Report on the Deliberation Results

December 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Zepbound Subcutaneous Injection 2.5 mg Ateos Zepbound Subcutaneous Injection 5 mg Ateos Zepbound Subcutaneous Injection 7.5 mg Ateos Zepbound Subcutaneous Injection 10 mg Ateos Zepbound Subcutaneous Injection 12.5 mg Ateos Zepbound Subcutaneous Injection 15 mg Ateos
Non-proprietary Name	Tirzepatide (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	February 9, 2024

Results of Deliberation

In its meeting held on December 2, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until September 25, 2030). The drug product is classified as a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 14, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Zepbound Subcutaneous Injection 2.5 mg Ateos Zepbound Subcutaneous Injection 5 mg Ateos Zepbound Subcutaneous Injection 7.5 mg Ateos Zepbound Subcutaneous Injection 10 mg Ateos Zepbound Subcutaneous Injection 12.5 mg Ateos Zepbound Subcutaneous Injection 15 mg Ateos
Non-proprietary Name	Tirzepatide
Applicant	Eli Lilly Japan K.K.
Date of Application	February 9, 2024
Dosage Form/Strength	A solution for injection in a kit (0.5 mL): Each kit contains 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, (10) Other drugs (during the re-examination period)
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of obesity, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition.

Indication

Obesity

Zepbound should be used only in patients with any of hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not responded sufficiently to diet therapy and exercise therapy, and meet the following conditions:

- BMI of ≥27 kg/m^2 in the presence of at least 2 obesity-related health disorders
- BMI of ≥35 kg/m^2

Dosage and Administration

The usual starting dosage for adults is 2.5 mg of tirzepatide injected subcutaneously once weekly. The dose should be increased in 2.5 mg increments every 4 weeks, up to 10 mg once weekly.

The dose may be adjusted depending on the patient's condition. It may be reduced to 5 mg once weekly or increased in 2.5 mg increments at intervals of at least 4 weeks, up to 15 mg once weekly.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 13, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Zepbound Subcutaneous Injection 2.5 mg Ateos Zepbound Subcutaneous Injection 5 mg Ateos Zepbound Subcutaneous Injection 7.5 mg Ateos Zepbound Subcutaneous Injection 10 mg Ateos Zepbound Subcutaneous Injection 12.5 mg Ateos Zepbound Subcutaneous Injection 15 mg Ateos
Non-proprietary Name	Tirzepatide
Applicant	Eli Lilly Japan K.K.
Date of Application	February 9, 2024
Dosage Form/Strength	A solution for injection in a kit (0.5 mL): Each kit contains 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide

Proposed Indication

Obesity

Zepbound should be used only in patients with any of glucose tolerance impaired (such as type 2 diabetes mellitus or impaired glucose tolerance), dyslipidaemia, or nonalcoholic fatty liver disease who have not responded sufficiently to diet therapy and exercise therapy and meet the following conditions:

- BMI of ≥27 kg/m^2 in the presence of at least 2 obesity-related health disorders
- BMI of ≥35 kg/m^2

Proposed Dosage and Administration

The usual adult dosage is a subcutaneous injection at a maintenance dose of 10 mg of tirzepatide once weekly. The treatment is initiated at 2.5 mg once weekly, with increments of 2.5 mg every 4 weeks until reaching 10 mg once weekly.

The dose may be adjusted depending on the patient's condition. If patients have an inadequate response to 10 mg once weekly, the dose may be increased in 2.5 mg increments at intervals of at least 4 weeks. The maximum dose is 15 mg once weekly.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Zepbound Subcutaneous Injection (hereinafter referred to as Zepbound) is a once-weekly subcutaneous injection containing tirzepatide as the active ingredient, which was discovered by Eli Lilly and Company (the US) as a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. In Japan, a drug product containing the same active ingredient, Mounjaro Subcutaneous Injection 2.5 mg Ateos, Mounjaro Subcutaneous Injection 5 mg Ateos, Mounjaro Subcutaneous Injection 7.5 mg Ateos, Mounjaro Subcutaneous Injection 10 mg Ateos, Mounjaro Subcutaneous Injection 12.5 mg Ateos, and Mounjaro Subcutaneous Injection 15 mg Ateos (Mounjaro Subcutaneous Injection), was approved in September 2022 for the indication of "type 2 diabetes mellitus."

Tirzepatide is expected to lower body weight through mechanisms such as increased energy expenditure due to enhanced lipid metabolism in adipocytes via GIP and GLP-1 receptors, as well as appetite regulation in the central nervous system. In light of this potential, the applicant initiated clinical development of tirzepatide in Japan in 2019 for the present application. The applicant has now submitted the application for marketing approval, asserting that the efficacy and safety of tirzepatide for obesity have been confirmed from clinical study results and other data.

Tirzepatide has been approved for weight management in obese or overweight individuals in the US (November 2023) and Europe (December 2023). As of August 2024, tirzepatide has been approved in ≥40 countries and regions, including the US and Europe.

2. Quality and Outline of the Review Conducted by PMDA

The present application relates to a new indication and a new dosage. Since the drug substance and drug product are identical to the approved drug product, Mounjaro Subcutaneous Injection, except for the labeling, the data related to quality have not been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

For the present application, primary pharmacodynamic studies included *in vitro* evaluations of glucose uptake capacity and lipid metabolism activity in adipocytes, as well as *in vivo* evaluations of c-Fos expression in the mouse brain and increased energy expenditure in mice. The main study results are presented below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinity to GIP receptor in adipocytes (CTD 4.2.1.1-1)

Adipose tissue collected from human subcutaneous tissue or mouse epididymis was treated with fluorescence-labeled tirzepatide (10-100 nmol/L) to observe under a confocal microscope. The fluorescent signal was detected on the adipocyte surface.

3.1.1.2 Activation of GIP receptor in adipocytes (CTD 4.2.1.1-1)

Human subcutaneous adipocytes were treated with tirzepatide, human GIP, or semaglutide (each at 1 fmol/L to 100 nmol/L). Intracellular cyclic adenosine monophosphate (cAMP) levels at each

concentration were measured by immunofluorescence staining with anti-cAMP antibody. Additionally, human subcutaneous adipocytes were co-treated with tirzepatide (10 nmol/L) and a GIP receptor antagonist (GIP [3-30]) (0.1 pmol/L to 1 nmol/L), and intracellular cAMP levels were measured using the same method.

Tirzepatide and human GIP increased intracellular cAMP levels in a concentration-dependent manner, with half maximal effective concentration (EC_{50}) values of 0.045 nmol/L and 3.0 nmol/L, respectively. In contrast, semaglutide did not increase intracellular cAMP levels. When adipocytes were co-treated with tirzepatide and GIP (3-30), the tirzepatide-induced increase in cAMP levels was attenuated in a concentration-dependent manner in response to GIP (3-30).

3.1.1.3 Glucose uptake in adipocytes (CTD 4.2.1.1-1)

Human subcutaneous adipocytes were incubated overnight in insulin-free medium, followed by treatment with tirzepatide, human GIP, or insulin (each at approximately 10 fmol/L to 100 nmol/L), or co-treatment with insulin (approximately 100 fmol/L to 100 nmol/L) and tirzepatide (10 nmol/L). Cells were then incubated with ^{14}C-labeled glucose, and intracellular radioactivity was measured to evaluate glucose uptake.

Tirzepatide, human GIP, and insulin increased glucose uptake in a concentration-dependent manner, with EC_{50} values of 0.28 nmol/L, 1.7 nmol/L, and 13.3 nmol/L, respectively. At the maximum concentration (100 nmol/L), intracellular radioactivity levels were 1694.9 cpm for tirzepatide, 1138.4 cpm for human GIP, and 2560.9 cpm for insulin. When adipocytes were co-treated with tirzepatide and insulin, glucose uptake increased compared to single treatment with either agent. The EC_{50} value for insulin when co-treated with tirzepatide was 13.0 nmol/L, and the intracellular radioactivity level when co-treated with tirzepatide (10 nmol/L) and insulin at the maximum concentration (100 nmol/L) was 3733.8 cpm.

3.1.1.4 Lipid metabolism in adipocytes (CTD 4.2.1.1-1)

3.1.1.4.1 LPL activity in adipocytes

Human subcutaneous adipocytes were incubated in fatty acid-free medium with glucose (5.5 mmol/L), followed by treatment with tirzepatide, human GIP, or insulin (10 pmol/L to 100 nmol/L). A lipoprotein lipase (LPL) substrate that fluoresces upon decomposition was then added to the medium, and LPL activity was assessed by measuring the fluorescence intensity generated by substrate degradation. Tirzepatide, human GIP, and insulin increased LPL activity in a concentration-dependent manner, with EC_{50} values of 0.19 nmol/L, 0.58 nmol/L, and 0.81 nmol/L, respectively.

3.1.1.4.2 Fatty acid uptake in adipocytes

Human subcutaneous adipocytes were treated with tirzepatide, human GIP, or insulin (approximately 1 fmol/L to 100 nmol/L) and incubated with fluorescence-labeled fatty acids. Intracellular fluorescence intensity was then measured to assess fatty acid uptake. Tirzepatide, human GIP, and insulin increased fatty acid uptake in a concentration-dependent manner, with EC_{50} values of 1.4 nmol/L, 2.6 nmol/L, and 14.7 nmol/L, respectively.

3.1.1.4.3 Fatty acid degradation in adipocytes

Human subcutaneous adipocytes were incubated in fatty acid-free medium, followed by treatment with tirzepatide, human GIP, or insulin (approximately 1 pmol/L to 100 nmol/L). Fatty acid degradation was assessed by converting free glycerol in the medium to quinoneimine and measuring its absorbance. Human subcutaneous adipocytes were co-treated with tirzepatide (10 nmol/L) and insulin (approximately 1 pmol/L to 300 nmol/L), and fatty acid degradation was evaluated using the same method.

Tirzepatide and human GIP increased free glycerol levels in a concentration-dependent manner, with EC_{50} values of 0.11 nmol/L and 3.0 nmol/L, respectively. In contrast, insulin decreased free glycerol levels in a concentration-dependent manner, with a half maximal inhibitory concentration (IC_{50}) value of 0.49 nmol/L. When adipocytes were co-treated with tirzepatide and insulin, the increase in free glycerol levels observed with tirzepatide alone decreased in an insulin concentration-dependent manner. When insulin was simultaneously added at a concentration of approximately ≥1 nmol/L, the increase in free glycerol levels induced by tirzepatide was no longer observed (IC_{50} value, 0.68 nmol/L).

