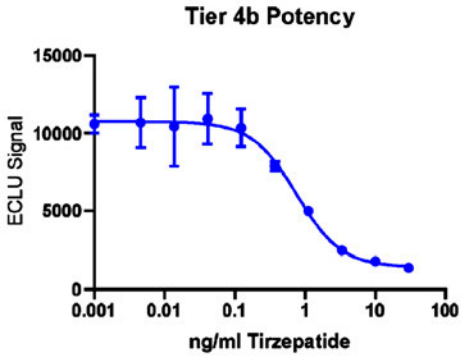
Figure 3. Tier 4a (GIPR) stimulation curves.

Table 2. Summary of Tier 4a Cell Stimulation

Stimulation	Stimulation Concentrations	Signal Window	Average Variability CV%	Median % Neutralization
EC_{60}	0.40 ng/ml	>3x	18%	85%
EC_{70}	0.61 ng/ml		18%	89%
EC_{80}	1.01 ng/ml		23%	100%
EC_{90}	2.20 ng/ml		36%	120%

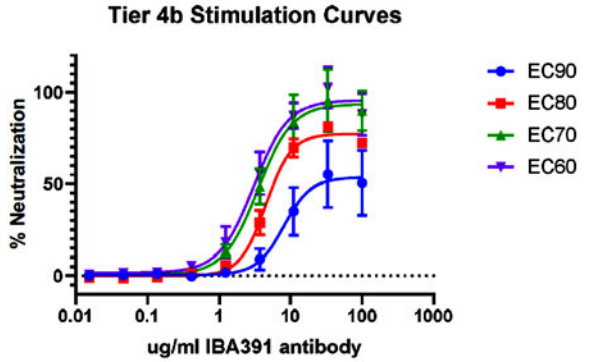
Abbreviations: CV% = percent coefficient of variation; $EC_{\#}$ = effective concentration.
Note: Signal window > 3x was met for all conditions. The average variability CV% was calculated using the linear portion of antibody concentrations of the stimulation curves. The median % neutralization was calculated using the highest antibody concentration of the curve (200 µg/mL).

- For Tier 4b NAb - stimulation concentration



Abbreviations: ECLU = electrochemiluminescence units; GLP-1R = glucagon-like peptide-1 receptor.

Figure 4. Tier 4b (GLP-1R) potency.



Abbreviations: EC_{60} = effective concentration at 60% response; EC_{70} = effective concentration at 70% response; EC_{80} = effective concentration at 80% response; EC_{90} = effective concentration at 90% response.
Note: The selected stimulation was EC70 = 5.6 ng/mL.

Figure 5. Tier 4b (GLP-1R) stimulation curves.

Table 3. Summary of Tier 4b Cell Stimulation

Stimulation	Stimulation Concentrations	Signal Window	Average Variability CV%	Median % Neutralization
EC_{60}	5.6 ng/ml	>6x	13%	87%
EC_{70}	8.3 ng/ml		17%	89%
EC_{80}	13.7 ng/ml		8%	72%
EC_{90}	29.9 ng/ml		42%	51%

Abbreviations: CV% = percent coefficient of variation; EC60 = effective concentration at 60% response; EC70 = effective concentration at 70% response; EC80 = effective concentration at 80% response; EC90 = effective concentration at 90% response;

Note: Signal window >3x was met for all conditions. The average variability CV% was calculated using the linear portion of antibody concentrations of the stimulation curves. The median % neutralization was calculated using the highest antibody concentration of the curve (100µg/mL).

Reviewer comment: Lily justifies that the potency experiments performed during assay validation confirmed that the selected stimulation concentrations were within the linear portion of the potency curves, as advised by the FDA (FDA 2019), had minimal assay variability (CV%), and had a signal window >3x. Based on this criteria, Lilly submitted additional data that supports the use of these concentrations of tirzepatide for NAb assays on the GIPR and GLP-1R cell lines as appropriate concentrations for these inhibition assays. The response is adequate. No further comments are needed.

FDA comment 4:
You determined the sensitivity for the Tier 4a anti-LY3298176 GIP Receptor (GIPR) NAb assay to be 901ng/mL using normal human sera (NHS) and 866 ng/mL using the T2DM serum samples. This sensitivity limit appears high in comparison to the increased Tier 4b GLP-1R NAb assay sensitivity of 398ng/mL using NHS and 375ng/mL using T2DM sera. The low assay sensitivity for GIPR NAbs suggests that the potential of detecting a low level of neutralizing antibodies may not be adequate. Since even a low level of neutralizing antibodies may potentially alter the PK, PD, safety, or efficacy profiles of the therapeutic drug, you should provide a justification on the adequacy of the Tier 4a assay in detecting NAbs and your approach to ensure sensitive detection of tirzepatide drug neutralization activity in ADA positive sera.

Lilly Response to Request 4: Lilly stated that the mean values for tirzepatide $C_{ss,avg}$ in patients with T2DM were 491 ng/mL, 983 ng/mL, and 1470 ng/mL with once-weekly dosing of tirzepatide 5, 10, and 15 mg, respectively based on population PK analysis. This suggests that the Tier 4a NAb assay can sensitively detect the levels NAb more than 10-fold below the steady-state concentrations of TPZ at trough.

Lilly also stated that the Tier 4a cell-based NAb assay detection limit is sufficient for clinical use because they did not observe that the detectable Tier 4a NAb had any discernable influence on the PK, PD, or efficacy profiles of tirzepatide (ISI Sections 4.5.3-4.5.4). This demonstrates that the Tier 4a NAb assay detects NAb levels below clinically meaningful concentrations. Tier 4b NAb, TE-ADA status, and ADA titer also had no discernable influence on the PK, PD, or efficacy profiles of tirzepatide.

Reviewer comment:
The sponsor's response is unclear. Characterizing the neutralizing capacity of ADA responses is important in understanding the effect of the ADA on drug safety and efficacy. The assay sensitivity and drug tolerance are two important characteristics of an ADA assay. The assay sensitivity assessment involves the detection of ADA in the absence of drug within the sample, whereas the drug tolerance scenario involves the detection of ADA in the presence of excess drug. Although the sponsor determined a high

drug tolerance due to the ACE method assay, the sponsors Tier 4a NAb assay sensitivity was 866 ng/mL in T2DM serum sample. The sensitivity of the assay is defined as the lowest concentration of the ADA that is required to generate an assay signal above the CP, which is recommended to be ≤100ng/mL for ADA binding assay. For NAb assay, however it is not well defined, and FDA acknowledges that NAb assays may not achieve that level of assay sensitivity[7]. The PC dose response curve demonstrated a good response to the drug and the sensitivity limit is appropriately placed, which is towards the lower linear part of the curve of % delta neutralization versus NAb concentration (DARRTS Reference ID: 4858440, 9/16/2021). The sensitivity of NAb assays is largely dependent upon the concentration of drug used in the assay and these two characteristics bear an inverse relationship to each other[8]. Since, for a small peptide, the molar ratio of peptide to an antibody molecule is much higher, it is not unexpected that the sensitivity of the assay would be lower.

The sponsor stated that they had encountered challenges in producing adequate neutralizing material, so, the choice of what PC material to use was dictated primarily by performance in terms of sensitivity and also drug tolerance performance as an additional parameter. Initially they considered affinity purified hyperimmune monkey serum (HIMS), affinity purified hyperimmune rabbit serum (HIRS) and monoclonal antibodies (mAb) generated by Lilly to use as PC for the NAb assays. The mAb targeting the N-terminus of tirzepatide (5H12), was identified as most appropriate PC material for the assay which is a mouse monoclonal immunoglobulin G1 (mIgG1) antibody and was chosen as the PC material based on the sensitivity and superior drug tolerance demonstrated (based on 1% FPR) in the assay.
The sponsor determined the steady state mean values for tirzepatide in patients with T2DM were 491 ng/mL, 983 ng/mL, and 1470 ng/mL with once-weekly dosing of tirzepatide 5, 10, and 15 mg indicating that the serum samples with a steady state drug level of 1470ng/mL in patients treated with 15mg/mL tirzepatide may not be able to detect NAb reliably. The level of free drug in washout immunogenicity samples will be less than 100 ng/mL, drawn 4-weeks (≥5half-lives) post-treatment in all Phase 3 clinical trials (BAL-17-061-585 ADDENDUM 2; METHOD HISTORY REPORT VERSION 2). Therefore, no interference is expected from free drug during FU sample analysis. Nevertheless, Lilly stated that the Tier 4a NAb assay detection limit was sufficient for clinical use because they did not observe any detectable influence of NAbs on the PK, PD, or efficacy profiles of tirzepatide demonstrating that the Tier 4a NAb assay detects NAb levels below clinically meaningful concentrations. The assessor reviewed the sponsor's data on the primary end point (%HbA1c change from baseline) (Source: ISI Table ISI.4.25) and found that there is no correlation of NAb-positivity and change in HbA1c from baseline. Thus, the sponsor concluded that the development of NAb antibodies did not appear to have significant effect on drug effectiveness and the Tier 4a NAb assay is able to detect the neutralizing antibodies below clinically meaningful concentrations.

Therefore, all together the sensitivity of the Tier 4a anti-LY3298176 GIP Receptor (GIPR) NAb assay is acceptable.

FDA comment 5:
You determined the drug tolerance for the Tier 4a anti-LY3298176 GIPR NAb Assay for Protocol I8FMC-GPGH(a) to be 200ng/mL in the presence of **5µg/mL** 5H12 mAb by interpolation of the LY3298176 concentration for each control antibody concentration curve with the in-study CP of 7.5%.

[7] Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection - FDA Guidance for Industry, 2019.
[8] S. Gupta et al. (2011): Recommendations for the validation of cell-based assays used for the detection of neutralizing antibody immune responses elicited against biological therapeutics. J. of Pharma and Biomed Anal., 55, 878–888.

However, you stated that the trough drug concentration for clinical studies is expected to be <2 **µg/mL** (BAL-20-061-1158-REP, Page 35), which is up to 10-fold higher that the drug tolerance level. Although you applied an ACE method, we are concerned that the expected levels of the free drug may interfere the assay if not removed completely by ACE method.

a. Provide data demonstrating that the level of free drug in immunogenicity samples should not exceed the drug tolerance level determined during the assay validation.
b. Alternatively, or in addition, provide support for the acceptability of the calculated drug tolerance with data demonstrating that the relatively high trough level of the drug will not interfere with the assay.

Lilly Response to Request 5: The sponsor stated that the drug tolerance (DT) in Tier 4a (using DSCP) determined the limits of tirzepatide (314, 159, and 65 ng/mL) in the presence of 10, 5, and 2.5 µg/mL of 5H12 mAb, respectively.

They included washout samples in clinical samples for immunogenicity testing, as recommended in the 2019 FDA immunogenicity guidance for industry. The washout samples were collected at least 30 days after last drug dose administration, which represents 5 half-lives of tirzepatide elimination. Mean tirzepatide concentrations during the washout period (FU Visit 801) from 7 combined Phase 3 trials were 32.4, 61.5, and 82.5 ng/mL for tirzepatide 5, 10, and 15-mg doses, respectively (Table 4), which are substantially lower than the average tirzepatide concentrations at steady-state (ranged from 491 to 1470 ng/mL).

Table 4. Mean Tirzepatide Concentrations (ng/mL) in Washout Samples

	TZP Dose	Trials							
		GPGK	GPGL	GPGH	GPGM	GPGI	GPGO	GPGP	All[a]
Mean tirzepatide concentration (ng/mL) at washout period (V801)*	5mg	54.1	22.2	22.5	54.7	29.8	26.0	17.2	**32.4**
	10mg	98.4	62.2	65.0	76.2	42.7	46.8	39.2	**61.5**
	15mg	118.0	75.6	67.7	127.0	65.9	65.6	57.5	**82.5**

Abbreviations: Ph3 = Phase 3; TZP = tirzepatide; V = visit.
a Overall mean tirzepatide concentration calculated from each trial mean concentration.
Source: Tables presented in Clinical Study Reports of SURPASS Ph3 trials, Section 5.3 (pharmacokinetics).

Table 5. Percent of Washout Samples with Tirzepatide Concentration below the Drug Tolerance Limit of Tier 4a NAb Assay

	TZP Dose	Trials							
		GPGK	GPGL	GPGH	GPGM	GPGI	GPGO	GPGP	All
Percent of washout samples with tirzepatide concentration <159 ng/mL[a]	5mg	93.8	98.2	98.2	93.7	96.5	96.8	100.0	**96.9**
	10mg	88.0	96.1	95.7	93.7	95.7	95.4	98.6	**95.0**
	15mg	92.0	95.0	95.6	92.0	97.2	92.9	95.1	**94.2**
	Mean Total	**91.3**	**96.4**	**96.5**	**93.1**	**96.4**	**95.0**	**97.9**	**95.4**

Abbreviations: MAb = monoclonal antibody; NAb = neutralizing antibody; T2DM = type 2 diabetes mellitus.
a Drug tolerance limit of Tier 4a T2DM: 159 ng/mL of tirzepatide at 5 µg/mL of mAb 5H12.

The DT of the Tier 4a NAb assay (159 ng/mL) was established in the presence of 5 µg/mL PC material. This represents the amount of NAb that can be detected in the washout samples. The sponsor stated that they further investigated the appropriateness of the Tier 4a assay detection limits in the presence of drug in washout samples, they converted the drug concentration into molar units using 150 kDa as the approximate molecular weight of an IgG (ADA). Likewise, tirzepatide levels in ng/mL were converted using the molecular weight of tirzepatide, which is 4.81 kDa. With the conversion applied, the Tier 4a NAb assay can detect 33.3 nM of ADA in the washout samples. In comparison, based on population PK analysis, the mean values for tirzepatide Css,avg in patients with T2DM were 102 nM (491 ng/mL), 204 nM (983 ng/mL), and 306 nM (1470 ng/mL) with once-weekly dosing of tirzepatide 5, 10, and 15 mg,

respectively. Thus, in the washout samples (i.e., in the presence of <159 ng/mL of tirzepatide), the Tier 4a NAb assay can detect levels of NAb approximately 3- to 10-fold below the steady-state concentrations of tirzepatide at trough and is sufficient to detect NAb levels below clinically meaningful concentrations, where 95.4% of washout samples from all 7 Phase 3 trials had tirzepatide concentrations below the drug tolerance limit of the Tier 4a NAb assay (159 ng/mL for T2DM) (Table 5).

In addition, the sponsor stated that since they defined a NAb+ patient as one who was TE-ADA+ and had one or more NAb-detected samples in the postbaseline period (ISI Section 4.4.2, page 48), the washout sample was sufficient to detect persistent NAb. The acceptability of Tier 4a was reinforced by the finding that only 5.7% of patients in Phase 3 studies were NAb-inconclusive during the entire post-baseline period, as presented in the ISI Appendix (Table APP.2.4, page 20). The NAb-inconclusive patients are defined as a patient who is TE ADA+, is not NAb+, and all samples that have TE ADA+ titer have a NAb-inconclusive sample result.

Reviewer comment: The DT for the Tier 4a NAb assay was established to 159 ng/mL. The sponsor stated that based on population PK analysis, the mean steady-state levels of tirzepatide in patients with T2DM were 491 ng/mL, 983 ng/mL, and 1470 ng/mL with once-weekly dosing of tirzepatide 5, 10, and 15 mg, respectively. Therefore, across all 7 Phase 3 trials, most washout samples (5 half-lives of tirzepatide) are expected to have tirzepatide concentrations below the DT limit of the Tier 4a NAb (Tables 4 and 5). However, their response does not address the issue of detecting NAbs developed during the treatment period. The sponsor stated that the detection of NAb in washout sample should be sufficient to detect persistent NAb in ADA-positive samples. This approach will not be able to capture NAbs that may develop transiently. Nevertheless, the incidence of persistently positive patients may pose a greater risk for worse clinical output in terms of safety and efficacy than a transiently NAb+ patient.

Additionally, the sponsor provided a post hoc analysis that was conducted via boxplot to explore the NAb effect on HbA1c change from baseline to each study's corresponding primary endpoint (ISI Table ISI.4.25) from tirzepatide-treated TE ADA+ patient who had detected NAb against tirzepatide activity on GIPR, or on GLP-1R, respectively. The comparison of the primary endpoint (HbA1c change from baseline) data suggests that there is no correlation of NAb-positivity and change in HbA1c from baseline. Thus, the sponsor concluded that the development of NAb antibodies did not appear to have significant effect on drug effectiveness or patient safety. The assessor reviewed the data and found that the sponsor's conclusion was supported by the data. Therefore, the sponsor's response is acceptable, and no further comment is needed.