3.1.2 *In vivo* studies

3.1.2.1 Brain distribution of tirzepatide in mice (CTD 4.2.1.1-2)

Male C57BL/6 mice (9-10 weeks old, 6/group) received a single subcutaneous dose of fluorescent-labeled tirzepatide (30 nmol/kg) or vehicle.[1)] The brains were excised 2 hours post-dose. Fluorescence microscopy revealed no detectable fluorescent signals in the vehicle group. In contrast, the tirzepatide-treated group exhibited fluorescent signals in the organum vasculosum of the lamina terminalis, subfornical organ, paraventricular nucleus of the hypothalamus, arcuate nucleus of the hypothalamus, median eminence, nucleus of the solitary tract, and area postrema.

3.1.2.2 c-Fos expression in mouse brain (CTD 4.2.1.1-3)

Male C57BL/6 mice (9-10 weeks old, 8/group) received a single subcutaneous dose of tirzepatide (30 nmol/kg) or vehicle.[1)] The brains were excised 2 hours post-dose. The excised brains were subjected to immunofluorescence staining using an anti-c-Fos antibody to subsequently examine via light-sheet microscopy. The results showed an increased number of c-Fos-positive cells in the lateral hypothalamic area, central nucleus of the amygdala, pedunculopontine tegmental nucleus, nucleus of the solitary tract, dorsal motor nucleus of the vagus, and area postrema in the tirzepatide group compared to the vehicle group.

3.1.2.3 Effects on feeding behavior in mice (CTD 4.2.1.1-4)

Male C57BL/6 diet-induced obesity (DIO) mice (22 weeks old, 6/8 per group) received once-daily subcutaneous doses of tirzepatide (1, 3, 10, or 30 nmol/kg) or vehicle[2)] for 19 days. Table 1 shows the percentage change in body weight on Day 19 relative to Day 0 and cumulative food intake from Day 0 to Day 19, indicated a dose-dependent reduction in body weight and cumulative food intake in the tirzepatide groups. In all tirzepatide groups, both the number of feeding episodes per day and the amount of food consumed per feeding episode were lower than those in the vehicle group from Day 1 to Day

1) 40 mmol/L Tris buffer containing 0.02% polysorbate 80 (pH 8.0)
2) 40 mmol/L Tris buffer (pH 8.0)

10, with the greatest difference observed around Day 3. By Day 13 and thereafter, these parameters were comparable between the tirzepatide and the vehicle group.

Table 1. Percentage change in body weight on Day 19 relative to Day 0 and cumulative food intake from Day 0 to Day 19

Parameter	Dose of tirzepatide (nmol/kg)				
	0	1	3	10	30
Body weight change (%)	2.95 ± 0.88	−6.53 ± 2.09	−12.99 ± 0.52	−17.24 ± 1.74	−24.13 ± 2.83
Cumulative food intake (g)	41.56 ± 1.08	33.86 ± 2.64	29.20 ± 1.34	24.32 ± 1.45	19.43 ± 1.54

Mean ± standard error (SE)

3.1.2.4 Effects on energy expenditure in a caloric restriction mouse model (CTD 4.2.1.1-6)

Male C57BL/6 DIO mice (7-8 months old, 6/group) were provided with half of their normal daily food intake measured under ad libitum conditions. They received once-daily subcutaneous doses of tirzepatide (3 nmol/kg), semaglutide (3 nmol/kg), or vehicle[1)] for 14 days. A pair-fed group was included, in which food intake was restricted to match that of the tirzepatide group, and observations were conducted for 14 days. Table 2 shows food intake, percentage change in body weight from Day 0, energy expenditure, and fat oxidation evaluated on Days 0 (baseline), 3, 7, 11, and 14.

Table 2. Time course of food intake, percentage change in body weight, energy expenditure, and fat oxidation

Parameter	Time	Tirzepatide	Semaglutide	Pair-fed	Vehicle
Food intake (kcal/day)	Day 0	12.9 ± 0.38	13.2 ± 0.34	12.4 ± 0.35	12.3 ± 1.19
	Day 3	2.5 ± 0.59	5.6 ± 0.86	2.7 ± 0.08	6.5 ± 0.08
	Day 7	6.0 ± 0.52	6.5 ± 0.07	6.0 ± 0.00	6.5 ± 0.08
	Day 11	6.5 ± 0.07	6.5 ± 0.08	6.5 ± 0.08	6.5 ± 0.08
	Day 14	6.5 ± 0.08	6.6 ± 0.09	6.6 ± 0.09	6.5 ± 0.08
Change in body weight (%)	Day 3	−9.8 ± 0.69	−8.9 ± 0.77	−8.0 ± 0.47	−5.6 ± 0.88
	Day 7	−16.2 ± 1.35	−13.4 ± 0.75	−13.1 ± 0.50	−10.4 ± 0.72
	Day 11	−20.4 ± 1.10	−17.6 ± 1.13	−16.0 ± 0.48	−13.3 ± 0.96
	Day 14	−22.4 ± 1.26	−20.0 ± 1.34	−17.4 ± 0.61	−15.2 ± 1.15
Energy expenditure (kcal/kg/day)	Day 0	263.2 ± 7.09	253.2 ± 5.24	248.4 ± 5.30	246.5 ± 2.87[a)]
	Day 3	246.0 ± 7.15	235.5 ± 4.29	224.7 ± 10.31	220.3 ± 5.04[a)]
	Day 7	283.4 ± 8.40	250.6 ± 10.19	228.3 ± 12.84	217.5 ± 6.65[a)]
	Day 11	261.5 ± 11.70	230.8 ± 6.58	230.6 ± 12.35	212.8 ± 7.62[a)]
	Day 14	248.9 ± 15.18	238.3 ± 10.11	243.1 ± 16.52	215.3 ± 8.03[a)]
Fat oxidation (kcal/kg/day)	Day 0	104.9 ± 7.28	90.5 ± 9.55	92.9 ± 16.74	91.2 ± 14.04
	Day 3	178.3 ± 9.12	141.8 ± 15.18	121.0 ± 12.08	115.4 ± 13.60
	Day 7	168.2 ± 9.44	128.3 ± 20.76	90.8 ± 15.55	110.7 ± 13.31
	Day 11	136.9 ± 17.58	100.7 ± 19.06	106.3 ± 16.88	100.8 ± 14.27
	Day 14	123.4 ± 16.59	97.1 ± 19.51	73.8 ± 11.11	92.5 ± 13.53

Mean ± SE
a) n = 5

Male C57BL/6 DIO mice (7-8 months old, 6/group) were provided with half of their normal daily food intake measured under ad libitum conditions. They received once-daily subcutaneous doses of tirzepatide (3 nmol/kg), semaglutide (3 nmol/kg), vehicle,[2)] or a combination of tirzepatide (3 nmol/kg) and a GIP receptor antagonist (1000 nmol/kg) for 14 days. Table 3 shows food intake, percentage change in body weight from Day 0, energy expenditure, and fat oxidation evaluated on Days 0 (baseline), 3, 7, 11, and 14.

Table 3. Time course of food intake, percentage change in body weight, energy expenditure, and fat oxidation

Parameter	Time	Tirzepatide	Semaglutide	Vehicle	Tirzepatide + GIP receptor antagonist
Food intake (kcal/day)	Day 0	11.9 ± 0.99	12.9 ± 0.28	11.7 ± 0.76	12.0 ± 0.55
	Day 3	4.1 ± 0.79	6.4 ± 0.29	6.8 ± 0.00	4.2 ± 0.53
	Day 7	5.8 ± 0.98	6.8 ± 0.00	6.8 ± 0.00	6.8 ± 0.00
	Day 11	6.8 ± 0.00	6.8 ± 0.00	6.8 ± 0.00	6.8 ± 0.00
	Day 14	6.8 ± 0.00	6.8 ± 0.00	6.8 ± 0.00	6.8 ± 0.00
Change in body weight (%)	Day 3	−9.0 ± 0.59	−7.2 ± 0.49	−4.8 ± 0.44	−7.1 ± 0.55
	Day 7	−15.2 ± 1.43	−12.7 ± 0.24	−8.7 ± 0.66	−11.8 ± 0.60
	Day 11	−20.2 ± 1.33	−16.1 ± 0.35	−11.4 ± 0.61	−15.6 ± 0.61
	Day 14	−23.0 ± 1.55	−19.0 ± 0.38	−13.9 ± 0.52	−18.1 ± 0.66
Energy expenditure (kcal/kg/day)	Day 0	266.3 ± 5.00	255.1 ± 4.74	242.6 ± 2.88	251.4 ± 2.75
	Day 3	249.7 ± 2.65	238.5 ± 5.38	221.6 ± 2.20	242.0 ± 3.76
	Day 7	272.0 ± 9.01	240.7 ± 5.93	220.0 ± 4.30	245.0 ± 2.82
	Day 11	275.3 ± 13.36	237.7 ± 3.99	218.0 ± 3.15	235.5 ± 4.41
	Day 14	261.7 ± 15.38	233.0 ± 3.99	208.5 ± 5.22	234.7 ± 3.89
Fat oxidation (kcal/kg/day)	Day 0	96.3 ± 7.35[a)]	82.6 ± 8.54	101.5 ± 7.39	102.8 ± 7.21
	Day 3	139.4 ± 4.41[a)]	109.6 ± 7.31	94.7 ± 4.10	132.3 ± 6.21
	Day 7	159.6 ± 19.04[a)]	121.6 ± 8.54	107.9 ± 4.18	122.4 ± 2.24
	Day 11	90.6 ± 8.00[b)]	62.5 ± 8.52	58.5 ± 3.18	62.6 ± 5.46
	Day 14	97.2 ± 13.08[b)]	77.5 ± 4.03	75.2 ± 6.97	80.7 ± 2.22

Mean ± SE
a) n = 5, b) n = 4

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of tirzepatide

The applicant's explanation:

Tirzepatide acts as an agonist for both GIP receptor and GLP-1 receptor, promoting weight loss by increasing energy expenditure through its effects on adipocytes and by regulating appetite via the central nervous system.

As for the increase in energy expenditure, *in vitro* studies have shown that tirzepatide enhances glucose and fatty acid uptake as well as fatty acid breakdown in adipocytes. In an *in vivo* study, administration of tirzepatide to DIO mice resulted in lower daily food intake frequency and per-meal food intake in the tirzepatide group compared to the vehicle group from Day 1 to Day 10. In another study using DIO mice, the tirzepatide group exhibited higher energy expenditure compared to the vehicle group, the semaglutide group, and the pair-fed group, in which food intake was adjusted to match that of the tirzepatide group. The energy expenditure-enhancing effect of tirzepatide was attenuated when co-administered with a GIP receptor antagonist. The precise mechanism by which GIP receptor activation affects glucose and lipid metabolic pathway remains unclear, but GIP receptor activation influences metabolic transcription factors and transcriptional regulation of hormone receptors independently of insulin (*Cell Metabolism.* 2024;36:1534-49). Tirzepatide may possibly enhance lipid metabolism and increase energy expenditure by acting on GIP receptors in adipocytes.