FDA comment 6:
Your immunogenicity method SOPs could not be found in the submission. SOPs should be provided, for example, to enable evaluation of limits defined during validation of method robustness. Submit SOPs and all relevant assay development data including the validation summary in the appropriate section of Integrated Summary of Immunogenicity (ISI) with the license application.

Lilly Response to Request 6: The sponsor provided a table indicating the location of all immunogenicity method SOPs (bioanalytical methods) for all validated assays within the submission:

Bioanalytical Method	File Name	Location in Validation Report,
Ligand Binding Assay (Tiers 1-3)	BAL-16-061-MTH-018	BAL-15-061-360 Amendment 2, Appendix C (page 71)
Tier 4a NAb Assay	BAL-18-061-MTH-056	BAL-20-061-1158, Appendix A (page 52)
Tier 4b NAb Assay	BAL-18-061-MTH-055	BAL-20-061-1158, Appendix B (page 97)

Reviewer comment: SOPs are provided, no further comment needed.

1. FDA additional IR comment e-mailed on Nov 01, 2021 and Lilly's response is reviewed below:

FDA Comment (IR Date 11/01/2021):
During our on-going evaluation of the neutralizing antibody (NAb) assay validation reports submitted to the NDA, specifically the Tier 4a neutralizing antibody assay report for tirzepatide on the GIPR, we note that limits for incubation time were demonstrated during robustness validation that might affect assay performance. The assay validation for incubation time robustness indicates that a 20% decrease in incubation time was not tolerated in the assay. A statement regarding assay monitoring during sample analysis to control for incubation time was included in Report Bal-17-061-585. A similar situation is found for the Tier 4b (tirzepatide on GLP1R) NAb assay regarding drug potency robustness. However, we could not readily locate references to these limits in the NAb assay method SOPs. Explain how you ensure that the assay methods are being run within their validated operational parameters, particularly regarding the limits to NAb assay robustness noted above.

Lilly Response: Lilly described the validation results and explained how the NAb assay methods are being run within their validated operational parameters to further demonstrate the assay robustness. For Tier 4a assay (NAb against tirzepatide activity on GIPR), the sponsor stated that the robustness was assessed on HPC, MPC and LPC and all controls passed the plate acceptance criteria as summarized (BAL-17-061-585, Table 5, page 14), the assay was shown to tolerate ±20% incubation time. In addition to the assay controls, NHS samples were also included in the Tier 4a robustness validation. Based on those results, the sponsor stated that they introduced an improved method for subsequent Tier 4a validation work to normalize the NAb assay signal (Delta % Neutralization), which improved run-to-run NAb assay variability (Ref: BAL-17-061-585 Adden2, cNAb MHR, Section 4.1.3.1, page 25), and was used for all Phase 3 sample analysis. The sponsor stated that with the application of this normalization method, the results from the NHS samples (Table 4.1.) from the robustness assessment were comparable and support that the Tier 4a method can tolerate incubation times ±20%.

Table 4.1. Delta Percent Neutralization Applied to Normal Human Serum Samples from Validation Report BAL-17-061-585

Delta % Neutralization		
Sample	**+20%**	**-20%**
NHS 1	4.7%	8.3%
NHS 2	7.8%	11.7%
NHS 3	3.1%	4.0%
NHS 4	-1.1%	2.1%
NHS 5	4.1%	14.2%
NHS 6	11.3%	8.5%
NHS 7	4.9%	4.4%
NHS 8	-1.3%	2.6%

Abbreviation: NHS = normal human serum

For incubation time robustness, the sponsor stated that the acceptable incubation time in the Tier 4a NAb assay method was limited to ±10% (±3 minutes; SOP BAL-18-061-MTH-056.01, located in BAL-20-061-1158, Appendix A, page 52), in contrast to the validated parameter of ±20% standard limit for

incubation time, which is therefore, more conservative approach. To ensure the method incubation time was within the ±10% allowed by the method during sample analysis, the sponsor placed several procedures, which are adequate to maintain the incubation time robustness.

The sponsor also stated that on-plate PC performance has been consistent throughout sample analysis, such that greater than 90% of runs have passed the plate acceptance criteria as established in the NAb assay bioanalytical method (SOP BAL-18-061-MTH-056.01, located in BAL-20-061-1158, Appendix A, page 60). Taken together, all demonstrated sufficient assay robustness and support the current Tier 4a NAb assay method for clinical use.

For Tier 4b assay (NAb against tirzepatide activity on GLP-1R) potency robustness, a -10% stimulation concentration did not meet the a priori acceptance criteria. In accordance with the robustness findings, the stimulation concentration was fixed to 5.6 ng/mL of LY3298176 in the NAb assay method, therefore, the sponsor states that to ensure that the Tier 4b NAb assay ran within its validated parameters, the method uses tirzepatide stimulation concentration at 5.6 ng/mL, fixed. The sponsor stated that they have several approaches or safeguards in place to ensure that the NAb assay performance remains robust. The sponsor stated that the PC acceptance criteria implemented a more rigorous ±2SD compared with one-sided 3SD control ranges. Furthermore, the observed sample analysis inter-assay precision for HPC, MPC, and LPC (9.1%, 17.1%, and 23.7% CV, respectively) was superior to the validated inter-assay precision, demonstrating sufficient assay control during clinical trial sample analysis.

Reviewer comment: In the response letter, the sponsor provided description of all measures that they applied and planned to apply during clinical sample analysis in Tier 4a and Tier 4b procedures to ensure that NAb assays perform adequately. Taken all into consideration, it appears that the sponsor's approaches are sufficiently robust and support the current Tier 4a NAb assay method for clinical use. Therefore, the response is adequate, and no further comment is needed.

Assessor's conclusion:

The sponsor's responses to OBP immunogenicity information requests (Oct 20, 2021) are adequate. Therefore, the review of the immunogenicity assay validation reports is complete, and the assays are determined to be suitable to use in analyzing the clinical immunogenicity samples from Phase 3 clinical studies.

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HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 15, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866
Drug Constituent Name and Strength	Mounjaro[a] (tirzepatide), 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Autoinjector
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Eli Lilly)
FDA Received Date:	September 15, 2021, October 29, 2021, January 3, 2022, January 10, 2022
OSE RCM #:	2021-1827
DMEPA 1 Human Factors Evaluator:	Neha Kumar, PharmD
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[a] The proprietary name, Mounjaro, was found conditionally acceptable on December 2, 2021

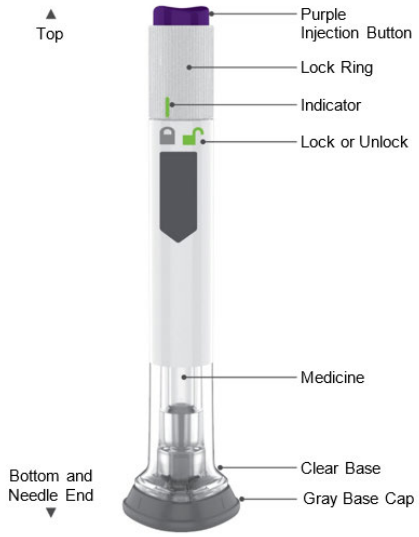
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study reports submitted under NDA 215866 for tirzepatide injection.

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed single-use autoinjector (AI) device constituent part that is intended as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to be administered once weekly. The carton contains 4 AIs, medication guide, instructions for use (IFU), and quick reference guide (QRG). Each AI contains a (b) (4) glass prefilled syringe (b) (4) needle for subcutaneous administration. For additional product information, see Table 5 in Appendix A.

Figure 1. Image of the tirzepatide autoinjector



1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVEOPMENT PROGRAM

- On December 21, 2020, the Applicant submitted a Type C meeting package under IND 128801 which included human factors related questions.[b] Since we were in the process of reviewing the Applicant's HF validation study protocol, submitted on December 18,

[b] Type C Meeting Briefing Document: Justification for Human Factors Differentiation for Tirzepatide Delivery Devices (IND 128801, Tirzepatide). Indianapolis (IN): Eli Lilly and Company; 2020 DEC 21. Available from: \\CDSESUB1\evsprod\ind128801\0134\m1\us\ly3298176-general-bd--type-c-fda-human-factors-dec-2020-.pdf.

2020, we denied the meeting request. We provided our responses to the Applicant's questions submitted under the Type C meeting request in our review of the Applicant's HF validation study protocol. We reviewed the protocol and provided recommendations to the Applicant.[c] The Applicant implemented our recommendations.

- On September 15, 2021, the Applicant submitted NDA 215866 to seek approval for tirzepatide. As such, the NDA submission included the results of their HF validation study for adults to support their marketing application, which is the subject of this review.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Human Factors Validation Study Report	C
Information Requests Issued During the Review	D
Labels and Labeling	E

[c] Bhalodia A. Human Factors Protocol Review for Tirzepatide (IND 128801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. RCM No.: 2020-2692

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

2.1 SUMMARY OF HF VALIDATION DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	<table><tr><th>User groups</th><th>Number of injection experienced participants</th><th>Number of injection naïve participants</th><th>Total number of participants</th></tr><tr><td>Untrained Type 2 Diabetes Mellitus Adult Patients</td><td>15</td><td>15</td><td>30</td></tr><tr><td>Untrained Adult Caregivers</td><td>15</td><td>15</td><td>30</td></tr><tr><td>Healthcare professionals (HCPs)</td><td>15</td><td>N/A</td><td>15</td></tr></table>
Training	No training was provided to the test participants.
Study Environment	Per the Applicant, the test room sufficiently represented the basic characteristics of the intended use environments (e.g., a private room in a patient's home or office, inpatient/outpatient facilities, and community settings). The room was equipped with a table, chairs, refrigerator, and trash can.
Sequence of Study	Simulated use scenario Root cause analysis Knowledge assessment Root cause analysis

2.1.1 METHODOLGY DISCUSSION OF HF VALIDATION STUDY

Our review of the HF validation study methodology finds that the knowledge assessment included leading language. Specifically, the participants were instructed to point out information in the IFU. The use of leading language may impact study participant performance and the study results. However, we noted that all critical tasks, except for store device and inspect device before use were observed during the simulated use scenario.

Additionally, we noted that of the 15 injection naïve caregiver participants recruited, 5 participants were injection naïve, but not caregivers. We issued an information request for the Applicant's justification of their rationale and recruitment efforts to attempt to recruit injection naïve caregivers (see Appendix D). The Applicant stated that due to COVID-19, ultimately only 10 injection naïve caregivers, in addition to 5 injection naïve participants, were recruited. Based on the aforementioned considerations, we find the Applicant's rationale for including 10 injection naïve caregivers acceptable.

2.2 SUMMARY OF SUPPLEMENTAL HF STUDY DESIGN

Table 3 presents a summary of the supplemental HF study design. See Appendix C for more details on the study design.

Table 3. Study Methodology for Supplemental Human Factors (HF) Study	
Study Design Elements	Details
Objective	The objective is to provide supplemental evidence to validate the safe and effective use of the tirzepatide autoinjector (AI) for the intended use, by the intended users, and in the intended use environment. The scope of this study was limited to evaluating the post-validation user interface changes associated with the critical task, "Place device at injection site". The changes included: • AI injection button color was changed (b) (4) to purple to introduce contrast to help identify the button from the gray base cap • The AI label was modified to add a color-coded arrow graphic as a background to the concentration listed on the container label; the arrow shape points to the device bottom and needle end • The IFU and QRG were updated to add a visual element and clarify text instructions that identify the AI bottom and needle end • IFU and QRG images, IFU Guide to parts, and text instructions were updated as necessary to be consistent with the modifications described above and represent the final design • The carton AI image was updated to reflect the final design (i.e., AI label modification and purple injection button)

<table>
<tr><td>Participants</td><td>
<table>
<tr><th>User groups</th><th>Number of injection experienced participants</th><th>Number of injection naïve participants</th><th>Total number of participants</th></tr>
<tr><td>Untrained Type 2 Diabetes Mellitus Adult Patients</td><td>15</td><td>15</td><td>30</td></tr>
<tr><td>Untrained Adult Caregivers</td><td>15</td><td>15</td><td>30</td></tr>
<tr><td>Healthcare professionals (HCPs)</td><td>15</td><td>N/A</td><td>15</td></tr>
</table>
</td></tr>
<tr><td>Training</td><td>No training was provided to the test participants.</td></tr>
<tr><td>Study Environment</td><td>Per the Applicant, the test room was sufficiently representative of the intended use environment with respect to lighting, sound levels, and temperature/humidity. The test room sufficiently represented the basic characteristics of the intended use environments (e.g., a private room in a patient's home or office, inpatient/outpatient facilities, and community settings). The room was equipped with a table, chairs, and trash can. Participants sat at a table with a session moderator while being monitored remotely by the sponsor and/or other study personnel.</td></tr>
<tr><td>Sequence of Study</td><td>Simulated use scenario
Root cause analysis</td></tr>
</table>

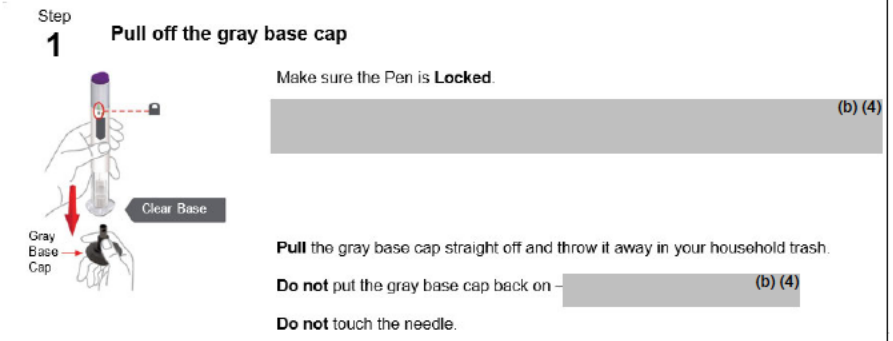
2.2.1 METHODLOGY DISCUSSION OF SUPPLEMENTAL HF STUDY

We noted in the supplemental HF study, of the 15 injection naïve caregiver participants recruited, 9 participants were injection naïve, but not caregivers. We issued an information request for the Applicant's justification of their rationale and recruitment efforts to attempt to recruit injection naïve caregivers (see Appendix D). The Applicant stated that due to COVID-19, ultimately only 6 injection naïve caregivers, in addition to 9 injection naïve participants, were recruited for the supplemental HF validation study. Based on the above considerations, we find the Applicant's rationale for including 6 injection naïve caregivers acceptable.

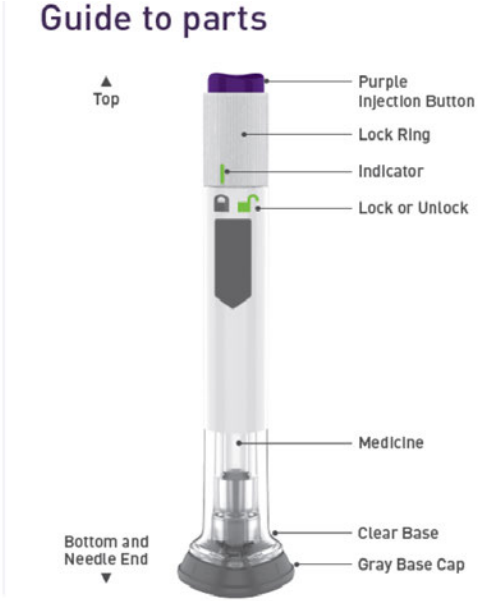
3 RESULTS AND ANALYSES

Table 4 describes the study results, the Applicant's analyses of the results, and DMEPA 1's analyses and recommendations.

Table 4: Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task "(b) (4) injection site", there were three use errors and one close call during the first injection attempt. The subjective data and the Applicant's root cause analysis indicated: • Perception error – failure to see visual information (three participants overlooked the "Choose your injection site" section in the instructions for use (IFU) or the quick reference guide (QRG) and went directly to Step 1; one participant folded the IFU in a way in which they could not see the section, "Choose your injection site", that comes before Steps 1-3 • Cognitive error – knowledge-based mistake (one participant had seen doctors inject in the bicep in the past) • Test artifact – context for use (two participants assumed that selecting the correct injection site did not matter since this study is just an "experiment") Based on the use-related risk analysis (URRA), if the injection is past subcutaneous tissue and is an intramuscular injection, there is risk that the patient experiences some discomfort, but therapeutic effects remain the same. Based on the URRA, if the injection is too shallow and is an intradermal injection, this will most likely lead to the same therapeutic effect, potential pain, and possible wheal at injection site. The Applicant did not propose any risk mitigation strategies for these use errors and close call.	Our review of the study results identified subjective feedback that indicated that multiple use errors were due to the participants not noticing the "Choose your injection site" section in the IFU and QRG. Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG can be improved. We noted that the task to "Choose your injection site" is not numbered and that the IFU must be fully unfolded to see this task. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
2.	For the task "(b) (4) base cap", there were three use errors and one close call during the first injection attempt.	Our review of the study results identified subjective feedback that indicated that two of the use errors were due to negative transfer and

	• one participant actuated the autoinjector (AI) while removing the gray base cap • one participant actuated the AI with the gray base cap on • one participant reattached the gray base cap before injection attempt • one participant attempted to inject with the gray base cap on, but self-corrected The subjective data and the Applicant's root cause analysis indicated: Cognitive error – knowledge-based mistake in which participant's action were intended but did not achieve the intended outcome due to: • inexperience, prior experience with other injection devices, and knowledge deficits, based on two participants' thought processes that the needle is at the "top" (b) (4) injection button) instead of at the base, and one participant's attempt to inject with the gray base cap on, referring to the QRG, and then removing the gray base cap • incomplete or inaccurate mental model of how the AI should operate based on one participant misinterpreting the QRG instruction to pull off the gray base cap and expecting the cap to twist off instead Based on the URRA, if the user: • actuates the AI while removing the gray base cap this may result in o no dose or underdose and there is risk of mild, symptomatic or asymptomatic hyperglycemia o exposed needle, the potential to inject someone other than the patient, and if	the mental model that the needle is at the "top" (i.e., (b) (4) injection button) instead of at the base. Our review of the study results also identified subjective feedback that a participant misinterpreted the QRG and said that he expected the gray base cap to twist off easily. Our review of the study results indicated that the root cause analysis was incomplete because the Applicant did not identify why the participant misinterpreted the QRG and thought the cap should be twisted off. Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG contain text and illustration on how to remove the gray base cap by pulling straight off and shows a directional arrow to indicate the direction to pull. See Figure 2 and Figure 3 below. **Figure 2.** IFU instructions to pull off the gray base cap 

	overdose > 2.5 mg, there is risk of adverse event in a child o drug product coming in contact with patient or caregiver eye and risk of eye irritation or injury • actuates the AI with the gray base cap on, user is unable to deliver dose, there is risk of underdose that may result in mild, symptomatic or asymptomatic hyperglycemia • removes and reattaches the gray base cap and needle is damaged, there is risk of excess injection site trauma and/or underdose that may lead to mild, symptomatic or asymptomatic hyperglycemia The Applicant did not propose any risk mitigation strategies for these use errors and close call.	Figure 3. QRG instruction to pull off the gray base cap  We have not identified additional changes to the user interface to further reduce the risks associated with these use errors and close call. We find that the residual risk in this case is acceptable.
3.	For the task "place (b) (4) ", there were eight use errors during the first attempt. Participants placed/actuated the AI upside down on the injection site. The subjective data and the Applicant's root cause analysis indicated: • Information overload during the task at hand (one participant may have created information overload by trying to simulate their typical patient interaction using	Our review of both HF study results indicates that several use errors were due to negative transfer and the mental model that the needle is at the "top" (i.e., (b) (4) injection button) instead of at the base. Our review of the study results also indicates the that the Applicant's root cause analysis was incomplete because it blames the participant for information overload for one of the use errors and does not identify elements of the user interface that may have contributed to the use error.

	an unfamiliar device for the first time in an artificial setting) • Failure to see visual information (one participant stated that they are a "visual learner" and "just looked at the pictures and surmised what to do") • Cognitive error - reverting to established habits and routines, inadequate or incorrect mental models (eight participants thought that the needle is at the "top" (i.e., (b) (4) injection button) instead of at the base) The Applicant implemented mitigation strategies to address these use errors. These mitigations strategies included: • AI injection button color was changed from (b) (4) to purple to introduce contrast to help identify the button from the gray base cap • The AI label was modified to add a color-coded arrow graphic as a background to the concentration listed on the container label; the arrow shape points to the device bottom and needle end • The IFU and QRG were updated to add a visual element and clarify text instructions that identify the AI bottom and needle end • IFU and QRG images, IFU Guide to parts, and text instructions were updated as necessary to be consistent with the modifications described above and represent the final design • The carton AI image was updated to reflect the final design (i.e., AI label modification and purple injection button) Based on the mitigation strategies implemented above, the Applicant conducted a supplemental HF validation study assessing these mitigations for use errors associated with the task, "Place (b) (4)	Our review of the labels and labeling (user interface, etc.), including the Applicant's mitigations, finds that the IFU and QRG illustrations and text in Steps 2-3 indicate how to appropriately place the AI at the injection site. The IFU Guide to parts section (see Figure 4) indicates the location of the injection button and needle end. However, our review finds that the post HF validation change to include the arrow pointing to the needle end on the container label can be improved. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review. Figure 4. Guide to parts section in IFU 

	<u>Supplemental HF study result</u> For the task "place [redacted] (b) (4) " there was one use error. On the first try the participant actuated the AI before placing on the injection pad, which prevented evaluation of the task, "place [redacted] (b) (4) The moderator allowed the participant to administer a second injection, during which the participant placed and actuated the AI upside down on the injection pad. The subjective data and the Applicant's root cause analysis indicated: conflicting mental model/negative transfer (participant only focused on the QRG text and not the QRG graphics; the participant did not fully process the proper steps and subsequently reverted to previously learned behavior using syringes). Upon looking at the QRG again, the participant realized her error, and stated that the QRG "could not have been more clear" on how to place the AI. Based on the URRA, if the user places/actuates the AI upside down on the injection site this may lead to: • injection of an incorrect site, such as the thumb, and there is risk of pain, injury • injection of someone other than the patient and there is risk of hypoglycemia, nausea, diarrhea, vomiting • drug expelled in the wrong direction and there is risk of mild, symptomatic or asymptomatic hyperglycemia • drug product coming in contact with patient or caregiver eye and risk of eye irritation or injury The Applicant did not propose any risk mitigation strategies for the use error seen in the supplemental study.	
4.	For the task [redacted] (b) (4) " there was one use error and two close calls during the first attempt, and one close call during a second attempt. For the use error, the participant did not	We disagree with the Applicant's clinical impact of use errors associated with the task to "[redacted] (b) (4) ". If the patient does not receive a

	unlock the AI, pressed the (b) (4) injection button, held the AI for 10 seconds, and disposed of the AI. For the close calls, the participants placed the locked AI on the injection pad, pressed the (b) (4) injection button, received no device feedback, and self-corrected by unlocking the AI. The subjective data and the Applicant's root cause analysis indicated: • Perception error - failure to see visual information o One participant who had a use error only read the bolded header of Steps 1, 2, 3. The Step 2 bolded header states "Place on skin and unlock", but the participant only read the "Place on skin" portion of the header. o One participant stated that the text in the QRG was too small, but self-corrected. o One participant referred to the QRG but did not see the unlock instruction because "he rushed through it" and eventually self-corrected. • Cognitive error – memory failure (one participant was used to vial and syringe, but eventually self-corrected) The Applicant also states that all three participants who experienced close calls self-corrected when they realized that they could not press the (b) (4) injection button. Based on the URRA, if this task is omitted or not performed correctly this may lead to no dose with no perceptible clinical impact. Additionally, based on the URRA, since a locked device cannot be actuated, this may lead to excessive manipulation of the AI and result in pain.	dose due to a locked AI, then the patient would also not receive the intended therapeutic benefit. Our review of the study results identified subjective feedback that indicated that one use error was due to negative transfer as the participant was accustomed to using a vial and a syringe. Additionally, our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why the participant only read the "Place on skin" portion of the "Place on skin, then unlock" bolded header. Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG contain text and illustrations on unlocking the AI. The AI displays lock and unlock symbols that align with the lock ring control. Additionally, we note that the AI will not provide its normal informative feedback, including injection button movement, audible clicks, and gray plunger movement, if the AI is not unlocked when the user attempts to press the injection button. It appears that the absence of informative feedback when the AI is locked may inform the user that the AI may be locked. However, based on subjective feedback that the QRG is too small, we provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

	The Applicant did not propose any risk mitigation strategies for these close calls and use error.	
5.	For the task [redacted] (b) (4), there were two use errors during the first attempt and one use error during the second attempt. The subjective data and the Applicant's root cause analysis indicated: • Cognitive error - knowledge-based mistake (one participant who did not refer to the QRG or IFU, and another participant who "kind of looked at the pictures" in Steps 2 and 3, lifted after the first click) • Perception error – failure to see visual information (one participant, had "preconceived notions about how basic [the injection would be]", decided to only look at the text below the header of Step 3 "Press and hold up to 10 seconds" in the QRG and lifted after the first click) Based on the URRA, if the task is omitted or not performed correctly this may lead to underdose and there is risk of mild, symptomatic or asymptomatic hyperglycemia. Additionally, based on the URRA, if the injection is too shallow or is an intradermal injection then this would most likely lead to the same therapeutic effect, but potentially cause pain or wheals at injection site. Unintended needle movement may lead to excess injection site trauma. The Applicant did not propose any risk mitigation strategies for these use errors.	Our review of the study results identified subjective feedback that indicated that use errors were due to participants misinterpreting the first click as injection completion. On October 27, 2021, we issued an information request (IR) to the Applicant to provide the time required for the AI to complete the delivery of the drug and the time each participant held the AI at the injection site during Step 3 "Press and hold up to 10 seconds". On October 29, 2021, the Applicant responded, stating that the injection time required for the AI to complete the delivery of the drug is 2 seconds. The Applicant also stated that the injection time (i.e., time (in seconds) from when the participant pressed the injection button until the AI injected the drug product and automatically retracted and locked the semi-finished syringe and needle) was 2 seconds for each participant who had a use error. See Appendix D for more information. Based on this information, for the three use errors, participants received the full dose from holding the AI for 2 seconds. Additionally, our review of the identified subjective feedback indicated that one participant only looked at the text under the bolded header "Press and Hold for up to 10 seconds" for Step 3 in the QRG. This text first states "Press and Hold the purple injection button" and does not state the appropriate hold time of 10 seconds. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
6.	For the task "dispose", there were nine use errors and five close calls during the first attempt and two use errors and one close call during the second attempt. For the use errors, five participants threw the used AI in the trash can, three	We disagree with the Applicant that instances in which participants disposed of the used AI into the trash and then later attempted to self-correct would be considered close calls. These instances should be

	participants placed the used AI on the table, and three participants put the used AI back in the carton. For the close calls, participants threw the used AI in the trash, tried to self-correct, but were stopped by the moderator. The subjective data and the Applicant's root cause analysis indicated: • Perception errors – failure to see visual information (eleven participants did not notice the disposal instructions in the QRG or IFU) • Cognitive errors – memory failure and knowledge-based mistake o Two participants stated that at home they throw injectable products, or certain parts of injectable products, in the household trash o One participant did not understand the term "sharps container" in the IFU statement "After your injection, place the used Pen in a sharps container". o Two participants did not see the disposal instructions and were unclear of the number of doses per AI or thought that there was more than one dose in the AI o Test artifact – context for use (one participant stated, "[I] wasn't sure if the sharps container was real because I was using an example pen.") Based on the URRA, if this task is omitted or not performed correctly and the user disposes the used AI in household trash then there is risk of pain and injury due to broken glass. The Applicant did not propose any risk mitigation strategies for these use errors and close calls.	considered use errors, because in this case the use error has already occurred. Our review of the study results identified subjective feedback that indicated that the use errors were due to participants not noticing disposal instructions in the IFU or QRG and negative transfer from participants disposing injectable products in the household trash at home. Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG can be improved. In the QRG and the front of the IFU, at the end of Step 3 "Press and Hold up to 10 seconds", the statements, "Put used Pen in a sharps container" and "After your injection, place the use Pen in sharps container", respectively, lack prominence and clarity. See Figure 5 and Figure 6 below. Additionally, the full details of the disposal instructions are on the back of the IFU and users may not realize this, as indicated by subjective feedback in which participants stated that they did not see disposal instructions in the IFU. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

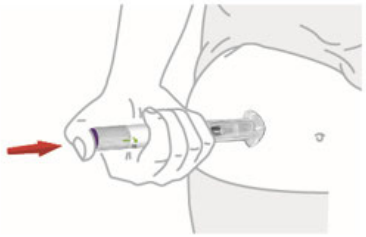
		Figure 5. “Put used Pen in a sharps container” instruction in the QRG Step **3 Press and Hold up to 10 seconds**  **Press and Hold** the purple injection button. **Listen** for: • First click = injection started • Second click = injection completed Injection is complete when you see the gray plunger.  Put used Pen in a sharps container.

		Figure 6. "After your injection, place the use Pen in sharps container" instruction in the IFU 
7.	For the knowledge-based question, **"What do the instructions say you should do if a pen has been frozen?"** there were four "unsuccessful answers". The subjective data and the Applicant's root cause analysis indicated: • Perception error – failure to see visual information (three participants could not find the instruction to not use a frozen pen, but they did not provide a reason for why they could not find the correct information) • Cognitive error – knowledge-based mistake (one participant misunderstood the question and interpreted the word "frozen" to mean a frozen mechanism (i.e., injection button was stuck). The	Our review of the study results identified subjective feedback that indicated that the Applicant's root cause analyses is incomplete, since the Applicant did not further probe the participants who stated that they did not see the relevant information. Our review of the labels and labeling (user interface, etc.) finds that the "Storage and handling" section of the IFU states, "**Do not** freeze your Pen. If the Pen has been frozen, throw the Pen away and use a new Pen." Additionally, the carton states, "DO NOT FREEZE". We did not identify additional changes to the user interface that may address the "unsuccessful answers" and we find the residual risk acceptable.

	Applicant states that the moderator did not redirect the participant to the correct question. Based on the URRA, if the user stores the AI in a freezer this can lead to: • degraded drug/loss of potency and there is risk of mild, symptomatic or asymptomatic hyperglycemia • loss of potency by less than 50%, which does not have clinical impact • non-retraction of needle due to freezing and there is risk of needle stick, including potential infection from contaminated needle stick • injection of particulate and there is risk of pain, injury, capillary embolism, granuloma, or immune response The Applicant did not propose any risk mitigation strategies for these "unsuccessful answers".	
8.	For the knowledge-based question, "What do the instructions say about inspecting the device before use?" there was one "unsuccessful answer". The subjective data and the Applicant's root cause analysis indicated: perception errors – failure to see visual information (participant did not see the relevant information in the IFU). Based on the URRA, if the user omits or does not inspect the device before use then there is risk of: • pain, injury, capillary embolism, granuloma, toxicity, immune response, possibly requiring medication treatment • mild symptomatic or asymptomatic hyperglycemia • needle stick and possible infection	Our review of the study results identified subjective feedback that indicated that the Applicant's root cause analyses is incomplete, since the Applicant did not further probe the participant who stated that they did not see the relevant information in the IFU. Our review of the labels and labeling (user interface, etc.) finds that the "Preparing to inject Mounjaro" section of the IFU states, "Inspect the Pen to make sure that it is not damaged. Make sure the medication is not frozen, not cloudy, colorless to slightly yellow, does not have particles". However, this section is not numbered as a step that is to be performed upon each use of the AI and thus may be overlooked. As such, our review of the IFU finds that the "Preparing to inject Mounjaro" section can be numbered as a step a user should complete. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

	The Applicant did not propose any risk mitigation strategies for this "unsuccessful answer".	
9.	For the knowledge-based question, "According to these materials, how should these devices be stored?" there was one "unsuccessful answer". The subjective data and the Applicant's root cause analysis indicated: perception error – failure to see visual information (participant did not read information under the "Storage and handling section" and stated that they only glanced at the information instead of reading it thoroughly because they are familiar with similar devices; therefore, the participant thought they already knew what information would be provided in the IFU). Based on the URRA, if the task is omitted or not performed there is risk of: • toxicity, immune response • mild, symptomatic, or asymptomatic hyperglycemia in some users • pain, injury The Applicant did not propose any risk mitigation strategies for this "unsuccessful answer".	Our review of the study results identified subjective feedback that indicated that the participant did not notice the relevant information in the IFU. Our review of the label and labeling (user interface, etc.) finds that the "Storage and handling" section of the IFU states, "Store your Pen in the refrigerator between 36°F to 46°F (2°C to 8°C)." and "You may store your Pen at room temperature (b) (4) 86°F (30°C) for up to (b) (4) 21 days." Additionally, the carton states, "Store refrigerated at 36°F to 46°F (2°C to 8°C) in original carton to protect from light." and "Mounjaro can be stored at room temperature up to 86°F (30°C) for up to 21 days in the carton. (b) (4) Discard if not used within 21 days after removing from the refrigerator." We did not identify additional changes to the user interface that may address this "unsuccessful answer" and we find the residual risk acceptable.
10.	For the knowledge-based question, "What do the instructions say about checking the pen label before use?" there were thirteen "unsuccessful answers". The subjective data and the Applicant's root cause analysis indicated: • Perception error – failure to see visual information (eleven participants focused on the "Important information you need to know before injecting	Our review of the study results identified subjective feedback that indicated that the participants expected to see the relevant information in the "Important information you need to know before injecting Mounjaro" which is the section that precedes the "Preparing to inject Mounjaro" section that contains information on checking the pen label. Our review of the labels and labeling (user interface, etc.) indicated that the "Preparing to inject Mounjaro" section of the IFU states, "Check the Pen label to make sure you have the right medicine and dose and that it