Regarding appetite regulation, neurons in the arcuate nucleus of the hypothalamus and the area postrema, which regulate brain regions by controlling the autonomic nervous system and behaviors related to food intake and energy metabolism, respond to energy status signals and transmit signals to the nucleus of the solitary tract and the parabrachial nucleus to regulate appetite. In patients with obesity, in contrast, impaired connectivity has been observed in brain regions related to appetite regulation, including the

prefrontal cortex, amygdala, and hypothalamus (*Human Brain Mapping.* 2017;38:1403-20), suggesting that dysregulation of this pathway may impact appetite. Moreover, GIP receptors and GLP-1 receptors are expressed in neurons in brain regions such as the arcuate nucleus of the hypothalamus and the area postrema, which are involved in regulating food intake (*Mol Metab*. 2022:55:1-10; *Am J Physiol Endocrinol Metab.* 2020:320:E326-32, etc.). Following administration of fluorescence-labeled tirzepatide in mice, fluorescence signals were detected in the area postrema, nucleus of the solitary tract, and arcuate nucleus of the hypothalamus. In some brain regions, including the area postrema and nucleus of the solitary tract, an increase in c-Fos-positive cells, an immediate-early gene and transcription factor involved in cell proliferation and differentiation, was also observed. In an *in vivo* study, administration of tirzepatide reduced the proportion of high-fat diet intake relative to total caloric intake while increasing the proportion of low-fat diet intake (*Diabetes Obes Metab.* 2023;25:56-67). The above findings suggest the possibility that tirzepatide acts on GIP and GLP-1 receptors in brain regions, influencing appetite and food preference.

On the basis of the above, tirzepatide is considered to have weight-loss effects.

PMDA's view:
Considering the results of primary pharmacodynamic studies, tirzepatide may exhibit weight-loss effects as explained by the applicant, through (i) increased energy expenditure associated with enhanced lipid metabolism in adipocytes and (ii) regulation of appetite and food preference via the central nervous system, mediated by GIP and GLP-1 receptors expressed in brain regions such as the arcuate nucleus of the hypothalamus and the area postrema. The detailed mechanism by which GIP receptor activation affects glucose and lipid metabolism remains unclear. The detailed mechanism by which GIP receptor activation affects glucose and lipid metabolism remains unclear. The insulinotropic effect and the inhibition of gastrointestinal peristalsis exerted by tirzepatide (see "Review Report on Mounjaro Subcutaneous Injection, dated August 10, 2022") may also contribute to its weight-loss effects. Thus, while the mechanism underlying the weight-loss effect of tirzepatide is not fully understood, the results of the primary pharmacodynamic studies conducted suggest that tirzepatide is expected to exert a weight-loss effect. The efficacy of tirzepatide in humans will be further discussed in Section "7.R.1 Efficacy."

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacokinetic data were previously evaluated for the initial approval of Mounjaro Subcutaneous Injection, and thus, no new study data have been submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application is intended for a new indication and a new dosage, and no data relating to toxicology have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Table 4 shows the formulations used in the clinical studies of tirzepatide. In the sections below, for Studies I8F-JE-GPGC and I8F-JE-GPHZ, the prefix "I8F-JE-" is abbreviated. Similarly, for Studies I8F-MC-GPGB, I8F-MC-GPGT, I8F-MC-GPGU, I8F-MC-GPHG, I8F-MC-GPHH, I8F-MC-GPHU, I8F-MC-GPHK, I8F-MC-GPHL, I8F-MC-GPHM, and I8F-MC-GPHN, the prefix "I8F-MC-" is abbreviated.

Table 4. Formulations used in each clinical study

Type of formulation		Development phase (study code)	
		Japanese study, global study	Foreign study
Formulation A		Phase I (GPGC)	Phase I (GPGT) Phase II (GPGB)
Liquid solution	Formulation B[note)]	-	Phase I (GPGU, GPHG, GPHH, GPHU)
	AI[a)]	Phase III (GPHK, GPHL, GPHZ)	Phase III (GPHM, GPHN)

Formulation B[note)]; AI, autoinjector; -, not applicable

a) Proposed formulation

[note)] The same formulation as in the proposed formulation, with the only difference being the container.

The concentration of tirzepatide in human plasma was measured using the liquid chromatography-mass spectrometry (LC/MS) method, with a lower limit of quantification of 2.0 or 4.0 ng/mL. Anti-tirzepatide antibodies in human serum were measured using the affinity capture elution-electrochemiluminescence (ACE-ECL) method, while neutralizing antibodies against GIP receptor activation and GLP-1 receptor activation were measured using cell-based assays.

6.2 Clinical pharmacology

The applicant submitted the results of 1 Japanese clinical study (Study GPHZ) and 2 global clinical studies (Studies GPHK and GPHL), as well as the results of population pharmacokinetic analysis and population pharmacokinetic/pharmacodynamic analysis as evaluation data. The applicant submitted the results of 1 Japanese clinical study (Study GPGC) and 8 foreign clinical studies (Studies GPGB, GPGT, GPGU, GPHG, GPHH, GPHM, GPHN, and GPHU) as reference data. The results of the main studies are summarized below.

6.2.1 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

A population pharmacokinetic analysis was conducted using 14196 plasma concentration data points of tirzepatide obtained from 1864 subjects (599 males and 1265 females) enrolled in the global phase III study (Study GPHK), which included patients with overweight or obese without type 2 diabetes mellitus (software used, NONMEM [ver.7.5.0]).

At baseline, the characteristics of the subjects included in the population pharmacokinetic analysis were as follows (median [range]): Age, 45 [18, 84] years; body weight, 101 [60.1, 214] kg; body mass index (BMI), 36.5 [27.0, 68.9] kg/m^2; and hemoglobin A1c (HbA1c), 5.5% [3.6%, 8.9%].

As the basic model, a 2-compartment model with first-order absorption was constructed, incorporating lean body weight and fat mass as covariates for clearance (CL) from the central compartment, inter-compartmental clearance between the central and peripheral compartments, central compartment

distribution volume (V_c), and peripheral compartment distribution volume. Age, body weight, race (Caucasian, Black, Asian, Pacific Islander, American Indian, other), sex, aspartate aminotransferase (AST), alanine aminotransferase (ALT), anti-tirzepatide antibodies, estimated glomerular filtration rate (eGFR), serum albumin, and injection site (abdomen, upper arm, thigh) were examined as covariates for the absorption rate constant, CL, or V_c. No new covariates were incorporated into the model, and the basic model, which included lean body weight and fat mass as pre-specified covariates, was selected as the final model.

The final model estimated that for body weights between 80 kg and 130 kg, $AUC_{0\text{-}168\ h}$ of tirzepatide decreases by approximately 1.1% for every 1 kg increase in body weight.

6.R Outline of the review conducted by PMDA

PMDA's view:

The clinical pharmacokinetics of tirzepatide have been appropriately evaluated from the submitted data. However, as discussed in Section 6.R.1, when tirzepatide was administered to Japanese patients with obesity disease or patients with overweight or obesity, the exposure to tirzepatide tended to be higher in Japanese patients than in non-Japanese patients. This difference was considered to be influenced by body weight. The impact of differences in tirzepatide exposure considered associated with body weight differences between Japanese and non-Japanese patients on the efficacy and safety of tirzepatide will be evaluated in light of the phase III study results. As discussed in Section 6.R.2, although a certain proportion of patients tested positive for anti-tirzepatide antibodies after tirzepatide administration, it was demonstrated that the production of anti-tirzepatide antibodies did not affect the pharmacokinetics of tirzepatide. The impact of anti-tirzepatide antibody production on the efficacy and safety of tirzepatide will be assessed from the efficacy and safety results of the phase III study as well.

6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese populations

The applicant's explanation:

In the evaluation of pharmacokinetics in the development of tirzepatide for type 2 diabetes mellitus, the exposures (C_{max} and $AUC_{0\text{-}168\ h}$) were similar when Japanese or non-Japanese patients with type 2 diabetes mellitus received a single subcutaneous dose of tirzepatide 5 mg. However, the exposure tended to be higher in Japanese patients with type 2 diabetes mellitus than in non-Japanese patients when tirzepatide 5 mg was administered as once-weekly multiple subcutaneous doses. The higher exposure to tirzepatide in Japanese patients was considered to be due to differences in body weight. Results from the phase III study in patients with type 2 diabetes mellitus indicated that differences in tirzepatide exposure due to body weight had minimal impact on the evaluation of the efficacy and safety of tirzepatide (see "Review Report on Mounjaro Subcutaneous Injection, dated August 10, 2022").

Table 5 shows the estimated pharmacokinetic parameters of tirzepatide 5 mg, 10 mg, or 15 mg at steady state following once-weekly multiple subcutaneous administration using population pharmacokinetic analysis[3)] in Studies GPHK, GPHL, and GPHZ conducted in patients with obesity disease or patients

[3)] The pharmacokinetic parameters in Study GPHK were estimated using the model described in Section "6.2.1 Population pharmacokinetic analysis." The pharmacokinetic parameters in the Studies GPHL and GPHZ were estimated using the model described in Section "6.2.1 Population pharmacokinetic analysis" based on the plasma tirzepatide concentration data from each study.

with overweight or obesity. Regardless of the dosage, the exposure to tirzepatide tended to be higher in Japanese patients than in non-Japanese patients. The population pharmacokinetic analysis showed that $AUC_{0\text{-}168\ h}$ of tirzepatide decreased by approximately 1.1% per 1 kg increase in body weight. Therefore, the higher exposure in Japanese patients was considered to be due to the lower mean body weight of Japanese patients compared to non-Japanese patients. No significant covariates other than body weight were identified in the population pharmacokinetic analysis.

Table 5. Estimated pharmacokinetic parameters of tirzepatide at steady state following once-weekly multiple subcutaneous administration of tirzepatide

Study	Dose	Subjects	N	Baseline body weight (kg)	$C_{max,\ ss}$ (ng/mL)	$AUC_{0\text{-}168\ h,\ ss}$ (ng•h/mL)
GPHK	5 mg	Japanese	24	89.0 ± 11.1	781 (16.2)	97000 (19.1)
		Non-Japanese	596	104 ± 20.8	707 (19.5)	88500 (20.2)
	10 mg	Japanese	22	86.2 ± 13.4	1700 (19.7)	217000 (20.6)
		Non-Japanese	599	107 ± 23.2	1400 (20.9)	175000 (21.7)
	15 mg	Japanese	30	86.8 ± 9.7	2390 (13.8)	308000 (13.1)
		Non-Japanese	593	106 ± 23.0	2110 (19.7)	264000 (20.5)
GPHL	10 mg	Japanese	14	89.0 ± 15.8	1340 (15.9)	169000 (17.9)
		Non-Japanese	284	102 ± 20.9	1210 (17.6)	152000 (19.5)
	15 mg	Japanese	15	89.0 ± 10.2	2040 (12.3)	252000 (15.0)
		Non-Japanese	285	101 ± 20.3	1850 (18.0)	232000 (19.4)
GPHZ	10 mg	Japanese	72	92.4 ± 15.1	1540 (16.6)	190000 (17.6)
	15 mg	Japanese	77	91.7 ± 14.8	2310 (14.0)	288000 (16.6)

Body weight is expressed in mean ± standard deviation (SD). $C_{max,\ ss}$ and $AUC_{0\text{-}168\ h,\ ss}$ are expressed in geometric mean (geometric coefficient of variation %).
$C_{max,\ ss}$, Maximum tirzepatide plasma concentration at steady state.; $AUC_{0\text{-}168\ h,\ ss}$, Area under the concentration versus time curve from 0 to 168 hours at steady state

PMDA's view:

Tirzepatide exposure tended to be higher in Japanese patients than in non-Japanese patients, and the applicant's explanation that this difference is attributable to body weight is reasonable. Considering the pharmacokinetic differences between Japanese and non-Japanese patients due to body weight, the applicability of the results from the global studies, GPHK and GPHL, in explaining the efficacy and safety of tirzepatide in Japanese patients will continue to be examined, taking into account the efficacy and safety results of the phase III studies [see Sections "7.R.1 Efficacy" and "7.R.2 Safety"].

6.R.2 Impact of antibody production on pharmacokinetics

The applicant's explanation:

Table 6 shows the status of anti-tirzepatide antibody and neutralizing antibody production in the phase III studies (Studies GPHZ, GPHK, and GPHL).

Table 6. Status of anti-tirzepatide antibody and neutralizing antibody production in phase III studies[a)]

Study	Treatment group	Anti-tirzepatide antibody positive[b)]	Positive for neutralizing antibodies against GIP receptor activation	Positive for neutralizing antibodies against GLP-1 receptor activation
GPHZ	Tirzepatide 10 mg	75.7 (53/70)	5.7 (4/70)	0.0 (0/70)
	Tirzepatide 15 mg	75.0 (57/76)	6.6 (5/76)	1.3 (1/76)
GPHK	Tirzepatide 5 mg	64.9 (398/613)	2.5 (15/604)	3.1 (19/604)
	Tirzepatide 10 mg	65.4 (403/616)	2.8 (17/609)	3.9 (24/609)
	Tirzepatide 15 mg	69.0 (423/613)	5.1 (31/606)	4.0 (24/606)
GPHL	Tirzepatide 10 mg	58.9 (175/297)	3.0 (9/297)	1.3 (4/297)
	Tirzepatide 15 mg	61.2 (180/294)	1.0 (3/294)	0.0 (0/294)

Incidence % (number of subjects with development/number of subjects evaluated),

a) Neutralizing antibodies were not assessed in samples collected from participants in Study GPHK in China. Therefore, subjects who participated in Study GPHK in China are not included in the count of those positive for neutralizing antibodies against GIP receptor or GLP-1 receptor activation, although they are included in the count of those positive for anti-tirzepatide antibodies.

b) The criteria for defining anti-tirzepatide antibody positivity were as follows:
   (1) Negative for anti-tirzepatide antibodies at baseline and positive at least once from the start of administration of the study drug through the follow-up period, with a titer ≥2-fold the minimum required dilution of the anti-tirzepatide antibody assay; or
   (2) Positive for anti-tirzepatide antibodies both at baseline and after the start of administration of the study drug through the follow-up period, with a post-dose titer ≥4-fold the baseline titer.

Table 7 shows the estimated pharmacokinetic parameter values of tirzepatide at steady state following once-weekly multiple subcutaneous administration of tirzepatide, stratified by the presence or absence of anti-tirzepatide antibodies and neutralizing antibodies, in the phase III studies (Studies GPHZ, GPHK, and GPHL). No substantial difference in tirzepatide exposure was observed between subjects positive and negative for anti-tirzepatide antibodies. Among subjects positive for neutralizing antibodies against GIP receptor or GLP-1 receptor activation, there was no trend toward reduced tirzepatide exposure compared to subjects negative for anti-tirzepatide antibodies.

Table 7. Estimated pharmacokinetic parameters of tirzepatide at steady state by presence or absence of anti-tirzepatide antibody and neutralizing antibody

Study	Treatment group	Pharmacokinetic parameter	Anti-tirzepatide antibody negative	Anti-tirzepatide antibody positive		
				Anti-tirzepatide antibody positive	Positive for neutralizing antibodies against GIP receptor activation	Positive for neutralizing antibodies against GLP-1 receptor activation
GPHZ	Tirzepatide 10 mg	$C_{max, ss}$ (ng/mL)	1580 (19.9) (N = 17)	1520 (15.4) (N = 53)	1440 (33.3) (N = 4)	-
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	191000 (21.0) (N = 17)	189000 (16.4) (N = 53)	180000 (35.6) (N = 4)	-
	Tirzepatide 15 mg	$C_{max, ss}$ (ng/mL)	2310 (13.2) (N = 19)	2310 (14.5) (N = 57)	2330 (7.14) (N = 5)	2360 (N = 1)
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	278000 (14.6) (N = 19)	291000 (17.3) (N = 57)	322000 (13.3) (N = 5)	368000 (N = 1)
GPHK	Tirzepatide 5 mg	$C_{max, ss}$ (ng/mL)	701 (19.9) (N = 214)	716 (19.2) (N = 398)	746 (20.6) (N = 15)	712 (15.2) (N = 19)
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	86500 (20.7) (N = 214)	90200 (19.8) (N = 398)	93000 (17.9) (N = 15)	91900 (15.7) (N = 19)
	Tirzepatide 10 mg	$C_{max, ss}$ (ng/mL)	1400 (21.1) (N = 212)	1420 (21.3) (N = 403)	1400 (20.9) (N = 17)	1480 (22.2) (N = 24)
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	173000 (22.0) (N = 212)	178000 (22.0) (N = 403)	176000 (22.6) (N = 17)	192000 (16.5) (N = 24)
	Tirzepatide 15 mg	$C_{max, ss}$ (ng/mL)	2110 (20.3) (N = 188)	2120 (19.5) (N = 423)	2260 (18.8) (N = 31)	2110 (20.8) (N = 24)
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	263000 (20.1) (N = 188)	267000 (20.6) (N = 423)	281000 (20.1) (N = 31)	264000 (19.6) (N = 24)
GPHL	Tirzepatide 10 mg	$C_{max, ss}$ (ng/mL)	1200 (18.2) (N = 119)	1230 (17.2) (N = 174)	1370 (13.7) (N = 9)	1160 (12.1) (N = 4)
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	148000 (18.9) (N = 119)	155000 (19.6) (N = 174)	167000 (15.9) (N = 9)	149000 (19.5) (N = 4)
	Tirzepatide 15 mg	$C_{max, ss}$ (ng/mL)	1850 (16.5) (N = 113)	1870 (18.9) (N = 179)	1710 (24.7) (N = 3)	-
		$AUC_{0-168\ h, ss}$ (ng•h/mL)	229000 (19.0) (N = 113)	235000 (19.6) (N = 179)	217000 (28.2) (N = 3)	-

Geometric mean (geometric coefficient of variation %) (number of subjects evaluated); individual value in a single subject; -, not applicable
$C_{max, ss}$, Maximum tirzepatide plasma concentration at steady state; $AUC_{0-168\ h, ss}$, Area under the plasma concentration versus time curve from 0 to 168 hours at steady state

From the above results, it was determined that the presence of anti-tirzepatide antibodies and neutralizing antibodies did not affect the pharmacokinetic parameters of tirzepatide.

PMDA's view:

The results of the Japanese phase III study (Study GPHZ) and the global phase III studies (Studies GPHK and GPHL) did not show any impact of anti-tirzepatide antibody and neutralizing antibody production on the pharmacokinetics of tirzepatide. The impact of antibody production on the efficacy and safety of tirzepatide will continue to be examined, taking into account the efficacy and safety results of the phase III studies [see Section "7.R.2.5 Antibody production"].

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation and reference data for efficacy and safety from the clinical study results shown in Table 8.

Table 8. List of clinical studies on efficacy and safety

Category	Region	Study code	Phase	Study population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	GPHZ	III	Patients with obesity disease	225	Once-weekly subcutaneous administration of placebo, tirzepatide 10 mg, or tirzepatide 15 mg	Efficacy Safety
	Global	GPHK	III	Patients with overweight or obesity without type 2 diabetes mellitus	2517	Once-weekly subcutaneous administration of placebo, tirzepatide 5 mg, 10 mg, or 15 mg	Efficacy Safety
	Global	GPHL	III	Patients with overweight or obesity with type 2 diabetes mellitus	912	Once-weekly subcutaneous administration of placebo, tirzepatide 10 mg, or 15 mg	Efficacy Safety
Reference	Foreign	GPGB	II	Patients with type 2 diabetes mellitus	318	Once-weekly subcutaneous administration of placebo, tirzepatide 1 mg, 5 mg, 10 mg, or 15 mg, or dulaglutide (genetical recombination) 1.5 mg	Efficacy Safety Pharmacokinetics
	Foreign	GPHM	III	Patients with overweight or obesity without type 2 diabetes mellitus	579[a)]	Once-weekly subcutaneous administration of placebo, tirzepatide 10 mg, or 15 mg	Efficacy Safety
	Foreign	GPHN	III	Patients with overweight or obesity without type 2 diabetes mellitus	670[b)]	Once-weekly subcutaneous administration of placebo, tirzepatide 10 mg, or 15 mg	Efficacy Safety

a) Number of randomized subjects. A total of 806 subjects were enrolled during the lead-in period for lifestyle intervention prior to randomization.
b) Number of randomized subjects. A total of 783 subjects were enrolled during the open-label tirzepatide lead-in period prior to randomization.

The results of the main clinical studies are presented below.

7.1 Japanese phase III study in patients with obesity disease (CTD 5.3.5.1.2, Study GPHZ [May 2021 to June 2023])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with obesity disease (target sample size, 261 subjects[4)]; 87 per group) to evaluate the efficacy and safety of tirzepatide as an adjunct to diet and exercise therapy.