	Mounjaro" section preceding the "Preparing to inject Mounjaro" section of the IFU, which instructs the user to check the pen label) • Cognitive error – knowledge-based mistake due to misunderstanding or misinterpreting the question due to an incorrect mental model or knowledge deficit (two participants did not understand what "pen label" meant) Based on the URRA, if the task is omitted or not performed there is risk of toxicity, immune response. The Applicant did not propose any risk mitigation strategies for these "unsuccessful answers".	has not expired." Additionally, next to this task is an illustration indicating the location of the expiration date on the AI (see Figure 7 below). However, the IFU "Preparing to inject Mounjaro" section is not numbered as a step that is to be completed when using each AI and thus may be overlooked. We provide a recommendation in Table A to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review. Figure 7. Illustration indicating expiration date location in the "Preparing to inject Mounjaro" section of the IFU 

3.1 LABELS AND LABELING

Tables A below includes the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table A: Identified Issues and Recommendations for Eli Lilly (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Autoinjector (AI) label			
1.	The added color-coded arrow graphic (see below) on the AI label is not labeled to indicate that it is pointing to the needle end. 	We are concerned that if the user places/actuates the autoinjector upside down on the injection site this may lead to: • injection of an incorrect site, such as the thumb, and there is risk of pain, injury • injection of someone other than the patient and there is risk of hypoglycemia, nausea, diarrhea, vomiting • drug expelled in the wrong direction and there is risk of mild, symptomatic or asymptomatic hyperglycemia • drug product coming in contact with patient or caregiver eye and there is risk of eye irritation or injury	We recommend that you consider adding text to the autoinjector label to indicate to the user which end is the needle-end.
Instructions for Use (IFU) and Quick Reference Guide (QRG)			
1.	The step “Preparing to inject Mounjaro” is not numbered as a step that is to be completed when using each autoinjector and thus may be overlooked.	We are concerned that if a user omits or does not perform the tasks associated with “Preparing to inject Mounjaro” there is risk of pain, injury, capillary embolism, granuloma, toxicity, immune response, mild, symptomatic or asymptomatic	We recommend you number the step “Preparing to inject Mounjaro” in the IFU.

		hyperglycemia, and infection from needle stick. The human factors (HF) validation study results identified subjective feedback that indicated that participants did not notice the "Preparing to inject Mounjaro" step in the IFU. Several participants thought that relevant information would be stated in the preceding "Important information you need to know before injecting Mounjaro".	
2.	The step "Choose your injection site" is not numbered as a step that is to be completed when using each autoinjector and thus may be overlooked.	We are concerned that if a user injects at the wrong injection site there is risk of pain, injury, wheals at injection site. The HF validation study results identified subjective feedback that indicated that participants did not notice the "Choose your injection site" step. Instead, participants proceeded to "Step 1 Pull off the gray base cap", which is the task listed immediately after "Choose your injection site".	We recommend you number the step "Choose your injection site" in the IFU and QRG.
3.	The IFU and QRG text under (b) (4) Press and Hold up to 10 seconds" states "Press and Hold the purple injection button" but does not state the appropriate hold time of 10 seconds.	We are concerned that if this task is omitted or not performed correctly this may lead to mild, symptomatic or asymptomatic hyperglycemia. The HF validation study results identified a participant who overlooked the bolded header for (b) (4) and only read the text	We recommend that you make the following change to (b) (4) Press and Hold up to 10 seconds" of the QRG and IFU: Change the statement, "Press and Hold the purple injection button" to "Press and Hold the purple injection button for up to 10 seconds".

		underneath which states, “Press and Hold the purple injection button”.	
4.	The instructions “After your injection, place the used Pen in a sharps container” in the IFU and “Put used Pen in a sharps container” in the QRG lack prominence and clarity.	We are concerned that if a user omits or does not perform the disposal task then there is risk of injury. The HF validation study results identified several participants who did not see the disposal instruction. In the IFU the full disposal instructions, “Disposing of your used Pen” is the only task that is on the back of the IFU. Additionally, some participants who referred to the QRG did not know to dispose of the autoinjector after each injection.	• We recommend you revise the QRG statement, “Put used Pen in a sharps container” to align with the IFU and state the following: “After your injection, place the used Pen in a sharps container”. • We recommend that you make the aforementioned disposal instructions in the IFU and QRG more prominent. • We recommend that in IFU Step 3, after the statement, “After your injection, place the used Pen in a sharps container”, include instructions for the user to flip the IFU to the back to see the “Disposing of your used Pen” step. • We recommend you number the step “Disposing of your used Pen” in the IFU.
5.	The QRG text and illustrations may not be large enough for users to read or see.	We are concerned that patients with diabetes mellitus who are visually impaired may have difficulty reading the QRG due to small text size and illustrations.	We recommend that you increase the QRG text and illustration size.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation studies demonstrated several use errors with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Diabetes, Lipid Disorders and Obesity (DDLO) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATION FOR ELI LILLY

Our evaluation of the results of your human factors (HF) validation studies indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A and we recommend that you implement these recommendations and submit the revised label and labeling for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for tirzepatide that Eli Lilly submitted on September 15, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist
Active Ingredient (Drug or Biologic)	Tirzepatide
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL
Dose and Frequency	• Start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly. • If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg. • If a dose is missed administer within 4 days of missed dose
How Supplied	Tirzepatide a clear, colorless to slightly yellow solution available in pre-filled single-dose autoinjectors. Each autoinjector contains 0.5 mL of solution. <u>Carton of 4 Single-Dose Autoinjectors</u> • 2.5 mg/0.5 mL • 5 mg/0.5 mL • 7.5 mg/0.5 mL • 10 mg/0.5 mL • 12.5 mg/0.5 mL • 15 mg/0.5 mL
Storage	• Store tirzepatide in a refrigerator at 36°F to 46°F (2°C to 8°C).

	• If needed, each single-dose autoinjector can be stored unrefrigerated at temperatures not to exceed 86ºF (30ºC) for up to 21 days. • Do not freeze. Do not use if frozen. • Store in the original carton to protect from light.
Container Closure/Device Constituent	Single-dose, prefilled injection device enclosing a syringe containing the medication.
Intended Users	• Adult patients • Caregivers • Healthcare professionals
Intended Use Environment	Home or medical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On October 22, 2021, we searched the L:drive and AIMS using the terms tirzepatide, IND 128801 and NDA 215866 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous review[d], and we confirmed that our previous recommendations were implemented.

[d] Bhalodia A. Human Factors Protocol Review for tirzepatide (IND 128801). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC MAR 21. RCM No.: 2020-2692.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\nda215866\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\(b) (6)-other-stud-rep\human-factors-engineering-report\human-factors-engineering-report.pdf

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On October 27, 2021, we issued an Information Request (IR) to obtain:

- the protocols for the human factors validation study and human factors supplemental study referenced in the Tirzepatide Autoinjector Human Factors Engineering Report
- information on time required to for the autoinjector to complete drug delivery, actual time that each participant held the autoinjector at the injection site, time for the gray plunger to be visible in the viewing window

The Applicant provided an acceptable response on October 29, 2021 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215866\0012\m1\us\reg-response-oct-21.pdf

\\CDSESUB1\evsprod\nda215866\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\(b) (6)-other-stud-rep\human-factors-engineering-report\prt-92277-tirzepatide-autoinjector-human-factors-validation-.pdf

\\CDSESUB1\evsprod\nda215866\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\(b) (6)-other-stud-rep\human-factors-engineering-report\prt-93365-tirzepatide-autoinjector-supplemental-human-factor.pdf

On December 29, 2021, we issued an IR to obtain:

- clarification on the reported hold times for 65 participants
- information on why a patient choosing and injecting in the back of the arm is considered successful, when the IFU states that patients should inject in their thigh or abdomen
- information on why the injection naïve caregivers were substituted with injection naïve laypersons

The Applicant provided an acceptable response on January 3, 2022 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215866\0031\m1\us\reg-response-jan-2022.pdf

On January 7, 2022, we issued an IR to obtain:

- clarification on whether there were 10 or 14 participants who had use errors during first injection attempt
- the subjective feedback and root cause analyses for the use errors seen in the first injection attempts

- subjective feedback and root cause analyses for use errors seen in the human factors validation study for the task “place device at injection site”

The Applicant provided an acceptable response on January 10, 2022 that can be accessible in EDR via:

\\CDSESUB1\evsprod\nda215866\0022\m1\us\reg-response-jan-2022.pdf

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following tirzepatide labels and labeling submitted by Eli Lilly.

- Container labels received on September 15, 2021
- Carton labeling received on September 15, 2021
- Instructions for Use (image not shown) received on September 15, 2021, available from \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-usermanual-clean.docx
- Quick Reference Guide (image now shown) received on September 15, 2021, available from: \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-quickguide-clean.docx

E.2 Labels and Labeling Images

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NEHA KUMAR
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JASON A FLINT
02/15/2022 01:09:38 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 9, 2022
Requesting Office or Division:	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Application Type and Number:	NDA 215866
Product Name, Dosage Form, and Strength:	Mounjaro (tirzepatide) injection, 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Product Type:	Single Ingredient Product; Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Eli Lilly and Company (Lilly)
FDA Received Date:	September 15, 2021
OSE RCM #:	2021-1828
DMEPA 1 Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDCES
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Mounjaro (tirzepatide) injection, the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) requested that we review the proposed Mounjaro prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	N/A
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	B

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), container labels, and carton labeling for Mounjaro to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI and the proposed carton and container labels. We provide our recommendations below in Section 4.1 for the Division and Section 4.2 for Lilly.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Mounjaro are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Sections 4.1 and 4.2.

Note that DMEPA 1 is also evaluating the HF validation study results under separate cover and additional label and labeling comments may be forthcoming based on the outcome of that review.

4.1 RECOMMENDATIONS FOR DIVISION OF DIABETES, LIPID DISORDERS, AND OBESITY (DDLO)

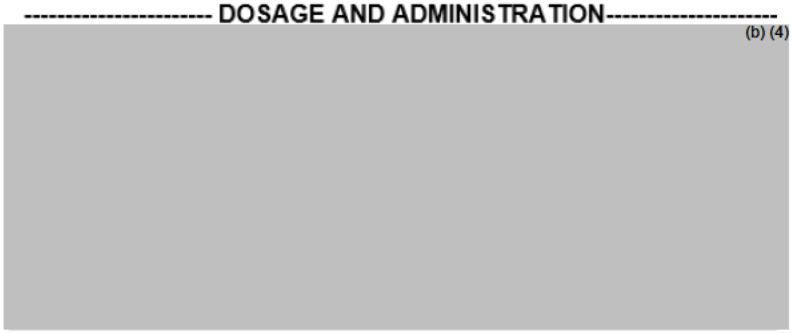
A. Prescribing Information

1. Highlights of Prescribing Information: Dosage and Administration

a. Recommendations are noted in track changes below:

---------- DOSAGE AND ADMINISTRATION----------

(b) (4)



2. Full Prescribing Information: Dosage and Administration Section 2

a. Recommendations to Section 2 are noted in track changes below:

(b) (4)

4.2 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. We note that the proprietary name and established name do not appear to more prominently placed on the principal display panel as the product strength; accordingly, increase the prominence of the proprietary and established name. In addition, we note that the established name does not appear to be at least half the size of the proprietary name. Revise the established name to be in accordance with 21 CFR 201.10(g)(2).

2. As currently presented, the strength statement lends itself to misinterpretation. The increased font size of the numerical component, which is cut in half by a

horizontal slash mark (as opposed to a typically depicted vertical slash) within the unit of measure demarcation, may lead to confusion. Revise the presentation of the product strengths to read "mg/0.5 mL" as a single line of text for improved clarity (e.g., 7.5 mg/0.5 mL).

3. Consider revising the statement [redacted] (b) (4) to read "For Subcutaneous Use".

4. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

5. There is inadequate differentiation between the 5 mg and 10 mg strengths as both use the [redacted] (b) (4). Consider the use of different colors or some other means to provide adequate differentiation between these product strengths.

6. Note that DMEPA 1 is also evaluating the HF validation study results under separate cover and additional label and labeling comments may be forthcoming based on the outcome of that review.

B. Container Labels

1. Decrease the prominence of the statement "Rx Only" by removing the bold font and relocating the statement to the bottom of the label as this information appears more prominent than the established name on the principal display panel. In addition, we recommend removing the bold font from the "Protect from light", "Do not freeze", and "Keep out of reach of children" statements on the principal display panel as these statements compete in prominence with required information.

2. To ensure consistency with the Prescribing Information, add the statement "Recommended Dosage: See prescribing information."

3. As currently presented, there are two barcodes (i.e., linear barcode and Quick Response Code) on the pen container label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers. Therefore, we recommend you move the barcode that does not contain the NDC number away from the barcode containing the NDC number and present it in a

size that does not compete with or distract from the presentation of other required or recommended information on the label.

4. We recommend adding revising the statement [redacted] (b) (4) to read "Store in original carton to protect from light" to clarify this recommendation for users. In addition, we recommend removing the bold font from this statement.

5. We recommend revising the net quantity statement to read "0.5 mL single-dose-pen" for improved clarity. In addition, considering this edit, we also recommend removing the "0.5 mL" statement currently located in the top corner of the label next to the NDC for decreased redundancy of this information.

C. Carton Labeling

1. We note that the current location of the pen image bifurcates the primary display panel (PDP) and interferes with the readers ability to easily access important product information. Therefore, to improve readability, we recommend presenting the pen image and the associated gray triangle, either on the right or left side of the PDP so that the important label information can be visible in the same line of site.

2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers to affix or imprint a human-readable and machine-readable (2D data matrix barcode) product identifier on the smallest saleable unit (usually the carton) for tracking and tracing purposes. We note that the proposed cartons do not appear to contain the machine-readable product identifier; thus, we recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

3. Decrease the prominence of the statement "Rx Only" by removing the bold font as this information appears more prominent than the established name on the principal display panel.

4. To ensure consistency with the Prescribing Information, revise the statement, "See package insert for dosing information" to read "Recommended Dosage: See prescribing information."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Mounjaro received on September 15, 2021 from Eli Lilly and Company.

Table 2. Relevant Product Information for Mounjaro	
Initial Approval Date	N/A
Active Ingredient	tirzepatide
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Route of Administration	subcutaneous
Dosage Form	injection
Strength	2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, 15 mg/0.5 mL
Dose and Frequency	start 2.5 mg once weekly then increase the dose to 5 mg once weekly after 4 weeks. If needed, can increase dose in 2.5 mg increments after a minimum of 4 weeks on the current dose. The maximum dose is 15 mg administered once a week.
How Supplied	Single dose prefilled pens for each strength (2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL, and 15 mg/0.5 mL) 4 pens per carton
Storage	refrigerate at 2°C to 8°C (36°F to 46°F)
Container Closure	single-dose prefilled pen (autoinjector) 

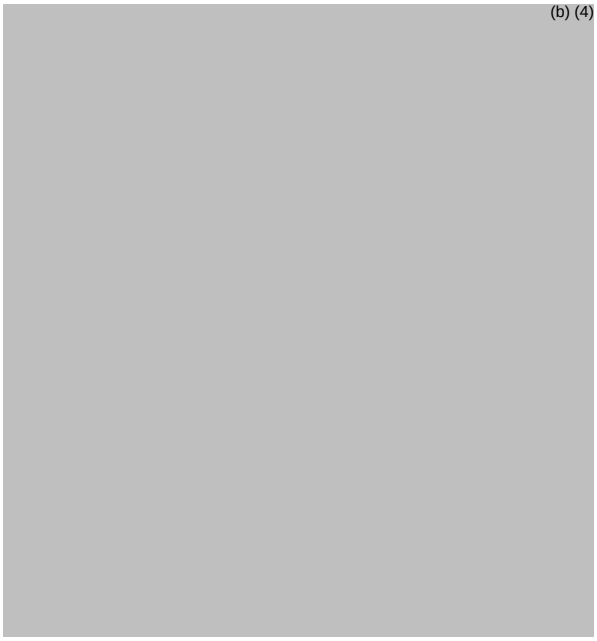
APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Mounjaro labels and labeling submitted by Eli Lilly and Company.

- Container label received on September 15, 2021
- Carton labeling received on September 15, 2021
- Instructions for Use received on September 15, 2021, available from \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-usermanual-clean.docx
- Quick Reference Guide received on September 15, 2021, available from \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-quickguide-clean.docx
- Prescribing Information received on September 15, 2021, available from \\CDSESUB1\evsprod\nda215866\0001\m1\us\annotated.pdf
- Medication Guide received on September 15, 2021, available from \\CDSESUB1\evsprod\nda215866\0001\m1\us\proposed-medguide-clean.docx

B.2 Label and Labeling Images



[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	10/7/2021		
To:	Hamet Toure		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	FDA/OC/CDER/OPQ/OPRO/DRBPMI/RBPMB1/
From	Sreya Tarafdar OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 215866 , Tirzepatide (LY3298176) ICC2100785 ICCR00786736 & ICCR00787356		
Recommendation	**Filing Recommendation Date: 10/18/2021** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 12/14/2021 ☐ CDRH did not provide a Mid-Cycle Recommendation ☑ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 1/27/2022 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Sreya Tarafdar -S Digitally signed by Sreya Tarafdar -S Date: 2022.01.28 11:10:36 -05'00'		Alan M. Stevens -S3

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 215866
Sponsor	Eli Lilly and Co
Drug/Biologic	Tirzepatide (LY3298176)
Indications for Use	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Device Constituent	Auto-Injector
Related Files	ICC1900434.(b) (4).tirzepatide.EliLilly. CDRH consult memo

Review Team	
Lead Device Reviewer	*Sreya Tarafdar*

Important Dates	
Final Lead Device Review Memo Due	02/01/2022
Interim Due Dates	**Meeting/Due Date**
Filing	11/14/2021
74-Day Letter	11/28/2021
Mid-Cycle	12/17/2021
Primary Review	02/15/2022
Internal Meeting(s)	CMC kick-off 10/15/2021 ; OND Filing 10/18/2021
	CMC Mid-cycle 11/22/2021; OND Midcycle 12/01/2021
	CMC Wrap-up 01/31/2021 ; OND late-cycle 02/25/2022
	OND Wrap-up 04/11/2022
Sponsor Meeting(s)	Mid-cycle 12/17/2021 ; Late cycle - 03/18/2022

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:
☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.
☐ Approvable with PMC or PMR, See Section 2.3
☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	Deferred to DMEPA
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.
☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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3. PURPOSE/BACKGROUND

3.1. Scope

Eli Lilly and Co is requesting approval of Tirzepatide (LY3298176). The device constituent of the combination product is a Auto-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

ICCR00786736
We request your review of the autoinjector proposed in this application. The CDRH assessors will be invited to the CMC Team meetings (Kick-off, Mid-cycle, and Wrap-up) and to the OND Team meetings.

ICCR787356
We request your determination of whether an inspection for the device is needed. The CDRH assessors will be invited to the CMC Team meetings (Kick-off, Mid-cycle, and Wrap-up) and to the OND Team meetings.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Autoinjector and Final finished product - Device performance, design verification/validation, facilities information for sites involved in device manufacture/assembly.

This review will not cover the following review areas:

Human Factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

Elvira Castro was the CDRH assessor and had provided boilerplate language in the prior interactions – consult memo is provided in the following link:
ICC1900434 (b) (4) .tirzepatide.EliLilly. CDRH consult memo

3.3. Indications for Use

Combination Product	Indications for Use
Tirzepatide (LY3298176)	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed		
Sequence	**Module(s)**	
	1.1	FDA form 356h
	3.2.P.3	Manufacture
	3.2.R	Medical Device
	1.14	Labeling
	1.16	Risk Management Plan

	2.5 and 2.7	Clinical Overview and Summary

4. DEVICE DESCRIPTION

4.1. Device Description

The delivery device consists of a single-use needle-based injection system (NIS) that, when activated, automatically inserts the needle into the subcutaneous tissue and delivers 0.5 mL of tirzepatide drug product. The autoinjector components do not contact the drug product. The device classification regulation applicable to the device constituent part of the combination product is 21 CFR 880.6920, product code KZH.

A semi-finished syringe of tirzepatide drug product as described in Section 3.2.P.7, Container Closure System (tirzepatide Injection) consists of parenteral tirzepatide drug products that are filled in (b) (4) glass syringe (b) (4) When activated, the autoinjector delivers the entire volume from the SFS in a single injection. The fluid path from the SFS is through the (b) (4) component of the primary drug container.

An engineering cross section view of the autoinjector in the assembled state is shown in the figure below. (b) (4)

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

The sponsor states in Section 3.2.R.2.2 :

The autoinjector, first developed for Trulicity, was designed according to the ISO standard for NISs with automated features as well as requirements derived from patient and user needs. The ISO Technical Committee 84, Working Group 3 (ISO/TC84/WG3) addressed the development of NIS's with automated features in the standard ISO 11608-5. This standard provides several general design requirements and dose accuracy, visual and functional requirements that the autoinjector must meet when conditioned and tested under specified conditions. In addition to ISO requirements, patient and user needs were evaluated to determine the features and functionality needed for the autoinjector. This feedback was translated into system requirements that guided development of the autoinjector design. Any reference to commercial autoinjector is referencing the same autoinjector used for Trulicity.

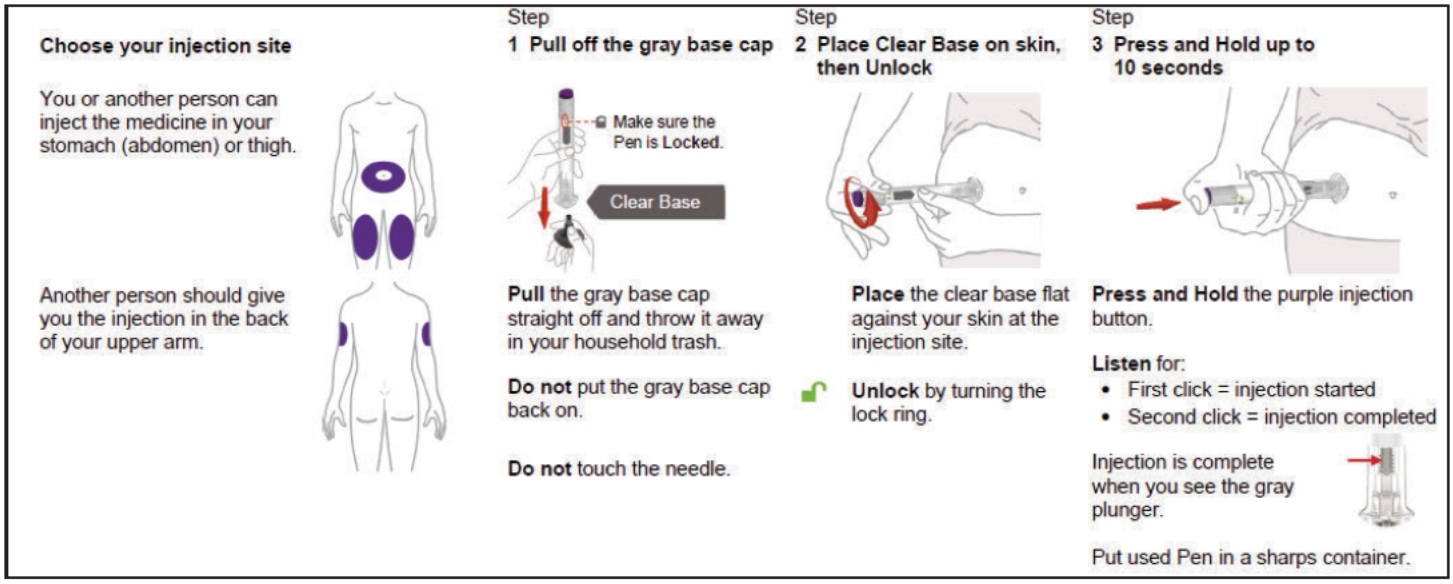
4.2. Steps for Using the Device

1. Pull off the gray base cap
2. Place on skin, then unlock
3. Press and hold up to 10 seconds

The activation end of the autoinjector incorporates the lock ring to prevent unintentional activation and an injection button to start the injection sequence. The injection end incorporates a base cap for needle shield removal and a clear base for stable positioning at the injection site.
The autoinjector is prepared by removing the gray base cap that pulls the syringe needle shield off. The autoinjector clear base is placed flush onto the patient's skin at the injection site. The flat base of the device helps to orient the needle perpendicular to the skin.
After placement on the skin, the device is unlocked by turning the lock ring to align the indicator on the lock ring to the unlock symbol. The autoinjector is designed to not be activated when the indicator is aligned with the lock symbol.
The user activates the device by pressing the injection button. This generates an audible and tactile click and the device automatically performs the following steps:

1. Needle insertion: (b) (4)
2. Drug injection: (b) (4)
3. Needle retraction: (b) (4)

The user must hold the device against the skin during the injection cycle but is not required to maintain pressure on the injection button. The device generates a (second) audible and tactile click at the end of the needle retraction process. The user can confirm that the injection is complete by looking for the gray plunger position as shown in the Instructions for Use (IFU) or quick reference guide (QRG). The device locks the retracted needle in place for disposal of the used autoinjector in a sharps container.



4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device portion of the tirzepatide autoinjector is functionally the same as the approved Trulicity (dulaglutide) autoinjector.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 10/25/2021	**Date/Sequence Received:** 11/1/2021
Information Request #	*In Section 3.2.R Medical Device of your submission, you have described the device portion of the tirzepatide autoinjector. However, some information is missing and/or not clearly stated. Please provide additional information to clarify the following concerns:* *a) In Section 3.2.R.2.2, you have provided a description of your device. However some information is missing. Please provide the following :-* i. *a detailed description of the device, including all features and/or functionalities including engineering drawings, schematics and descriptions of the individual device constituent components.*	
Sponsor Response	The tirzepatide autoinjector is a single-use needle-based injection system (NIS) that, when activated, automatically inserts the needle into the subcutaneous tissue and delivers 0.5 mL of tirzepatide drug product. Table 2.1 details the features and associated functional descriptions of the autoinjector. (copied above in section 4.1) An engineering cross section view of the autoinjector in the assembled state is shown in (b) (4) The device component constituents are detailed in the diagram above and their overall	

	functionality is included in Table 2.1. The following table (Table 2.2) provides a list of all the individual device constituent components and material details. An exploded view, Figure 2.3, shows the relationship of device constituent components to one another, but does not depict the assembly steps, nor part-to-part interface.
Reviewer Comments	All figures provided by sponsor in response to our issued IR is copied and pasted in section 4.1. The sponsor provided device description is complete and sufficient. This is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing		X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		

	Control Strategy provided for EPRs	X		

Reviewer Comment
This application is fileable.

5.2. Facilities Information

Firm Name:	Eli Lily and Company
Address:	Lilly Corporate Center, Indianapolis IN 46285 USA
FEI:	1819470
Responsibilities:	manufacture of semifinished syringes ;device assembly ; quality control testing - chemical /physical, microbiological - sterility /non sterility , packaging and labeling , storage and/or distribution

Inspectional History
An analysis of the firm's inspection history:
☑ Inspection was conducted 10/2/2017 to 10/6/2017. The inspection covered medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because of the following:

The firm has been routinely inspected under the medical device program since 2013 was most recently inspected under the medical device program on 10/2/2017. The most recent inspection included routine QSIT Level 1 coverage of the firms combination products consisting of a medical device and either drug or biologic components and focused on CAPA and Production and Process Controls subsystems.
(b) (4)
No inspection observations were issued at the conclusion of that inspection.
(b) (4)

Firm Name:	Eli Lilly Italia SPA
Address:	Via Antonio Gramsci 731/733, Sesto Fiorentino, FI 50019 Italy
FEI:	3002806895
Responsibilities:	device assembly , quality control testing -physical /chemical , packaging and labeling , storage and or distribution.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:

☑ Inspection was conducted 11/1/2021 to 11/5/2021. The inspection covered both drug CGMPs and medical device QS and was classified NAI. ☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product
Inspection Recommendation: ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☑ An inspection is not required because A recent medical device inspection of the firm was acceptable. The recent pre-approval inspection (PAI) of Eli Lilly Italia S.p.A. located in Sesto Fiorentino, Italy, a biological drug product manufacturer, was conducted in support of BLA 125469 Supplement 38 for Trulicity® (Dulaglutide) 1.5mg/0.5mL drug product. The inspection was conducted by CDER/OPQ under eNSpect Operation ID 207380 (and CMS WA 416778). The inspection was risk-based and conducted in accordance with applicable sections of CPGM 7356.002M, *Inspection of Licensed Therapeutic Drug Products*, CPGM 7346.832, *Preapproval Inspection/Investigations*, and ICH Q7. The profile class for the drug substance (b) (4). **The inspection covered Quality, Facilities/Equipment, Production, Materials, and Laboratory Control systems.** The **Packaging & Labeling system for the drug product device assembly, packaging and labeling,** was covered in the previous inspection (2016), and **cursory coverage for this system was provided during this inspection**. This inspection provided coverage of the following areas at the Eli Lilly Italia S.p.A. campus: (b) (4) ,(b) (4) The previous inspection on 10/31/2016 – 11/04/2016 was a comprehensive pre-license inspection of a single use injector pen device assembly and release testing facility for BLA 125469-SUPPL-10, Dulaglutide (Trulicity®) 1.5mg/0.5mL and 0.75mg/0.5mL, and was conducted by ORA under eNSpect assignment number 044868. This current inspection conducted from 11/01/2021 to 11/05/2021 resulted in no FDA Form 483 issued.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK

Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☑ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☑ No Inspection ☐ N/A **Site(s) needing inspection:**
Reviewer Comments This submission is acceptable for filing.
Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A **74-Day Letter Deficiencies:** ☐ Yes ☑ No ☐ N/A

	Date Sent: **10/25/2021**	**Date/Sequence Received:** **12/1/2021**
Information Request #	In Section 3.2.R.2.8, you have listed facilities associated with the manufacture of combination product. You have listed the facilities DDCS, IDM, IPM, IDAP etc. as organizations responsible for the final finished combination product. Besides you have stated that Lilly France Fegersheim and Lilly Italy Sesto sites are also responsible for assembly of the final finished combination product. It is unclear from your statements which facility /site is specifically responsible for manufacturing of the auto injector and assembly of the final finished combination produc. Please clearly state what each facility is responsible for and update the 356h form accordingly, if required.	
Sponsor Response	*Assembly of the autoinjector for tirzepatide will occur at one of the following manufacturing sites:* *Eli Lilly and Company* *Lilly Corporate Center* *Indianapolis, Indiana 46285* *USA*	

	FDA Establishment Number: 1819470 *Eli Lilly Italia SPA* *Via Antonio Gramsci 731/733* *Sesto Fiorentino FI 50019* *Italy* *FDA Establishment Number: 3002806895* *These two manufacturing sites are included in Module 3 Section 3.2.P.3.1, Manufacturers and the 356h form with device assembly as a manufacturing activity for tirzepatide. Section 3.2.R.2.8 provides a summary of the Lilly quality system for the manufacture of combination products, which is compliant with 21 CFR 820. This section includes references to Lilly functional areas and sites covered by the quality system including sites that are not currently performing commercial device assembly for tirzepatide (e.g., Lilly France Fegersheim). Details associated with the commercial manufacture of the tirzepatide injection combination product have been incorporated in the 3.2.P.3 sections including the device assembly information.* Reviewed in Quality Systems/Manufacturing Controls Section

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X (reviewed by DMEPA)		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X

MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
The provided labeling contains all necessary information. The provided human factors validation report and study results to ensure the adequacy of the provided instructions are deferred to DMEPA.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		

Reviewer Comments
The labeling contains all required elements (as listed above) and the instructions for use are acceptable. The labeling states that it is a single dose product and that it should be discarded after use. The labeling is acceptable from a device perspective. Please note that a human factors evaluation and a detailed review of the step by step instructions for use of the devices is deferred to DMEPA.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by
- ☐ Insert Consultant Name ; The full memo is located in Appendix B.
- ☑ The Lead Reviewer

Below is a summary of the review & recommendation:

The instructions for use are appropriate for the type of device. Please note that the human factors review is deferred to DMEPA. The IFUs for autoinjector were provided and no device specific clinical labeling concerns were identified.

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments
The provided labeling is appropriate for the device type. A usability review of the instructions and device design is covered by the human factors validation review by DMEPA.

CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations X adequate to reduce risk to health			
Version history demonstrates risk management throughout design / development activities			
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
The overall design control process is acceptable. Please see Section 8 for a review of the risk analysis that includes a general overview of the design control activities.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Base cap removal force	(b) (4)
Activation force	
Torque to unlock	
Exposed needle length	
Dose delivery	
Injection time	

Reviewer Comments
Autoinjectors representative of the commercial design containing tirzepatide SFSs were used for these tests except as noted. Performance of the autoinjector in the torque to unlock test was not repeated and is not affected by the syringe contents or external part colors. Therefore, data from previous testing of the approved autoinjector are representative.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	N/A
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
IEC 62366-1: 2015, Medical devices – Part 1: Application of usability engineering to medical devices	Y	Y
FDA guidance, "Technical Considerations for Pen, Jet and Related Injectors Intended for Use with Drugs and Biological Products" (June 2013)	Y	Y
ISO 11608-1:2014 Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems and	Y	Y
ISO 11608-5:2012 Needle-based injection systems for medical use – Requirements and test methods - Part 5: Automated functions and meets the requirements for dose accuracy and functionality of that standard	Y	Y
ISO 11040-4:2015 Glass barrels for injectables and sterilized sub-assembled syringes ready for filling	Y	Y
USP <671>, Containers-Performance Testing	Y	Y
USP <381> - Elastomeric Closure for Injections	Y	Y
USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems	Y	Y
USP <1664> Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery Systems	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 12/3/2021	Date/Sequence Received: 0025 1/7/2022
Information Request #	With regards to (b) (4) the plunger position, please provide justification for the different measuring methods and acceptance criteria employed by the two drug product manufacturing facilities.	
Sponsor Response	The Lilly Indianapolis B103 plunger position range is described as (b) (4) mm being measured from the bottom of the (b) (4) to the top of plunger and the (b) (4) plunger position range is described as (b) (4) mm being measured from the top of (b) (4) to the top of plunger. The Lilly Indianapolis B103 (b) (4) difference is due to the measurement reference point. The difference is dimension (b) (4), identified in Section 3.2.P.7 Container Closure System, Table 3.2.P.7.5-1. Thus, the plunger position ranges for the two manufacturing sites point to an identical plunger position as shown in Figure Q.3-1. The plunger position reference difference is related to the Lilly (b) (4) measurement systems. (b) (4) uses a (b) (4) as its reference plane for the measurement. Lilly uses a (b) (4) to measure the plunger and that system is optimized to use the bottom of the (b) (4) as the corresponding reference plane. The illustration below shows the relationship of the Lilly range, the (b) (4) range, (b) (4) (b) (4)	
Reviewer Comments	Response is acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

8. RISK ANALYSIS

8.1. Risk Management Plan

A risk management plan (compliance to ISO14971) was provided in 3.2.R.2.6. and a detailed report was provided in RPT392520 (Page 37 of 60) of the 32r-medical-device-v001.pdfThe sponsor states: *"The overall residual risk of the tirzepatide autoinjector has been reduced as far as possible given*
the limits of the autoinjector technology. The medical benefit of tirzepatide as a treatment for type 2 diabetes mellitus (T2DM) outweighs the residual risk of the autoinjector. Eli Lilly and Company performs risk management according to the requirements provided in ISO 14971. The tirzepatide autoinjector hazards are equivalent as those identified for the

approved autoinjector and similar to other autoinjectors on the market. A residual risk report that summarizes the results of the risk management process to date is provided as an attachment (Tirzepatide Residual Risk Report). Any new or updated potential risks are evaluated as they are identified (for example, through complaint handling) and modifications to the risk analysis and failure mode and effects analysis documents are made as appropriate."

The risk management process included:

- Identifying potential hazards and harms
- Performing Failure Mode and Effect Analyses (FMEAs) for application, design, and manufacturing processes
- Evaluating use-related risks through Human Factors formative analysis and validation studies

The cumulative residual risk is the total remaining risk presented by the device based on failure modes identified through the risk analysis process.

The risk assessments completed were as follows:

Risk Assessment Name
Gip-Glp PHA (aFMEA)
Combined REACH PHA (dFMEA and pFMEAs)
IRMA dFMEA (Design Failure Mode Effect Analysis)
Tirzepatide aFMEA (Application Failure Mode Effect Analysis)
R1 (b) (4) All Products Process Failure Mode Effect Analysis (pFMEA)
R1 (b) (4) Side Retraction Sub-Assembly pFMEA
R1 (b) (4) ide Body Lower Sub-Assembly pFMEA
R1 (b) (4) Side Drive Sub-Assembly pFMEA
R4A (b) (4) Sub-Assembly (b) (4) Injector pFMEA

Table 2 - Risk Acceptability Heat Map

Probability of Harm			Negligible (SEV. 1)	Minor (SEV. 2)	Moderate (SEV. 3)	Major (SEV. 4)	Severe (SEV. 5)
	Frequent (Prob. 5)	AFMEA	0	0	0	0	0
		DFMEA					
		R1 PFMEAs					
	Probable (Prob. 4)	AFMEA	0	0	0	0	0
		DFMEA	0	0			
		R1 PFMEAs	0	0			
	Occasional (Prob. 3)	AFMEA	0	11	0	0	0
		DFMEA	156	53	0		
		R1 PFMEAs	18	3	0		
	Remote (Prob. 2)	AFMEA	13	41	20	3	0
		DFMEA	12	13	11	0	
		R1 PFMEAs	324	319	201	0	
	Improbable (Prob. 1)	AFMEA	3	4	2	4	0
		DFMEA	1	0	0	65	
		R1 PFMEAs	554	496	326	379	
			Severity of Harm				

- Low level (acceptable) risks : (Green) total of 3032 risks identified across all eight tirzepatide autoinjector FMEAs
- Medium Level Risk : (yellow) Three (3) of the 3032 risks were 'yellow'
- High Level Risk : (Red) No residual risks were identified as red (high) in the tirzepatide risk assessments.

Table 3: Cumulative Residual Risk Assessment

Worst Case Cumulative Probability of Harm by Hazard Type			Fault Tree Linkage
A	Delivery Error - Overdose	0.00012%	2 0 Delivery Error-Overdose, 2 8 Use Error-Overdose
B	Delivery Error - Underdose	0.13565%	2 0 Delivery Error-Underdose, 2 5 Use Error-Underdose, 2 6 Incomplete Injection, 2 7 Premature Retraction

C	Delivery Error - No Dose	0.08022%	2 0 Delivery Error-No Delivery, 2 1 Fluid Path Occlusion, 2 2 Device Inoperable, 2 3 Use Error-No Dose, 2 4 Failure During Operation
D	Unintended Trauma	0.06694%	2 0 Delivery Error- Improper Depth, 2 9 Use Error-Improper Depth, 2 10 Injection Too Shallow, 2 11 Injection Too Deep, 3 Trauma, 3 1 Syringe Breaks-Trauma, 3 2 Damage Needle-Trauma
E	Sharps Hazards	0.00295%	4 Needle Stick, 4 1 Sterile Self-Needle Stick, 4 2 Contaminated Self-Needle Stick 4 3 Contaminated Other Person-Needle Stick
F	Contamination	0.00160%	1 0 Contamination, 1 1 Loss of Sterile Barrier-Contamination, 1 2 Use Error- Contamination
G	Other	0.00449%	N/A
X	Minor hazard with no significant harm	0.18173%	
Cumulative Probability of Harm		0.47370%	

Table 4: Probability of Harm from Essential Performance Requirements

Worst Case Cumulative Probability of Harm by EPR	(b) (4)
EPR 5.1.3 - Activation Force	
EPR 6.2.1 - Injection Process Time Maximum	
EPR 7.3.1 - Delivery Amount and Location	
EPR 7.4.1 - Exposed Needle Length	
Cumulative Probability of Harm from EPRs	

Reviewer Comments

- The current subject device constituent hazards are equivalent to the approved Trulicity Autoinjector.
- This assessment includes tirzepatide autoinjector combination products 2.5mg/0.5mL, 5mg/0.5mL, 7.5mg/0.5mL, 10mg/0.5mL, 12.5mg/mL, and 15mg/0.5 mL
- The sponsor has committed that post market surveillance data will be evaluated on a regular basis and risk management information will be updated accordingly.
- The risk management plan is divided into a User-FMEA, Design-FMEA, Process-FMEA, and a Fault Tree Analysis (FTA).
- The overall residual risk for the tirzepatide autoinjector was evaluated per PDS-SOP-PDS4025 and found to be acceptable and that the anticipated benefit derived from the device outweighs the level of risk remaining. The tirzepatide autoinjector product team and DSLT have reviewed and accepted the following items documented in the aFMEA, dFMEA, and the pFMEAs:
  - Hazards identified
  - Potential failure modes associated with identified risks
  - Controls implemented
  - Overall residual risk evaluation

8.2. Hazard Analysis and Risk Summary Report

(b) (4)

The sponsor has provided a fault tree chart in Appendix B of the RPT392520 (Page 37 of 60) of the 32r-medical-device-v001.pdf

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The risk analysis report and demonstration summary is acceptable.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

EPR	Performance Requirements	Verification Results	Shipping	Stability
Dose Accuracy	(b) (4)	Table 3.2.R.2.4.1-12	3.2.P.2.4.1.5 and 3.2.P.3.5.3.8	3.2.P.8.3.1
Injection Time		Table 3.2.R.2.4.1-17[a]	3.2.P.2.4.1.5 and 3.2.P.3.5.3.8[a]	3.2.P.8.3.1[a]
Button Activation Force		Table 3.2.R.2.4.1-8	3.2.P.2.4.1.5 and 3.2.P.3.5.3.8	3.2.P.8.3.1
Exposed Needle Length		Table 3.2.R.2.4.1-10	3.2.P.2.4.1.5 and 3.2.P.3.5.3.8	3.2.P.8.3.1

(b) (4)

Test	Analytical Procedure	Acceptance Criteria	
		Release	End of Shelf-life
Syringe Functionality: Break Loose Force Glide Force	Compression Test (B13167)	(b) (4)	
Device Functionality			
Dose Accuracy	Volume by Weight (PDS-00605-NC)	(b) (4)	
Visual/Functional Inspection	Inspection	Pass	
Injection Time	Timing (PDS-00604-NC)	(b) (4)	

*** **Additional Design Considerations**

Additional considerations such as visual inspection of the product, injection depth, graduation marks and fill lines, safety features, drug and device compatibility are the same for Trulicity.

Table 3.2.R.2.4.1-3 Design Verification Dose Accuracy Results

Test Condition	Syringe/ Strength	Specification Limits (mL)	Sample Size	Mean $\bar{x}$ (mL)	SD σ (mL)	Tolerance Interval $\bar{x} \pm$ Target k*σ	Pass/Fail
Standard Atmosphere	(b) (4) .5 mg	(b) (4)	60			(b) (4)	Pass
	15 mg						Pass
	15 mg						Pass
Cool Atmosphere	.5 mg		60				Pass
	15 mg						Pass
	15 mg						Pass
Warm Atmosphere	.5 mg		60				Pass
	15 mg						Pass
	15mg						Pass
Cold Storage	.5 mg		60				Pass
	15 mg						Pass
	15 mg						Pass
Dry Heat	.5 mg		60				Pass
	15 mg						Pass
	15 mg						Pass
Free Fall	.5 mg		21				Pass
	15 mg						Pass
	15mg						Pass
Vibration	.5 mg		20				Pass
	15 mg						Pass
	15 mg						Pass

v Abbreviations: SD = standard deviation. (b) (4)

Reviewer Comment

Dose accuracy requirements:

- When tested under standard, cool, and warm atmosphere conditions, 97.5% of all doses delivered were within specification limits.
- Following cold storage and dry heat preconditioning, 97.5% of all doses delivered were within specification limits when tested under standard atmosphere conditions.
- Following free fall and vibration testing, 95% of all doses delivered were within specification limits when tested under standard atmosphere conditions.

9.1.2. Verification of Design Inputs Evaluation

Table 3.2.R.2.4.1-7 Base Cap Removal

Name	LQL (%)	Sample Size	Target k	Specification (N)	Mean $\bar{x}$ (N)	SD σ (N)	Tolerance Interval $\bar{x}$ ± Target k*σ	Pass/Fail
Base Cap Removal Force, Straight Pull							(b) (4)	Pass

Abbreviation: LQL = limiting quality level.

Table 3.2.R.2.4.1-8 Actuation

Name	LQL (%)	Sample Size	Target k	Specification	Mean $\bar{x}$	SD σ	Tolerance Interval $\bar{x}$ ± Target k*σ	Pass/Fail
Torque to Unlock[a]							(b) (4)	Pass
Activation Force								Pass

Abbreviations: LQL = limiting quality level; SD = standard deviation.
[a] Data from approved autoinjector testing.

Table 3.2.R.2.4.1-9 Lock Mechanism Integrity

Name	LQL (%)	Sample Size	Acceptance Criteria	Number Non-conforming Devices Observed	Pass/Fail
Lock Security				(b) (4)	Pass

Abbreviation: LQL = limiting quality level.

Table 3.2.R.2.4.1-10 Exposed Needle Length

Name	LQL (%)	Sample Size	Target k	Specification Limits (mm)	Mean $\bar{x}$ (mm)	SD σ (mm)	Tolerance Interval $\bar{x}$ ± Target k*σ	Pass/Fail
Exposed Needle Length							(b) (4)	Pass

Abbreviations: LQL = limiting quality level; SD = standard deviation.

Table 3.2.R.2.4.1-11 Needle Damage

Name	LQL (%)	Sample Size	Acceptance Criteria	Number Non-conforming Devices Observed	Pass/Fail
Needle Damage During Automated Feature	(b) (4)			0	Pass
Base Cap Removal				0	Pass

Abbreviation: LQL = limiting quality level.

Table 3.2.R.2.4.1-12 Dose Delivery

Name	LQL (%)	Sample Size	Target k	Specification Limits (mL)	Mean $\bar{x}$ (mL)	SD σ (mL)	Tolerance Interval $\bar{x} \pm$ Target k*σ	Pass/Fail
Delivery Amount	(b) (4)							Pass

Abbreviations: LQL = limiting quality level; SD = standard deviation.

Table 3.2.R.2.4.1-13 Injection of the Medicinal Product

Name	LQL (%)	Sample Size	Target k	Specification Limits (mL)	Mean $\bar{x}$ (mL)	SD σ (mL)	Tolerance Interval $\bar{x} \pm$ Target k*σ	Pass/Fail
Cool Atmosphere Delivery Amount	(b) (4)							Pass
Standard Atmosphere Delivery Amount								Pass
Warm Atmosphere Delivery Amount								Pass

Abbreviations: LQL = limiting quality level; SD = standard deviation.

Table 3.2.R.2.4.1-14 Needle Shielding

Name	LQL (%)	Sample Size	Acceptance Criteria	Number Non-conforming Devices Observed	Pass/Fail
Needle Shielding Before Injection Cycle				(b) (4)	Pass
Needle Shielding After Injection Cycle					Pass

Abbreviation: LQL = limiting quality level.

Table 3.2.R.2.4.1-15 Needle Retraction Position

Name	LQL (%)	Sample Size	Acceptance Criteria	Number Non-conforming Devices Observed	Pass/Fail
Needle Retraction Position				(b) (4)	Pass

Abbreviation: LQL = limiting quality level.

Table 3.2.R.2.4.1-16 Disabling Autoinjector after Retraction

Name	LQL (%)	Sample Size	Acceptance Criteria	Number Non-conforming Devices Observed	Pass/Fail
Disabled Device Integrity				(b) (4)	Pass

Abbreviation: LQL = limiting quality level.

Table 3.2.R.2.4.1-17 Injection Time

Name	LQL (%)	Sample Size	Target k	Specification Limits (sec)	Mean $\bar{x}$ (sec)	SD σ (sec)	One sided Tolerance Bound $\bar{x}$ + Target k*σ	Pass/Fail
Injection Time							(b) (4)	Pass

Abbreviations: LQL = limiting quality level; sec = seconds; NMT = not more than; SD = standard deviation.

Reviewer Comment
The tirzepatide autoinjector complies with the applicable sections of ISO 11608-5:2012.

9.1.3. Evaluation of Test Methods

Title:	Dose Accuracy
Scope/Objective & Acceptance Criteria:	*To demonstrate the dose accuracy of the device:* (b) (4)
Methods	(b) (4)
Results:	Please refer to results above
Acceptable:	☒Yes ☐No

Title:	injection time
Scope/Objective & Acceptance Criteria:	*to demonstrate the injection time of the device, actuated devices into a collection container . A timing device detects each of the timed functions of the device to determine the start and end of the injection time*
Methods	

STEP	INSTRUCTION
1.	Prepare the device for injection following the steps in the user guide instructions
2.	Dispense the fluid from the device into the collection vial.
3.	Calculate the injection time by determining the time point at which the button is depressed (thereby activating the device) to the time point where the autoinjector completes each of the timed functions (for example, dose delivery, completed retraction).