4) For the percentage change in body weight from baseline to Week 72, which was one of the co-primary endpoints, the target sample size was 87 subjects per group (total of 261 subjects) to ensure a statistical power of >90% under the assumptions of an intergroup mean difference of 11%, a common SD of 10%, and a dropout rate of 25% for comparisons between the tirzepatide 10 mg and placebo groups, as well as the tirzepatide 15 mg and placebo groups, with a two-sided significance level of 2.5% for each hypothesis test using a t-test. With 87 subjects per group, sufficient statistical power of >90% was also ensured for another co-primary endpoint, which was the proportion of subjects who achieved a weight reduction of ≥5% at Week 72. This was based on the assumption that the proportion of responders would be 90% in the tirzepatide 10 mg or 15 mg groups and 25% in the placebo group, with a dropout rate of 25% for comparisons between the tirzepatide 10 mg and placebo groups, as well as the tirzepatide 15 mg and placebo groups, with a two-sided significance level of 2.5% for each hypothesis test using Fisher's exact test.

The key inclusion criteria were patients with obesity disease aged ≥20 years who met both of the following criteria: (1) BMI ≥27 kg/m^2 with at least 2 obesity-related health disorders,[5)] or BMI ≥35 kg/m^2 with at least 1 obesity-related health disorder[5)]; and (2) history of at least 1 unsuccessful attempt at dietary weight loss. Subjects with diabetes mellitus were excluded.

The study consisted of a 4-week screening period, a 72-week study drug treatment period, and a 4-week follow-up period.

The study drug was administered once weekly[6)] by subcutaneous injection (self-injection) in the abdomen or thigh at doses of placebo, tirzepatide 10 mg, or tirzepatide 15 mg. The starting dose of tirzepatide was 2.5 mg, which was increased in 2.5 mg increments every 4 weeks until the maintenance dose (10 mg or 15 mg) was achieved.[7)]

All of 267 randomized subjects (89 in the placebo group, 88 in the tirzepatide 10 mg group, 90 in the tirzepatide 15 mg group) received at least 1 dose of the study drug. Among them, 42 subjects enrolled at clinical study sites associated with a site management organization (SMO) that was found to be in violation of good clinical practice (GCP) were excluded.[8)] The remaining 225 subjects (75 in the placebo group, 73 in the tirzepatide 10 mg group, 77 in the tirzepatide 15 mg group) were included in the modified intent-to-treat (mITT) population and the safety analysis population, and the mITT population was used for primary efficacy analyses. A total of 10 subjects (5 in the placebo group, 4 in the tirzepatide 10 mg group, 1 in the tirzepatide 15 mg group) discontinued the study. Reasons for discontinuation included adverse events in 4 subjects (3 in the placebo group, 1 in the tirzepatide 10 mg group), consent withdrawal in 3 subjects (2 in the tirzepatide 10 mg group, 1 in the tirzepatide 15 mg group), lost to follow-up in 1 subject (placebo group), and other reasons in 2 subjects (1 in the placebo group, 1 in the tirzepatide 10 mg group).

Regarding efficacy, the study success criteria required demonstration of the superiority over placebo for both co-primary endpoints, i.e., the percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% weight loss at Week 72. The results, shown in Table 9, demonstrated the superiority of tirzepatide 10 mg and 15 mg over placebo for both endpoints.

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5) Subjects with impaired glucose tolerance (IGT), hypertriglyceridaemia, or non-alcoholic fatty liver disease (NAFLD) defined below at screening:
IGT: Subjects with a 0-hour oral glucose tolerance test (OGTT) result of ≥110 mg/dL or a 2-hour OGTT result of ≥140 mg/dL at Visit 2 (2 weeks before the start of study drug administration), who did not meet the diagnostic criteria for diabetes mellitus at Visit 1 (4 weeks before the start of study drug administration) or Visit 2. In Study GPHZ, IGT was defined to include impaired fasting glucose classified as "borderline type" according to the "Japanese Clinical Practice Guideline for Diabetes 2019" (*J Diabetes Investig.* 2020;11:1020-76).
Hypertriglyceridaemia: Subjects with fasting triglyceride levels of ≥150 mg/dL at both Visit 1 and Visit 2.
NAFLD: Subjects with hepatic fat fraction (HFF) ≥5% as measured by magnetic resonance imaging (MRI)-proton density fat fraction at Visit 2, assessed by a central laboratory.

6) If the study drug could not be administered on the scheduled dosing day, and more than 72 hours remained until the next scheduled dosing day, the dose was to be administered as soon as the subject or investigator became aware of the missed dose. If the remaining time until the next scheduled dosing was within 72 hours, the dose was to be skipped, and administration resumed on the next scheduled dosing day.

7) Subjects who experienced intolerable gastrointestinal symptoms were allowed a one-time dose reduction (from 15 mg or 12.5 mg to 10 mg; if already at or below 10 mg, the study drug was replaced with placebo). If intolerable gastrointestinal symptoms persisted despite the dose reduction, treatment discontinuation was mandated.

8) Due to findings from an on-site inspection conducted by the Ministry of Health, Labour and Welfare, which revealed that a contracted SMO had engaged in practices violating GCP in multiple clinical studies such as data falsification, the applicant determined that it was difficult to ensure the reliability of data from subjects enrolled at clinical study sites associated with this SMO. Accordingly, those subjects were excluded from the analysis.

Table 9. Percentage change in body weight from baseline to Week 72 and proportion of subjects achieving ≥5% weight loss at Week 72 (Study GPHZ, mITT population)

Endpoint	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Baseline body weight (kg)	92.0 ± 15.25 (N = 75)	92.5 ± 15.15 (N = 71)	91.9 ± 14.84 (N = 76)
Body weight at Week 72 (kg)	90.5 ± 16.01 (N = 66)	76.3 ± 16.07 (N = 59)	71.9 ± 14.70 (N = 65)
Body weight change (%) at Week 72	−1.8 ± 4.94 (N = 66)	−18.4 ± 7.61 (N = 59)	−22.6 ± 8.90 (N = 65)
Difference from placebo[a)] [95% CI]	-	−16.1[c)] [−18.7, −13.5]	−21.1[c)] [−23.6, −18.5]
% of subjects achieving ≥5% reduction in body weight at Week 72	21.2 (14/66)	94.9 (56/59)	96.9 (63/65)
Odds ratio compared to placebo[b)] [95% CI]	-	119.65[c)] [29.06, 492.67]	153.57[c)] [36.03, 654.53]

Mean ± SD (number of subjects evaluated) or percentage (number of applicable subjects/number of subjects evaluated); inter-group differences are expressed as least-squares mean difference [95% confidence interval (CI)]; -, not applicable.

a) Calculated using a mixed-effects model for repeated measures (MMRM) assuming an unstructured covariance matrix for within-subject errors, with treatment group, time point, treatment group-by-time point interaction, baseline body weight, status of impaired glucose tolerance (IGT), hypertriglyceridaemia, and non-alcoholic fatty liver disease (NAFLD) at screening, and sex as explanatory variables.

b) After imputing missing values using the predicted values of percentage change in body weight obtained from the MMRM described in footnote a), odds ratios were calculated using Firth's penalized logistic regression with treatment group, baseline body weight, status of IGT, hypertriglyceridaemia, and NAFLD at screening, and sex as explanatory variables.

c) $P < 0.001$. The overall type I error rate of the study was controlled at 5% by applying a two-sided significance level of 2.5% each for comparisons between the tirzepatide 10 mg group and the placebo group, and between the tirzepatide 15 mg group and the placebo group.

Figure 1 shows the time course of percentage change in body weight from baseline to Week 72. Tables 10, 11, and 12 show the results of the main secondary endpoints.

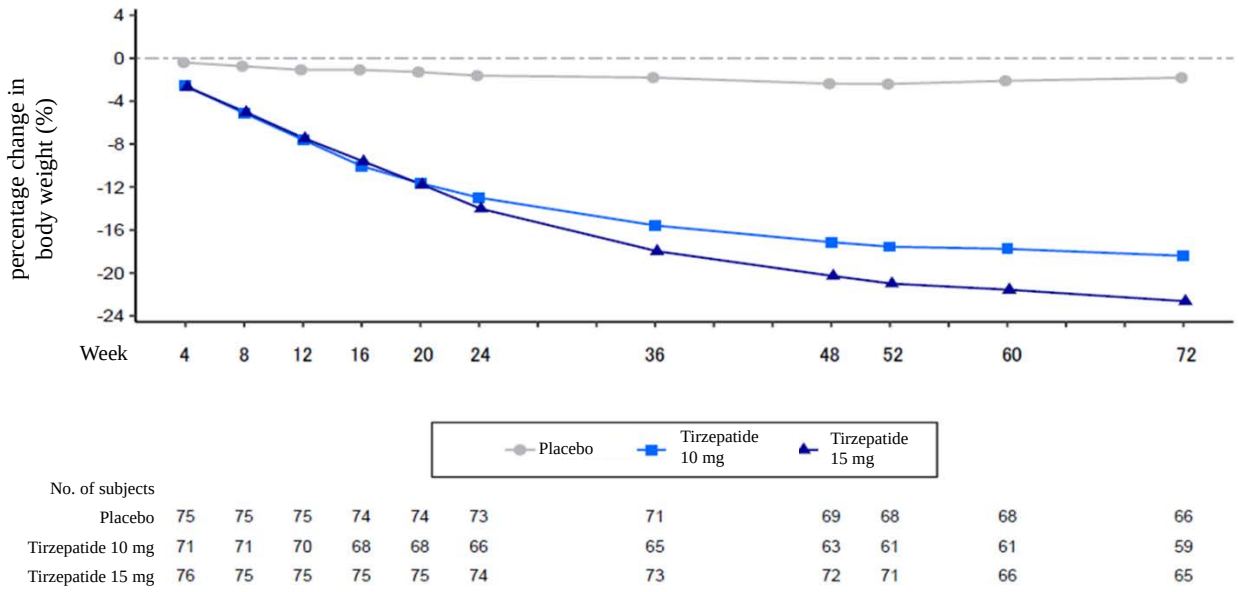

Figure 1. Time course of percentage change in body weight from baseline to Week 72 (mean, Study GPHZ, mITT population)

Table 10. Results of main secondary endpoints related to body weight (Study GPHZ, mITT population)