			T(Timed function) – T(activation) = IT of function	
Results:	Please refer to results above			
Acceptable:	☒Yes ☐No			

Accelerated aging and shelf life

The accelerated aging test was performed on the previously approved autoinjector that has the same design and functionality as the tirzepatide autoinjector. The only difference between the tirzepatide and approved autoinjector is the color of the injection button. The button color difference has a low risk to cause device functional failure because the colorant carrier is the same material and the ratio of colorant to carrier in the mix is the same between the two autoinjectors.

The individual device components were aged for the equivalent of 2 years at 25°C (60°C/40% relative humidity [RH] for 65 days). Subassemblies of the components were then aged for the equivalent of 2 years at 25°C and approximately 3 years at 5°C (60°C/40% RH for 85 days). Drug filled SFSs were assembled with the aged components and subassemblies. These were tested to confirm that the autoinjector met the specifications for the functions essential to clinical performance.

There was no evidence that aging of the components and subassemblies resulted in any loss of Function of the auto injector. This data demonstrates that the autoinjector meets performance requirements following exposure to elevated temperatures well above the (b) (4)

- The SFS glide force has a direct impact on autoinjector dose accuracy and injection process time performance. The tirzepatide drug product formulation has a similar viscosity relative to the approved drug product. The tirzepatide SFS stability studies show that the break loose force and glide force remained below specification limits upon storage:
  - 5°C, 24 months (Figure 3.2.P.2.4.1.4-2)
  - 30°C, 6 months (Figure 3.2.P.2.4.1.4-2)
  - 5°C, 11 months + 30°C 4 weeks (see Section 3.2.P.8.3.1, Primary Stability)

In addition to the accelerated aging results and SFS data supporting the acceptable performance of the autoinjector, the following tirzepatide autoinjector test data using autoinjectors that are representative of the commercial product demonstrates adequate performance of the autoinjector following long-term storage at various temperatures:

- Dose accuracy, injection time, button activation, exposed needle length, and stability visual/functional testing were performed following 0-, 3-, 6-, 9-, and 12-months storage at 5°C, and a separate arm following 11-months storage at 5°C plus up to 30 days storage at 30°C, and all specifications were met with no major changes observed during the study duration (see Section 3.2.P.8.3.1, Primary Stability).
- Dose accuracy, injection time, button activation, exposed needle length, and stability visual/functional testing were performed following 0-, 1-, 3-, and 6-months, storage at 30°C and 60% RH, and all specifications were met (see Section 3.2.P.8.3.1, Primary Stability).

- Dose accuracy and visual testing were performed following a minimum of 4-hours storage at 40°C, and specifications were met. This data demonstrates that the autoinjector is dose accurate following exposure to 40°C temperature (see Section 3.2.R.2.4.1, Compliance to ISO11608-1:2014 and ISO11608-5:2012).

In addition, the approved Trulicity autoinjector real time data supports the acceptable performance of the autoinjector, the following Trulicity test data using autoinjectors that are representative of the commercial product demonstrates adequate performance of the autoinjector following long-term storage at various temperatures:

- Dose accuracy, injection time, and visual/functional testing were performed following storage under multiple conditions including routine storage (2°C - 8°C for up to 24 months), room temperature storage (30°C for up to 2 weeks), and accelerated aging conditions (25°C or 30°C for up to 6-months). All specifications were met with no major changes observed during the study duration.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Design Verification testing and provided reports are acceptable.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9.3. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☑ There are clinical studies for review
This information was obtained from the following **documents**: 2.5 Clinical Overview
2.7 Clinical Summary
2.7.6 Synopses of Individual studies

The sponsor has tabulated a list of completed and ongoing studies for T2DM for the current indications and other indications.
There are about 19 **completed studies**. The tabulated listing is provided in Table 2.7.6.1 Synopses of Individual studies on pages 6-22. The detailed individual study reports are provided in the attached appendices, within the provided links in the table.
The tabulated listing for **ongoing studies for other indications** is provided in Table 2.7.6.3 Synopses of Individual studies on pages 27-35. The detailed individual study reports are provided in the attached appendices, within the provided links in the table.

The tabulated listing for ongoing studies for proposed indications is provided in Table 2.7.6.2 Synopses of Individual studies on pages 23-26. The table is copied here below for our reference.

Table 2.7.6.2. Tabular Listing of Ongoing Clinical Studies for T2DM

Study Identifier and Proposed Countries	Primary Objective	Study Design Including Type of Control	Test and Control Drugs, Dosage Regimen, and Route of Administration	Number of Healthy Participants or Patients	Healthy Participants or Diagnosis of Patients*	Duration of Treatment
Phase 1 Studies: T2DM						
I8F-MC-GPHG Austria	To compare the effect of TZP 15 mg QW and placebo on glucagon response during hypoglycemia in patients with T2DM following 12 weeks of treatment	Single-center, 2-period, patient-/investigator-blind, randomized, crossover study MoA study	**TZP; SC QW** Dose escalation: 2.5, 5 mg; each dose for 2 weeks Followed by 10 mg for 4 weeks Maintenance dose: 15 mg **Placebo; SC QW**	Planned Enrollment: approximately 38	Male or female patients with T2DM, treated with diet and exercise, on stable dose of metformin	12 weeks
I8F-MC-GPHT China	To investigate the safety and tolerability of TZP after multiple SC doses administered to Chinese patients with T2DM	Single-center, patient-/investigator-blind, placebo-controlled, randomized, multiple-dose titration study	**Cohort 1:** **TZP; SC QW** Dose escalation: 2.5, 5, 7.5, 10 mg; each dose for 4 weeks Or **Placebo; SC QW** **Cohort 2:** **TZP; SC QW** Dose escalation: 2.5, 5, 7.5, 10, 12.5, 15 mg; each dose for 4 weeks Or **Placebo; SC QW**	Planned Enrollment: approximately 24	Chinese male or female patients with T2DM, treated with diet and exercise	**Cohort 1** 16 weeks **Cohort 2:** 24 weeks

Study Identifier and Proposed Countries	Primary Objective	Study Design Including Type of Control	Test and Control Drugs, Dosage Regimen, and Route of Administration	Number of Healthy Participants or Patients	Healthy Participants or Diagnosis of Patients*	Duration of Treatment
Phase 3 Studies: T2DM						
I8F-MC-GPHD Argentina, Belgium, Brazil, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Romania, Russian Federation, Slovakia, Spain, Turkey, and United States	To demonstrate that QW TZP (pooled cohort of 5, 10, and 15 mg) is noninferior to insulin lispro (U100) TID, when added to insulin glargine (U100), with or without metformin, for mean change in HbA1c from baseline at 52 weeks	Multicenter, open-label[a], randomized study	**TZP 5 mg; SC QW** 2.5 mg for 4 weeks Maintenance dose: 5 mg **TZP 10 mg; SC QW** Dose escalation: 2.5, 5, 7.5 mg; each dose for 4 weeks Maintenance dose: 10 mg **TZP 15 mg; SC QW** Dose escalation: 2.5, 5, 7.5, 10, 12.5 mg; each dose for 4 weeks Maintenance dose: 15 mg **Insulin lispro (U100); SC TID** Titrated per protocol defined "treat-to-target algorithm"	Planned Enrollment: 1182	Male or female patients with T2DM with inadequate glycemic control on basal insulin with or without OAMs	52 weeks
I8F-MC-GPHO Australia, China, India, South Korea	To demonstrate that QW TZP 10 and/or 15 mg is noninferior to titrated insulin glargine as measured by change from baseline in HbA1c at 40 weeks	Multicenter, open-label[a], randomized, parallel-group study	**TZP 5 mg; SC QW** 2.5-mg dose for 4 weeks Maintenance dose: 5 mg **TZP 10 mg; SC QW** Dose escalation: 2.5, 5, 7.5 mg; each dose for 4 weeks	Planned Enrollment: 956	Male or female patients with T2DM with inadequate glycemic control on metformin with or without a sulfonylurea	40 weeks

Study Identifier and Proposed Countries	Primary Objective	Study Design Including Type of Control	Test and Control Drugs, Dosage Regimen, and Route of Administration	Number of Healthy Participants or Patients	Healthy Participants or Diagnosis of Patients*	Duration of Treatment
			Maintenance dose: 10 mg **TZP 15 mg; SC QW** Dose escalation: 2.5, 5, 7.5, 10, 12.5 mg; each dose for 4 weeks Maintenance dose: 15 mg **Insulin glargine 6IU; SC QD** Titrated per protocol defined "treat-to-target algorithm"			
I8F-MC-GPGN Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, France Germany, Greece, Hungary, India, Israel, Italy, Japan, South Korea, Mexico, the Netherlands, Poland, Romania, Russian Federation, Slovakia, Spain,	To assess efficacy of TZP MTD up to 15 mg QW compared to Dula 1.5 mg QW on time to first occurrence of the composite endpoint of death from CV causes, MI, or stroke (MACE-3) when both are added to standard of care in patients with T2DM and high CV risk. Primary analysis will be an assessment of NI of TZP to Dula for MACE-3. After	Multicenter, double-blind, active comparator, randomized, event-driven, parallel-group study	**TZP 15 mg; SC QW** Dose escalation to MTD: 2.5, 5, 7.5, 10, 12.5 mg; each dose for 4 weeks Maintenance dose: 15 mg or highest maintenance dose tolerated by the patient. **Dula 1.5 mg; SC QW** Dula will be dispensed every 4 weeks during the dose-escalation period, following a sham dose-escalation schedule to match the TZP dose escalation	Planned Enrollment: 12,500	Male or female patients with T2DM with established CV disease and elevated risk for MACE	54 months. Visits to continue until at least 1615 patients experience 1 or more components of the CEC-confirmed MACE-3 endpoint. The estimated average follow-up duration is expected to be 48 months.

Study Identifier and Proposed Countries	Primary Objective	Study Design Including Type of Control	Test and Control Drugs, Dosage Regimen, and Route of Administration	Number of Healthy Participants or Patients	Healthy Participants or Diagnosis of Patients*	Duration of Treatment
Sweden, Taiwan, Turkey, Ukraine, United Kingdom, and United States	establishing NI, superiority of TZP compared to Dula for MACE-3 will be evaluated.					
I8F-MC-GPGN *Diabetic Retinopathy addendum* Argentina, Australia, Brazil, Canada, Germany, Greece, Hungary, India, Israel, Mexico, Russia, Spain, Ukraine, and United States	To compare the effect of TZP dose up to 15 mg QW with Dula 1.5 mg QW on DR progression	Same as above	Same as above	Planned Enrollment: approximately 700	Patients eligible for the main study and who agree to participate in this substudy, which requires periodic visual acuity testing and dilated fundoscopic exams, and with any evidence of DR or macular edema in either eye according to the baseline ophthalmologic investigation or the patient is at high risk for developing or recurring or progressing DR	Same as above

Abbreviations: CEC = clinical endpoint committee; CV = cardiovascular; DR = diabetic retinopathy; Dula = dulaglutide; HbA1c = glycosylated hemoglobin A1c; OAM = oral antihyperglycemic medication; MACE-3 = major adverse cardiovascular events composite of myocardial infarction, stroke, or death from cardiovascular causes; MoA = mechanism of action; MI = myocardial infarction; MTD = maximally tolerated dose; NI = noninferiority; QD = once daily; QW = once weekly; SC = subcutaneous; TID = three times a day; TZP = tirzepatide; T2DM = type 2 diabetes mellitus.

[a] TZP dose is blinded to sponsor.

* All studies are conducted in adult healthy participants or patients.

Reviewer Comment

Based on the studies cited above, there were no specific adverse events that could be directly linked to the auto-injector. The Sponsor stated that the to-be-marketed auto-injector were used in the study. No device specific comments were found in the protocol. No adverse events were reported that would indicate an issue with the device.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐

Human Factors deferred to DMEPA	☑

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

12.2. Quality Systems Documentation Review

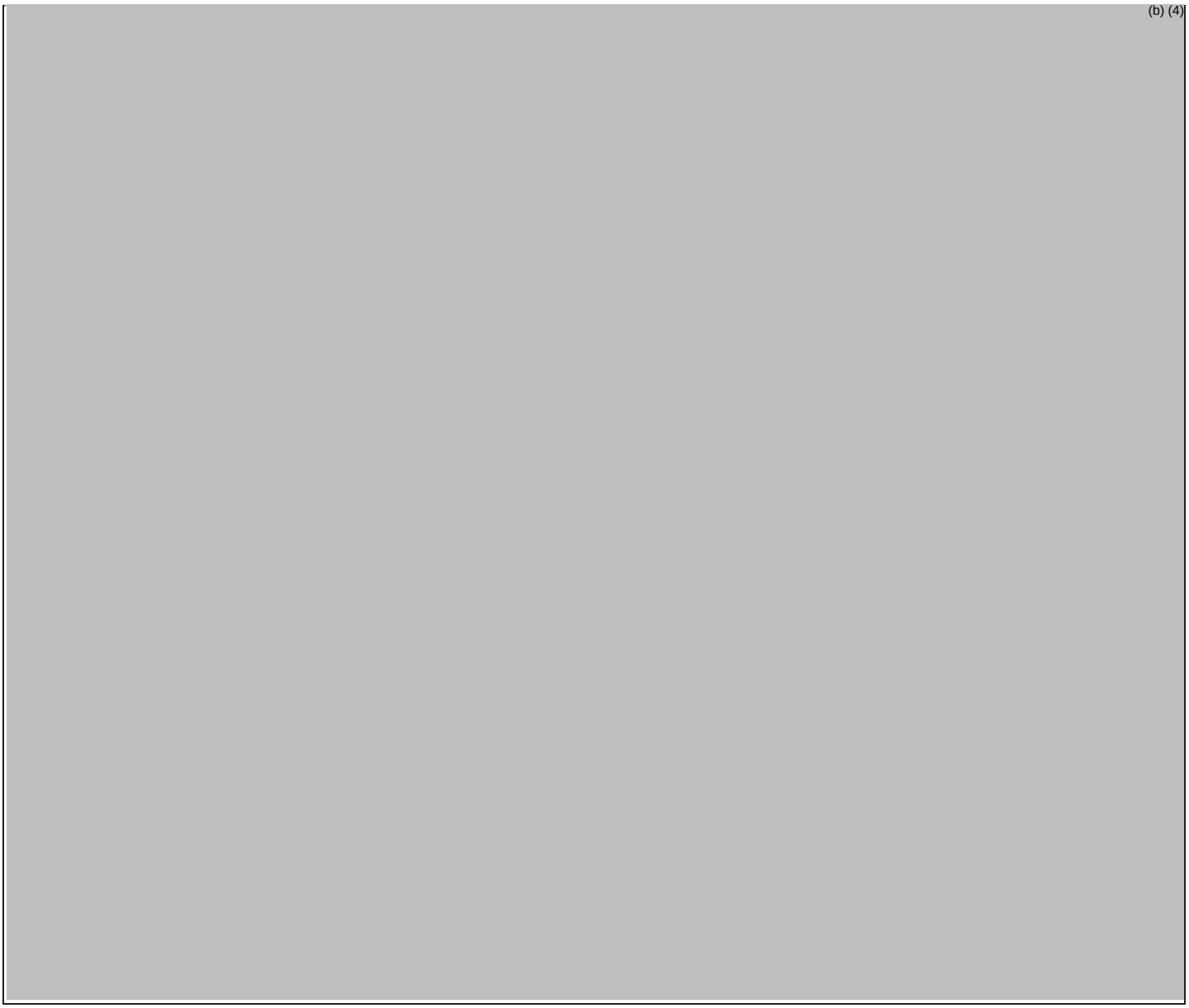
CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)



The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer Comments

The Sponsor provided a full description of the drug and device manufacturing processes. This is acceptable.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

12.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:
☐ Device QSR-based
☑ Drug cGMP-Based Streamline –
☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Lilly PDS	(b) (4) [redacted]

		(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s):Lilly PDS	
21 CFR 820.50 Summary of Purchasing Controls	Firm(s):Lilly PDS	

		(b) (4)
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Lilly PDS	
21 CFR 820.170 Summary of Installation	Firm(s):	
21 CFR 820.200 Summary Servicing	Firm(s):	
Subpart F – Identification and Traceability	Firm(s):	
Subpart G – Production and Process Controls	Firm(s):	
Subpart H – Acceptance Activities	Firm(s):	
Subpart I – Nonconforming Product	Firm(s):	
Subpart K – Labeling and Packaging Controls	Firm(s):	
Subpart L – Handling, Storage, Distribution	Firm(s):	
Subpart M – Records	Firm(s):	
Subpart O – Statistical Techniques	Firm(s):	

Reviewer Comments

The Quality System (QS) regulation (21 CFR 820) is the base streamlined operating system implemented at Lilly IDM and DDCS and, therefore, is compliant with all QS elements of 21 CFR 820 including management controls, design controls, purchasing controls, and corrective action and preventive action (CAPA) (installation and servicing are not applicable to the product). In accordance with the streamlined approach, PDS is compliant with applicable requirements of the drug cGMPs (21 CFR 210/211).See below for a review of the CAPA system.

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

(b) (4)

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Yes
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	Yes
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	Yes
Investigations into the cause of nonconformities relating to product, processes, and the quality system	Yes
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Yes
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Yes
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	Yes
Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Yes
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Yes

Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	Yes
Requires documentation of all CAPA activities	Yes

Reviewer Comments

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

(b) (4)

(b) (4)

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

2.1. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

3. APPENDIX A (INFORMATION REQUESTS)

3.1. Interactive Information Requests

3.1.1. Interactive Information Requests sent on 10/25/2021

In Section 3.2.R Medical Device of your submission, you have described the device portion of the tirzepatide autoinjector. However, some information is missing and/or not clearly stated. Please provide additional information to clarify the following concerns:

a) *In Section 3.2.R.2.8, you have listed facilities associated with the manufacture of combination product. You have listed the facilities DDCS , IDM, IPM, IDAP etc as organizations responsible for the final finished combination product . Besides you have stated that Lilly France Fegersheim and Lilly Italy Sesto sites are also responsible for assembly of the final finished combination product. It is unclear from your statements which facility /site is specifically responsible for manufacturing of the auto injector and assembly of the final finished combination product. Please clearly state what each facility is responsible for and update the 356h form accordingly, if required .*
b) *In Section 3.2.R.2.2, you have provided a description of your device. However some information is missing. Please provide the following :-*
    i. *a detailed description of the device, including all features and/or functionalities including engineering drawings, schematics and descriptions of the individual device constituent components.*

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/

NOWRIN S KAKON
01/31/2022 05:48:13 PM
Entering on behalf of CDRH

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 1/19/2022 **Date consulted:** 9/19/2021

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Diabetes, Lipid Disorders, and Obesity (DDLDO)

Drug: Mounjaro (tirzepatide) Injection, for subcutaneous use

NDA: 215866

Applicant: Eli Lilly and Company

Subject: Pregnancy and Lactation Labeling

Proposed Indication: A dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP 1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 215866
- DDLDO consult form for DPMH, DARRTS Reference ID 4861517

Consult Question:

The review team requests DPMH's input on the labeling to be consistent with the Pregnancy and Lactation Labeling Rule.

INTRODUCTION AND BACKGROUND

On September 15, 2021, the applicant (Eli Lilly and Company) submitted an original NDA for Mounjaro (tirzepatide) Injection, NDA 215866, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The Division of Diabetes, Lipid Disorders, and Obesity (DDLDO) consulted the Division of Pediatric and Maternal Health (DPMH) on September 17, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Tirzepatide Injection is a once weekly drug that the sponsor proposes has agonist effects on both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP 1) receptor that integrates the actions of both incretins into a single product.
- On February 19, 2021, the Agency informed the applicant that the Proprietary Name Mounjaro was conditionally acceptable.
- On May 24, 2021, the applicant informed the Agency on using a Material Threat Medical Countermeasure Priority Review Voucher for this application.
- On September 15, 2021, the applicant submitted NDA 215866 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- This submission is in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.
- On September 17, 2021, DDLDO consulted DPMH to assist with development of subsections 8.1 and 8.2 of the product's labeling.

Drug Characteristics

Tirzepatide Characteristics[1]

Drug Class	(b) (4)
Mechanism of action	
Molecular weight	4813 Dalton
Half-life	5 days
Protein Binding	99%
Bioavailability	80%

Tirzepatide is a long-acting, (b) (4) selective, dual GIP/GLP 1 receptor agonist, administered once weekly. It is a 39-amino acid peptide with a C20 fatty diacid moiety that enables albumin

[1] Based on applicant proposed labeling and discussion with DDLDO review team.

binding and prolongs the half-life. It is a subcutaneous injection in the abdomen, thigh, or upper arm.

- Start at 2.5 mg once weekly. After 4 weeks, increase the dose to 5 mg once weekly.
- If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose, up to 15 mg.

There is no information regarding tirzepatide or GIP or GLP1 drug classes that suggests that these drugs will behave differently during pregnancy. For a more information on GIP and GLP-1, the reader is referred to Appendix A.

Serious adverse reactions[2]

- Pancreatitis
- Hypoglycemia
- Hypersensitivity
- Acute kidney injury
- Severe gastrointestinal reaction
- Medullary thyroid carcinoma
- Diabetic retinopathy

PREGNANCY

Pregnancy and Type II Diabetics[3]

Pregestational diabetes mellitus complicates 1-2% of all pregnancies and accounts for 13 to 21% of diabetes in pregnancy (remainder are due to gestational diabetes).[4] Poorly controlled pregestational diabetes increases the risk of adverse maternal and fetal outcomes including preeclampsia, preterm delivery, macrosomia, congenital malformations, and perinatal mortality. Maternal glycemic control before and during pregnancy, however, reduces the risk of adverse outcomes. Insulin is the preferred pharmacotherapy for pregnant women with pregestational diabetes.[5]

REVIEW

Nonclinical Experience

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.45-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights (b) (4) In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.23-fold the MRHD) during organogenesis, pharmacologically-mediated effects on the gastrointestinal system resulting in

[2] Based on applicant proposed labeling and discussion with the Clinical Review Team. 11/12/2021

[3] DPMH review of BLA (b) (4) on March 22, 2021. DARRTS Reference ID 4766051.

[4] https://www.uptodate.com/contents/pregestational-preexisting-diabetes-preconception-counseling-evaluation-and-management?search=pregestational%20diabetes&topicRef=4806&source=see_link

[5] Maka S. Hedrington & Stephen N. Davis (2017) The care of pregestational and gestational diabetes and drug metabolism considerations, Expert Opinion on Drug Metabolism & Toxicology, 13:10, 1029-1038.

maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg.

In pre-and post-natal study in rats, F1 pups from F0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and postnatal day 56 for females. (b) (4)

The reader is referred to full Pharmacology/Toxicology report by Federica Basso, Ph.D. and Elena Braithwaite, Ph.D.

Review of Clinical Trials

There have been seven pregnancies in the clinical trials. Six pregnancies were exposed during pregnancy. One was a paternal exposure. All maternal exposures occurred during the first trimester. The reader is referred to Appendix A for applicant's table of exposed pregnancy outcomes in the clinical trials.

- One had an elective termination.
- One ended in spontaneous abortion.
- One resulted in live birth in "good condition."
- Three have no pregnancy outcomes reported.

Review of Literature

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,[6] ReproTox,[7] Shepard's)[8] regarding tirzepatide use in pregnancy.

- There are no published data on the use of tirzepatide in pregnancy.

Reviewer comment:

Tirzepatide is being reviewed for use in the treatment of Type 2 Diabetes Mellitus. There is no information about the use of tirzepatide for the treatment of other conditions at this time. The available human data regarding the use of tirzepatide in pregnancy are insufficient to assess a drug-related risk of congenital malformations, miscarriage, or adverse maternal or fetal outcomes. Based on animal studies, tirzepatide may cause fetal harm. Increased incidences of external, visceral, and skeletal malformations and increased incidences of visceral and skeletal developmental variations were observed in rats at maternal exposures less than the human clinical dose. Although these findings coincide with tirzepatide exposure, they are presumably due to maternal toxicity caused by the pharmacological activity of tirzepatide (decreased body weight and reduced weight gain observed in pregnant dams). This information was confirmed in discussion with the Pharmacology Toxicology Review Team. The reader is referred to the

[6] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 8/30/2021.
[7] ReproTox Website: www.Reprotox.org. REPROTOX was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 8/30/21.
[8] 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 8/30/2021.

Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION

(b) (4)

The reader is referred to full Pharmacology/Toxicology report by Federica Basso, Ph.D. and Elena Braithwaite, Ph.D.

DPMH Review of Literature
DPMH performed a search of published literature using PubMed, Embase, and reference sites (Micromedex,[9] LactMed,[10] Brigg's,[11] or Hales[12]) regarding tirzepatide use in lactation, and no information was found.

Information about tirzepatide is not found in LactMed,[10] Brigg's,[11] or Hales.[12]

In humans, GLP-1 is present in milk fat and is higher in hindmilk than foremilk. The presence of GLP-1 and other hormones, leptin and peptide YY, in human milk may be important in infant appetite and growth regulation.[13]

Reviewer comment:
There are no data on the presence of tirzepatide in human or animal milk and the effect of tirzepatide on the breastfed infant and on milk production. Although tirzepatide has a molecular weight of greater than 4000 Daltons and would not be expected to be present in milk based on its molecular weight, other GLP-1 receptors that have similar molecular weights to tirzepatide,

[9] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 9/30/2021.
[10] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 9/30/21.
[11] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 9/30/2021.
[12] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 9/30/2021.
[13] Schueler J, et al. Presence and Dynamics of Leptin, GLP-1, and PYY in Human Breast Milk at Early Postpartum. Obesity (2013) 21, 1451-1458. doi:10.1002/oby.20345

including semaglutide (molecular weight 4113.58 Daltons),[14] exenatide (molecular weight 4186.6 Daltons),[15] liraglutide (molecular weight 3751.2 Daltons),[16] and lixisenatide (4858.5 Daltons),[17] are present in rat milk. GLP-1 is naturally present in milk.[13] Since tirzepatide mimics the action of GLP-1, and since other GLP-1 agonists are present in animal milk, it is likely that tirzepatide will be present in human milk. Although tirzepatide is likely to be present in human milk, it is a peptide and will likely be degraded in the infant's gastrointestinal (GI) tract.

The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

The reader is referred to full Pharmacology/Toxicology report by Federica Basso, Ph.D. and Elena Braithwaite, Ph.D.

DPMH Review of Literature

DPMH performed a search of published literature using PubMed, Embase, and the reference sites regarding adverse effect of tirzepatide on fertility. No information was found.

[14] Approved labeling for Ozempic subcutaneous solution, NDA 209637, last updated 4/12/2021. Drugs@FDA. Accessed 11/17/2021. https://www.accessdata fda.gov/drugsatfda_docs/label/2021/209637s008lbl.pdf
[15] Approved labeling for Byetta subcutabous injection, NDA 21773, last updated 11/4/2021. Drugs@FDA. Accessed 11/17/2021. https://www.accessdata fda.gov/drugsatfda_docs/label/2021/021773s045lbl.pdf
[16] Approved labeling for Saxenda subcutaneous solution, NDA 206321, last updated 12/4/2020. Drugs@FDA. Accessed 11/17/2021. https://www.accessdata fda.gov/drugsatfda_docs/label/2020/206321s012s013s014lbl.pdf
[17] Approved labeling for Adlyxin subcutaneous solution, BLA 208471, last updated 7/20/2021. Drugs@FDA. Accessed 11/17/2021. https://www.accessdata fda.gov/drugsatfda_docs/label/2021/208471s004lbl.pdf

Reviewer comment:
There are no data regarding the effect of tirzepatide on human fertility. Animal reproductive studies did not show tirzepatide adversely effecting fertility in rats. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

DISCUSSION AND CONCLUSIONS

(b) (4)

Current guidelines recommend insulin for the treatment of type II diabetes in pregnancy.[18] Therefore, tirzepatide is not likely to be recommended for use routinely during pregnancy. However, inadvertent exposure may occur particularity during early pregnancy. There are insufficient data regarding tirzepatide use in pregnancy currently, therefore, DPMH recommends a postmarking descriptive pregnancy safety study to collect this information.

Lactation

There are no data on the presence of tirzepatide in human or animal milk, the effects of tirzepatide on the breastfed infant and the effects on milk production.

(b) (4)

DPMH recommends a postmarketing clinical lactation study because there are no human data regarding the use of tirzepatide during lactation and since the drug will be used in females of reproductive potential.

(b) (4)

[18] ACOG Practice Bulletin No. 201: Pregestational Diabetes Mellitus. Obstetrics & Gynecology 2018:132(6): e228-e248.

(b) (4)

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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APPENDIX A. GIP and GLP-1[19]

Gastric inhibitory polypeptide (or gastric inhibitory peptide or glucose-dependent insulinotropic polypeptide (GIP)) and glucagon-like peptide (GLP-1) are the two primary incretin hormones secreted from the pancreatic β cells.

- GIP is synthesized by K cells that are found in the mucosa of the duodenum and the jejunum of the gastrointestinal tract.
- GLP-1 is produced and secreted by intestinal enteroendocrine L-cells and certain neurons within the nucleus of the solitary tract in the brainstem upon food consumption.

GIP and GLP-1 exert their effects by binding to their specific receptors, the GIP receptor and the GLP-1 receptors, which belong to the G-protein coupled receptor family. Binding activates and increases the level of intracellular cyclic adenosine monophosphate in the pancreatic b cells, thereby stimulating insulin secretion glucose-dependently.

GIP and GLP-1 play critical roles in various biological process in various tissues including pancreases, fat, bone, and the brain. The reader is referred to Figure 1.

- GIP and GLP-1 inhibit apoptosis of the pancreatic beta cells and promote their proliferation thus expanding pancreatic b cell mass.
- GIP enhance postprandial glucagon response and GLP suppress it.
- GLP-1 inhibit gastric emptying.
- GIP, but not GLP-1, stimulates fat accumulation.
- GIP promotes bone formation while GLP-1 inhibits bone absorption.
- In the brain, both GIP and GLP-1 influence hippocampal memory formation and regulate appetite and satiety.

Figure 1. The effects of GIP and GLP-1[20]

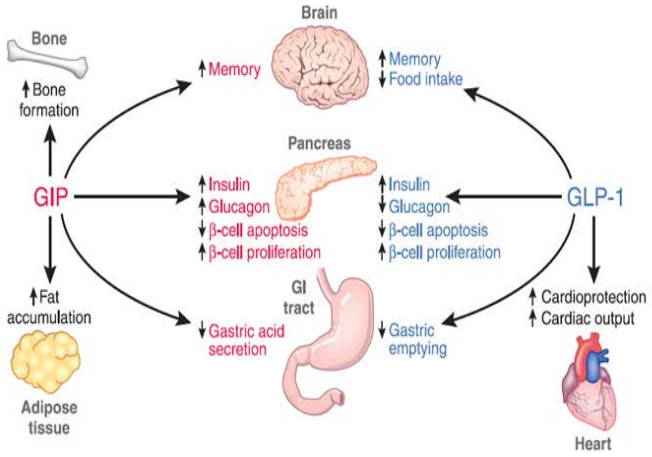

Figure 2 | Pancreatic and exopancreatic function of glucose-dependent insulinotropic polypepide (GIP) and glucagon-like peptide (GLP)-1. GIP acts directly on the endocrine pancreas, bone, fat, gastrointestinal (GI) tract and brain. GLP-1 acts directly on the endocrine pancreas, gastrointestinal tract, heart and brain.

[19] Senino Y, et al. GIP and GLP-1, the two incretin hormones: similarities and differences. Journals of Diabetes Investigation 2010;1(1): 8-23.

APPENDIX B. Pregnancy Outcomes from the Clinical Trials[20]

Table 2.7.4.121. List of Pregnancies Reported in Completed Tirzepatide Clinical Studies

Study Patient ID	Age of Mother (years)	Study Drug	Estimated Period of Exposure (weeks)	Pertinent Clinical Information	Maternal Complications	Fetal Outcome
(b) (6)	28	TZP 5 mg	7.9	• Contraception: cyproterone/ ethinylestradiol • Preexisting condition of polycystic ovaries	None reported	Good condition
	28	Sema 1 mg	9.1	• Contraception: drospirenone and ethinylestradiol	No report	No report
	35	TZP 15 mg	5.6	• Contraception: ethinylestradiol/ norelgestromin	No report	No report
	27	TZP 5 mg	8.9	• Contraception: drospirenone and ethinylestradiol • Medical history of Cesarean section	No report	No report
	39	TZP 10 mg	16.3	• Contraception: birth control pills (unspecified)	None reported	No report
	41	TZP 10 mg	5.1	• Contraception: Male or female condom with spermicide • Medical history of miscarriages, infertility due to excision of fallopian tube, postoperative adhesions, pregnancy (2014), gestational diabetes.	Spontaneous abortion	--
	26	TZP 5 mg	1.7	• Negative medical history specific to pregnancy • Previously used drospirenone and ethinylestradiol and during screening for study	Elective termination	--
				• Study OC was her contraception during active dosing phase • Did not resume previous OC contraception after end of study dosing phase • Used only condom without an additional effective method as required per protocol, during final follow-up period when no longer on any OC.		

Abbreviations: ID = identification; OC = oral contraception; Sema = semaglutide; TZP = tirzepatide.

[a] Male patient reported pregnancy of partner.

Source: GPGK, GPGL, GPGH, GPGR narratives

[20] Applicant's Table 2.7.4.121. from "Clinical Safety Summary."

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/s/

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