Endpoint		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
% of subjects achieving body weight loss[a)]	≥10%	4.6 (3/66)	88.1 (52/59)	92.3 (60/65)
	≥15%	1.5 (1/66)	67.8 (40/59)	83.1 (54/65)
	≥20%	0.0 (0/66)	44.1 (26/59)	66.2 (43/65)
BMI (kg/m^2)	Baseline	33.6 ± 4.88 (N = 75)	33.3 ± 4.15 (N = 71)	33.7 ± 4.31 (N = 76)
	Change at Week 72	−0.6 ± 1.66 (N = 66)	−6.0 ± 2.35 (N = 59)	−7.7 ± 3.28 (N = 65)
Waist circumference[b)] (cm)	Baseline	108.7 ± 10.93 (N = 75)	107.7 ± 9.89 (N = 71)	107.7 ± 10.41 (N = 76)
	Change at Week 72	−1.4 ± 5.28 (N = 66)	−12.9 ± 7.16 (N = 59)	−16.6 ± 8.01 (N = 65)
Visceral adipose tissue area[c)] (cm^2)	Baseline	237.0 ± 66.41 (N = 61)	232.4 ± 84.66 (N = 60)	236.3 ± 80.61 (N = 63)
	Change at Week 72[d)]	−10.7 ± 34.43 (N = 61)	−87.5 ± 54.75 (N = 60)	−102.3 ± 53.34 (N = 63)

Proportion (number of applicable subjects/number of subjects evaluated) or mean ± SD (number of subjects evaluated)

a) Proportion (%) of subjects who achieved ≥10%, ≥15%, or ≥20% reduction in body weight from baseline to Week 72.

b) Measured at the level of the umbilicus.

c) Measured by a central imaging facility using a single-slice scan at the level of the umbilicus in the supine position using computed tomography or a magnetic resonance imaging (MRI) scanner.

d) Missing data were imputed using the last observation carried forward (LOCF) method.

Table 11. Results of main secondary endpoints related to blood glucose, blood pressure, and lipid parameters (Study GPHZ, mITT population)

Endpoint		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
HbA1c (%)	Baseline	5.66 ± 0.32 (N = 74)	5.65 ± 0.34 (N = 70)	5.67 ± 0.35 (N = 75)
	Change at Week 72	0.01 ± 0.27 (N = 66)	−0.54 ± 0.35 (N = 59)	−0.61 ± 0.29 (N = 65)
Fasting plasma glucose (mg/dL)	Baseline	97.20 ± 9.85 (N = 72)	96.13 ± 9.14 (N = 66)	97.55 ± 10.94 (N = 73)
	Change at Week 72	3.08 ± 11.40 (N = 66)	−11.36 ± 9.16 (N = 59)	−9.84 ± 10.27 (N = 65)
Systolic blood pressure (mmHg)	Baseline	125.0 ± 12.95 (N = 75)	125.4 ± 12.99 (N = 71)	125.5 ± 11.97 (N = 76)
	Change at Week 72	1.7 ± 9.08 (N = 66)	−11.4 ± 13.37 (N = 59)	−12.1 ± 13.04 (N = 65)
Diastolic blood pressure (mmHg)	Baseline	80.0 ± 9.65 (N = 75)	79.3 ± 9.05 (N = 71)	79.7 ± 8.28 (N = 76)
	Change at Week 72	0.3 ± 8.25 (N = 66)	−6.2 ± 10.35 (N = 59)	−6.3 ± 8.80 (N = 65)
Total cholesterol (mg/dL)	Baseline	212.5 ± 36.48 (N = 72)	210.1 ± 38.40 (N = 66)	213.7 ± 35.82 (N = 73)
	Percentage change at Week 72 (%)	0.07 ± 10.44 (N = 66)	−8.40 ± 14.27 (N = 59)	−11.95 ± 13.54 (N = 65)
LDL cholesterol (mg/dL)	Baseline	132.8 ± 31.55 (N = 72)	132.1 ± 33.92 (N = 66)	133.7 ± 31.14 (N = 73)
	Percentage change at Week 72 (%)	1.8 ± 15.05 (N = 66)	−8.6 ± 26.52 (N = 59)	−13.3 ± 19.14 (N = 65)
HDL cholesterol (mg/dL)	Baseline	50.9 ± 11.47 (N = 72)	49.8 ± 12.05 (N = 66)	49.3 ± 10.42 (N = 73)
	Percentage change at Week 72 (%)	3.7 ± 12.34 (N = 66)	15.4 ± 17.77 (N = 59)	17.5 ± 21.55 (N = 65)
Triglycerides[a)] (mg/dL)	Baseline	179.4 ± 90.71 (N = 72)	180.9 ± 89.16 (N = 66)	191.4 ± 91.88 (N = 73)
	Percentage change at Week 72 (%)	−3.7 ± 34.40 (N = 66)	−33.1 ± 29.43 (N = 59)	−42.4 ± 23.73 (N = 65)

Mean ± SD (number of subjects evaluated)

a) Fasting

Table 12. Results of main secondary endpoints related to IGT, hypertriglyceridaemia, and NAFLD (Study GPHZ, mITT population)

Endpoint	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Percentage of subjects showing improvement in IGT[a)]	28.0 (14/50)	92.5 (37/40)	97.8 (45/46)
Percentage of subjects showing improvement in hypertriglyceridaemia[b)]	25.0 (9/36)	72.4 (21/29)	81.1 (30/37)
Percentage of subjects showing improvement in NAFLD[c)]	9.8 (6/61)	69.5 (41/59)	77.4 (48/62)

Percentage (number of applicable subjects/number of subjects evaluated)

a) Evaluated in subjects who had IGT at enrollment, and improvement was defined as restoration of blood glucose to within the normal range (0-hour oral glucose tolerance test [OGTT] <110 mg/dL and 2-hour OGTT <140 mg/dL). Missing values were imputed using the LOCF method.

b) Evaluated in subjects who had hypertriglyceridaemia at enrollment, and improvement was defined as either fasting triglyceride levels returning to the normal range (<150 mg/dL) or a ≥30% reduction from baseline. Missing values were excluded.

c) Evaluated in subjects who had NAFLD at enrollment, and improvement was defined as either hepatic fat fraction (HFF) returning to the normal range (<5%) or a ≥30% reduction from baseline. Missing values were imputed using the LOCF method.

Table 13 shows the incidence of adverse events and adverse drug reactions occurring in ≥5% of subjects in any treatment group.

Table 13. Incidence of adverse events and adverse drug reactions occurring in ≥5% of subjects in any treatment group (Study GPHZ, safety analysis population)

Event	Placebo (N = 75)		Tirzepatide 10 mg (N = 73)		Tirzepatide 15 mg (N = 77)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	69.3 (52)	10.7 (8)	83.6 (61)	56.2 (41)	85.7 (66)	63.6 (49)
Constipation	6.7 (5)	2.7 (2)	16.4 (12)	13.7 (10)	27.3 (21)	23.4 (18)
Nausea	4.0 (3)	0 (0)	13.7 (10)	13.7 (10)	23.4 (18)	22.1 (17)
COVID-19	17.3 (13)	0 (0)	21.9 (16)	0 (0)	19.5 (15)	0 (0)
Pyrexia	14.7 (11)	0 (0)	13.7 (10)	0 (0)	14.3 (11)	1.3 (1)
Vomiting	4.0 (3)	0 (0)	6.8 (5)	4.1 (3)	11.7 (9)	9.1 (7)
Diarrhoea	4.0 (3)	1.3 (1)	12.3 (9)	8.2 (6)	9.1 (7)	7.8 (6)
Decreased appetite	1.3 (1)	1.3 (1)	12.3 (9)	12.3 (9)	7.8 (6)	7.8 (6)
Abdominal discomfort	0 (0)	0 (0)	6.8 (5)	6.8 (5)	5.2 (4)	3.9 (3)
Injection site reaction	0 (0)	0 (0)	5.5 (4)	5.5 (4)	5.2 (4)	5.2 (4)
Immunisation reaction	5.3 (4)	0 (0)	1.4 (1)	0 (0)	5.2 (4)	0 (0)
Arthralgia	1.3 (1)	0 (0)	1.4 (1)	0 (0)	5.2 (4)	0 (0)
Back pain	5.3 (4)	0 (0)	5.5 (4)	0 (0)	3.9 (3)	0 (0)
Headache	6.7 (5)	0 (0)	2.7 (2)	0 (0)	2.6 (2)	0 (0)
Nasopharyngitis	10.7 (8)	0 (0)	9.6 (7)	0 (0)	1.3 (1)	0 (0)

Incidence % (number of subjects with events), Medical Dictionary for Regulatory Activities Japanese version (MedDRA/J) ver.26.0

No deaths were observed. Serious adverse events were reported in 5 subjects in the placebo group (oesophageal carcinoma, otitis media chronic, acute myocardial infarction, benign prostatic hyperplasia, and vertigo positional in 1 subject each), 8 subjects in the tirzepatide 10 mg group (coronavirus disease 2019 [COVID-19], gastroenteritis, cerebral infarction, rhegmatogenous retinal detachment, brain stem infarction, pneumonia bacterial, large intestine polyp, and prostate cancer in 1 subject each), and 5 subjects in the tirzepatide 15 mg group (uterine cancer, pyelonephritis acute, appendicitis, acute kidney injury, and endometrial adenocarcinoma in 1 subject each); none of them were determined to be adverse drug reactions. Adverse events leading to treatment discontinuation were reported in 5 subjects in the placebo group (acute myocardial infarction, chest pain, generalised oedema, abdominal neoplasm, and oesophageal carcinoma in 1 subject each), 7 subjects in the tirzepatide 10 mg group (nausea, abdominal discomfort, dyspepsia, malaise, decreased appetite, prostate cancer, and brain stem infarction in 1

subject each), and 8 subjects in the tirzepatide 15 mg group (nausea in 4 subjects, constipation, eosinophil count increased, endometrial adenocarcinoma, and uterine cancer in 1 subject each). Among them, 5 subjects in the tirzepatide 10 mg group (nausea, abdominal discomfort, dyspepsia, malaise, and decreased appetite in 1 subject each) and 6 subjects in the tirzepatide 15 mg group (nausea in 4 subjects, constipation, and eosinophil count increased in 1 subject each) were determined to have experienced adverse drug reactions. Among the 42 subjects excluded from the mITT population after randomization, no deaths were observed. Serious adverse events were reported in 2 subjects in the tirzepatide 10 mg group (facial bones fracture and coronary artery disease in 1 subject each) and 2 subjects in the tirzepatide 15 mg group (cartilage injury and inguinal hernia/hepatic function abnormal in 1 subject each); none of them were determined to be adverse drug reactions. Adverse events leading to treatment discontinuation were reported in 2 subjects in the tirzepatide 15 mg group (nausea and diarrhoea in 1 subject each), and both events were determined to be adverse drug reactions.

7.2 Global phase III study in patients with overweight or obesity without type 2 diabetes mellitus (CTD 5.3.5.1.3, Study GPHK [December 2019 to April 2022])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of tirzepatide as an adjunct to diet and exercise therapy in patients with overweight or obesity[9)] including Japanese patients (target sample size, 2400 subjects[10)]; 600 per group).

Key inclusion criteria were patients aged ≥18 years with overweight or obesity who met both of the following criteria: (a) BMI ≥27 kg/m^2 with any of hypertension,[11)] dyslipidaemia,[12)] obstructive sleep apnoea syndrome, or cardiovascular disease, or BMI ≥30 kg/m^2; and (b) at least 1 prior unsuccessful attempt at dietary weight loss. Subjects with diabetes mellitus, those who had undergone or were planning to undergo bariatric surgery, were excluded.

The study consisted of a screening period (2 weeks), treatment period (72 weeks), and follow-up period (4 weeks).

Subjects received placebo, tirzepatide 5 mg, tirzepatide 10 mg, or tirzepatide 15 mg once weekly via subcutaneous injection (self-injection)[6)] in the abdomen or thigh. The starting dose of tirzepatide was 2.5 mg, with increments of 2.5 mg every 4 weeks until reaching the maintenance doses (5 mg, 10 mg, or 15 mg).[13)]

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9) Japan, Argentina, Brazil, China, India, Mexico, Russia, Taiwan, and the US (including Puerto Rico).

10) For the percentage change in body weight from baseline to Week 72, which was one of the co-primary endpoints, the target sample size was 600 subjects per group (including the tirzepatide 5 mg group, totaling 2400 subjects). This was calculated to ensure a statistical power of >90% under the assumptions of an intergroup mean difference of 11%, a common SD of 10%, and a dropout rate of 25% for comparisons between the tirzepatide 10 mg and placebo groups, as well as the tirzepatide 15 mg and placebo groups, with a two-sided significance level of 2.5% for each hypothesis test using a t-test. With 600 subjects per group, sufficient statistical power of >90% was also ensured for another co-primary endpoint, which was the proportion of subjects achieving ≥5% weight reduction at Week 72. This was based on an assumed achievement rate of 90% in the tirzepatide 10 mg and 15 mg groups, 25% in the placebo group, and a dropout rate of 25% for comparisons between the tirzepatide 10 mg and placebo groups, as well as the tirzepatide 15 mg and placebo groups, with a two-sided significance level of 2.5% for each hypothesis test using Fisher's exact test.

11) Hypertension was defined as treatment with antihypertensive drugs or systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg.

12) Dyslipidaemia was defined as treatment with lipid-lowering drugs or low-density lipoprotein (LDL) cholesterol ≥160 mg/dL, triglycerides ≥150 mg/dL, or high-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women.

13) Subjects experiencing intolerable gastrointestinal symptoms were allowed a one-time dose reduction (from 15 mg to 10 mg, 10 mg to 5 mg, or 5 mg to placebo). If intolerable gastrointestinal symptoms persisted despite dose reduction, treatment should be discontinued.

All of 2539 randomized subjects (643 in the placebo group [33 Japanese subjects], 630 in the tirzepatide 5 mg group [30 Japanese subjects], 636 in the tirzepatide 10 mg group [30 Japanese subjects], 630 in the tirzepatide 15 mg group [31 Japanese subjects]) received at least 1 dose of the study drug. After excluding 22 subjects enrolled at study sites involving a SMO which was found to be in violation of GCP,[8)] 2517 subjects (637 in the placebo group [27 Japanese subjects], 624 in the tirzepatide 5 mg group [24 Japanese subjects], 628 in the tirzepatide 10 mg group [22 Japanese subjects], 628 in the tirzepatide 15 mg group [29 Japanese subjects]) were included in the mITT and safety analysis populations. The mITT population was used for primary efficacy analyses. A total of 354 subjects (148 in the placebo group [4 Japanese subjects], 69 in the tirzepatide 5 mg group [1 Japanese subject], 73 in the tirzepatide 10 mg group [1 Japanese subject], 64 in the tirzepatide 15 mg group [2 Japanese subjects]) discontinued the study. The reasons for discontinuation were as follows: Consent withdrawal in 147 subjects (68 in the placebo group [3 Japanese subjects], 28 in the tirzepatide 5 mg group [1 Japanese subject], 29 in the tirzepatide 10 mg group [1 Japanese subject], 22 in the tirzepatide 15 mg group); lost to follow-up in 95 subjects (41 in the placebo group, 19 in the tirzepatide 5 mg group, 20 in the tirzepatide 10 mg group, 15 in the tirzepatide 15 mg group); adverse events in 33 subjects (7 in the placebo group, 7 in the tirzepatide 5 mg group, 11 in the tirzepatide 10 mg group, 8 in the tirzepatide 15 mg group [1 Japanese subject]); pregnancy in 16 subjects (4 in the placebo group, 4 in the tirzepatide 5 mg group, 3 in the tirzepatide 10 mg group, 5 in the tirzepatide 15 mg group); death in 10 subjects (4 in the placebo group, 4 in the tirzepatide 5 mg group, 1 in the tirzepatide 10 mg group, 1 in the tirzepatide 15 mg group); physician's decision in 4 subjects (3 in the tirzepatide 10 mg group, 1 in the tirzepatide 15 mg group); missing body weight measurement at Week 72 in 2 subjects (1 in the placebo group, 1 in the tirzepatide 10 mg group); protocol deviation in 1 subject (placebo group); and other reasons in 46 subjects (22 in the placebo group [1 Japanese subject], 7 in the tirzepatide 5 mg group, 5 in the tirzepatide 10 mg group, 12 in the tirzepatide 15 mg group [1 Japanese subject]).

With regard to efficacy, the success criteria for the study were defined as demonstrating the superiority over placebo for both of the co-primary endpoints, i.e., the percentage change in body weight from baseline to Week 72 and the percentage of subjects who achieved a ≥5% reduction in body weight at Week 72. As shown in Table 14, tirzepatide 10 mg and 15 mg demonstrated the superiority over placebo for both endpoints.

Table 14. Percentage change in body weight from baseline to Week 72 and proportion of subjects achieving ≥5% weight reduction at Week 72 (Study GPHK, mITT population)

Endpoint	Entire population				Japanese subpopulation			
	Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
Body weight at baseline (kg)	104.9 ± 21.45 (N = 629)	103.2 ± 20.68 (N = 617)	106.2 ± 23.29 (N = 621)	105.6 ± 22.96 (N = 623)	87.9 ± 10.66 (N = 26)	89.0 ± 11.12 (N = 24)	86.2 ± 13.37 (N = 22)	86.6 ± 9.74 (N = 29)
Body weight at Week 72 (kg)	101.5 ± 22.77 (N = 466)	86.0 ± 20.58 (N = 535)	83.2 ± 23.35 (N = 526)	81.8 ± 21.87 (N = 533)	88.3 ± 14.76 (N = 22)	77.8 ± 10.77 (N = 23)	67.5 ± 13.55 (N = 21)	68.1 ± 11.60 (N = 24)
Body weight change (%) at Week 72	−3.3 ± 6.96 (N = 466)	−16.5 ± 9.13 (N = 535)	−21.9 ± 10.16 (N = 526)	−22.9 ± 10.16 (N = 533)	−0.5 ± 7.34 (N = 22)	−12.3 ± 7.26 (N = 23)	−22.5 ± 8.41 (N = 21)	−22.2 ± 9.40 (N = 24)
Difference from placebo[a] [95% CI]	-	−13.5 [−14.6, −12.4]	−18.9[c] [−20.0, −17.8]	−20.1[c] [−21.2, −18.9]	-	−11.7 [−16.4, −7.1]	−22.1 [−26.8, −17.4]	−21.8 [−26.2, −17.3]
% of subjects achieving ≥5% reduction in body weight at Week 72	34.1 (159/466)	90.3 (483/535)	96.4 (507/526)	96.3 (513/533)	18.2 (4/22)	91.3 (21/23)	100.0 (21/21)	95.8 (23/24)
Odds ratio compared to placebo[b] [95% CI]	-	23.41 [17.00, 32.23]	74.84[c] [47.39, 118.17]	74.08[c] [46.97, 116.82]	-	204.34 [16.00, 2610.24]	873.62 [22.57, 33817.03]	365.61 [24.05, 5558.38]

Mean ± SD (number of subjects evaluated) or percentage % (number of applicable subjects/number of subjects evaluated); inter-group differences are expressed as least-squares mean difference [95% CI]; -, not applicable

a) For the entire population, calculated using a MMRM, with treatment group, time point, treatment group-by-time point interaction, baseline body weight, status of prediabetes at randomization, region, and sex as explanatory variables, assuming an unstructured covariance matrix for within-subject errors. For the Japanese subpopulation, calculated using a MMRM, with treatment group, time point, treatment group-by-time point interaction, baseline body weight, status of prediabetes at randomization, and sex as explanatory variables, assuming an unstructured covariance matrix for within-subject errors.

b) For the entire population, after imputing missing data using predicted values for the percentage change in body weight as calculated by the MMRM described in footnote a) for the entire population, calculated using Firth's penalized logistic regression with treatment group, baseline body weight, status of prediabetes at randomization, region, and sex as explanatory variables. For the Japanese subpopulation, after imputing missing data using predicted values for the percentage change in body weight as calculated by the MMRM described in footnote a) for the Japanese subpopulation, calculated using Firth's penalized logistic regression with treatment group, baseline body weight, status of prediabetes at randomization, and sex as explanatory variables.

c) $P < 0.001$. To control the overall type I error rate at 5% across the study, a graphical approach was employed, using a two-sided significance level of 2.5% for each comparison between the tirzepatide 10 mg group and the placebo group, and between the tirzepatide 15 mg group and the placebo group, while also incorporating secondary endpoints and the comparison between the tirzepatide 5 mg group and the placebo group.

Figure 2 shows the time course of percentage change in body weight from baseline to Week 72. Tables 15 and 16 show the results of the main secondary endpoints.

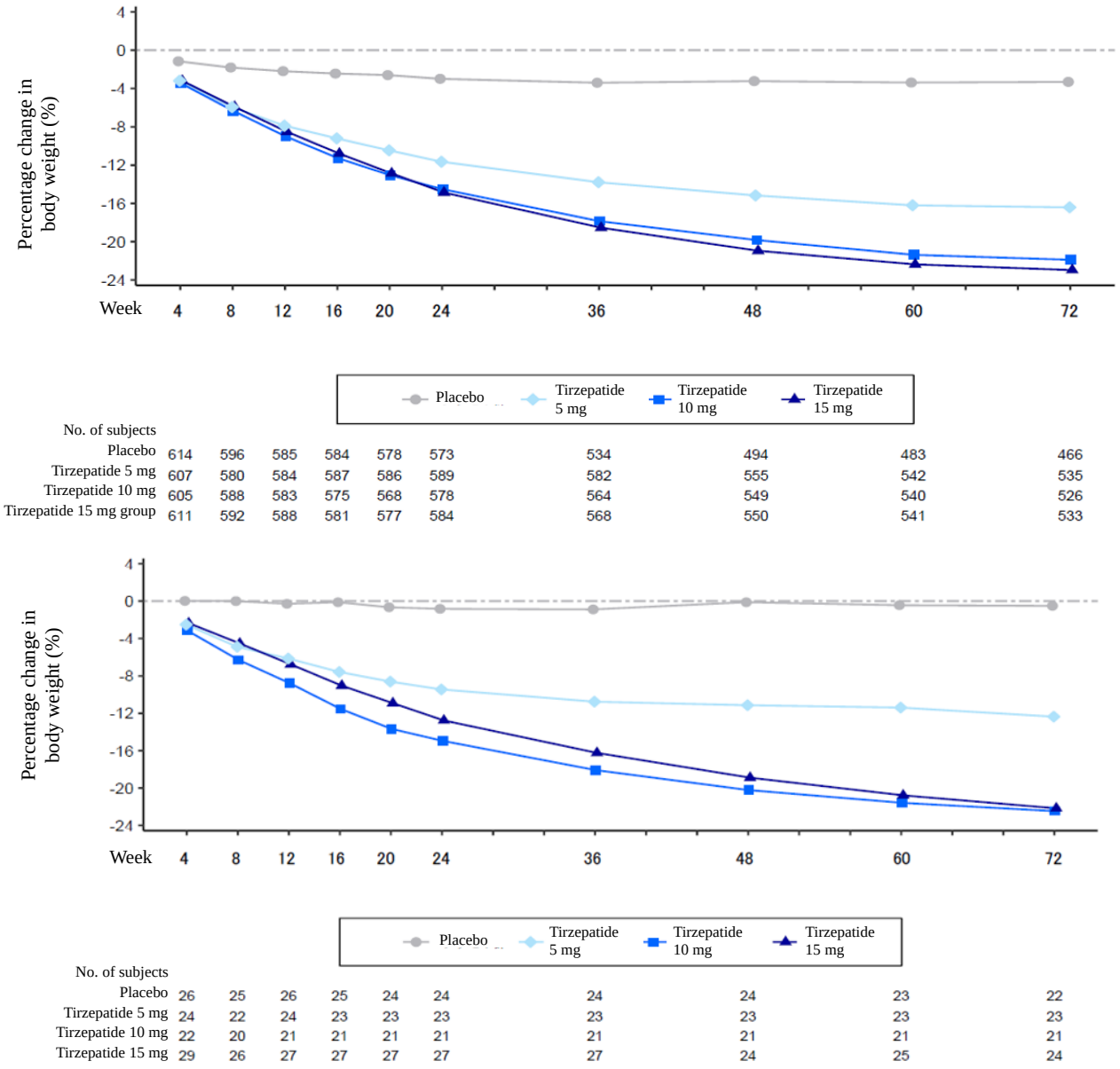

Figure 2. Time course of percentage change in body weight from baseline to Week 72 (upper panel, entire population; lower panel, Japanese subpopulation) (mean values, Study GPHK, mITT population)

Table 15. Results of main secondary endpoints related to body weight (Study GPHK, mITT population)

Endpoint		Entire population				Japanese subpopulation			
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
% of subjects achieving body weight loss[a)]	≥10%	17.4 (81/466)	75.0 (401/535)	86.1 (453/526)	90.2 (481/533)	9.1 (2/22)	65.2 (15/23)	95.2 (20/21)	95.8 (23/24)
	≥15%	7.3 (34/466)	53.5 (286/535)	74.3 (391/526)	78.2 (417/533)	4.6 (1/22)	30.4 (7/23)	76.2 (16/21)	79.2 (19/24)
	≥20%	1.5 (7/466)	34.0 (182/535)	56.8 (299/526)	64.0 (341/533)	4.6 (1/22)	8.7 (2/23)	61.9 (13/21)	62.5 (15/24)
	≥25%	0.4 (2/466)	17.8 (95/535)	36.9 (194/526)	41.3 (220/533)	0.0 (0/22)	8.7 (2/23)	38.1 (8/21)	33.3 (8/24)
BMI (kg/m^2)	Baseline	38.3 ± 6.90 (N = 629)	37.5 ± 6.63 (N = 617)	38.4 ± 7.00 (N = 621)	38.1 ± 6.70 (N = 623)	31.9 ± 3.42 (N = 26)	32.5 ± 4.61 (N = 24)	31.6 ± 3.41 (N = 22)	31.3 ± 2.88 (N = 29)
	Change at Week 72	−1.2 ± 2.70 (N = 466)	−6.1 ± 3.61 (N = 535)	−8.3 ± 4.22 (N = 526)	−8.8 ± 4.24 (N = 533)	0.0 ± 2.32 (N = 22)	−4.0 ± 2.45 (N = 23)	−7.1 ± 2.87 (N = 21)	−7.2 ± 3.43 (N = 24)
Waist circumference[b)] (cm)	Baseline	114.1 ± 14.98 (N = 628)	113.3 ± 14.26 (N = 616)	115.0 ± 15.82 (N = 621)	114.4 ± 15.63 (N = 623)	101.8 ± 8.55 (N = 26)	103.1 ± 8.91 (N = 24)	100.2 ± 8.92 (N = 22)	100.8 ± 7.44 (N = 29)
	Change at Week 72	−4.1 ± 8.02 (N = 466)	−14.9 ± 10.42 (N = 534)	−19.6 ± 10.21 (N = 525)	−20.2 ± 10.45 (N = 533)	−1.1 ± 6.04 (N = 22)	−7.5 ± 7.03 (N = 23)	−17.4 ± 7.92 (N = 21)	−16.9 ± 8.55 (N = 24)

Percentage (number of applicable subjects/number of subjects evaluated) or mean ± SD (number of subjects evaluated)

a) Percentage of subjects who achieved ≥10%, ≥15%, ≥20%, or ≥25% weight loss from baseline to Week 72.

b) Measured at the midpoint between the lower margin of the rib cage and the upper margin of the iliac crest.

Table 16. Results of main secondary endpoints related to blood glucose, blood pressure, and lipid parameters (Study GPHK, mITT population)

Endpoint		Entire population				Japanese subpopulation			
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
HbA1c (%)	Baseline	5.57 ± 0.38 (N = 606)	5.56 ± 0.36 (N = 602)	5.55 ± 0.37 (N = 600)	5.55 ± 0.41 (N = 606)	5.67 ± 0.39 (N = 26)	5.53 ± 0.33 (N = 24)	5.54 ± 0.29 (N = 21)	5.50 ± 0.33 (N = 26)
	Change at Week 72	−0.08 ± 0.30 (N = 459)	−0.41 ± 0.30 (N = 527)	−0.49 ± 0.32 (N = 516)	−0.51 ± 0.36 (N = 524)	−0.03 ± 0.26 (N = 22)	−0.49 ± 0.24 (N = 23)	−0.66 ± 0.23 (N = 21)	−0.66 ± 0.22 (N = 24)
Fasting plasma glucose (mg/dL)	Baseline	95.77 ± 9.57 (N = 606)	95.34 ± 9.84 (N = 603)	95.58 ± 10.77 (N = 599)	95.18 ± 10.27 (N = 606)	95.48 ± 7.76 (N = 26)	97.50 ± 7.23 (N = 24)	95.31 ± 9.93 (N = 21)	97.81 ± 9.58 (N = 27)
	Change at Week 72	0.66 ± 13.50 (N = 457)	−7.70 ± 13.47 (N = 524)	−9.98 ± 12.02 (N = 517)	−10.40 ± 12.63 (N = 521)	0.25 ± 10.54 (N = 22)	−10.81 ± 6.59 (N = 23)	−11.24 ± 7.87 (N = 21)	−15.69 ± 8.83 (N = 24)
Systolic blood pressure (mmHg)	Baseline	122.7 ± 12.60 (N = 628)	123.6 ± 12.52 (N = 618)	123.8 ± 12.86 (N = 621)	122.9 ± 12.91 (N = 623)	124.4 ± 10.50 (N = 26)	126.6 ± 11.20 (N = 24)	126.2 ± 12.82 (N = 22)	127.1 ± 13.56 (N = 29)
	Change at Week 72	−1.1 ± 11.70 (N = 466)	−7.5 ± 12.85 (N = 535)	−9.1 ± 12.98 (N = 526)	−8.0 ± 13.03 (N = 533)	−1.8 ± 11.01 (N = 22)	−9.7 ± 9.92 (N = 23)	−17.3 ± 7.72 (N = 21)	−12.9 ± 13.74 (N = 24)
Diastolic blood pressure (mmHg)	Baseline	79.5 ± 7.91 (N = 628)	79.2 ± 8.17 (N = 618)	79.9 ± 8.32 (N = 621)	79.3 ± 8.21 (N = 623)	79.4 ± 8.79 (N = 26)	79.1 ± 9.13 (N = 24)	79.8 ± 9.74 (N = 22)	82.2 ± 10.86 (N = 29)
	Change at Week 72	−1.2 ± 8.23 (N = 466)	−5.2 ± 8.76 (N = 535)	−6.0 ± 8.82 (N = 526)	−4.7 ± 9.23 (N = 533)	−0.5 ± 9.49 (N = 22)	−5.7 ± 7.57 (N = 23)	−10.4 ± 5.39 (N = 21)	−8.1 ± 10.90 (N = 24)
Total cholesterol (mg/dL)	Baseline	190.0 ± 38.67 (N = 606)	191.0 ± 40.03 (N = 603)	194.4 ± 38.75 (N = 599)	190.9 ± 37.88 (N = 606)	204.8 ± 42.53 (N = 26)	202.8 ± 36.14 (N = 24)	197.6 ± 27.35 (N = 21)	217.8 ± 39.96 (N = 27)
	Percentage change at Week 72 (%)	0.52 ± 18.09 (N = 458)	−3.68 ± 16.31 (N = 523)	−4.60 ± 17.05 (N = 517)	−6.46 ± 15.96 (N = 520)	1.5 ± 12.74 (N = 22)	−10.1 ± 12.49 (N = 23)	−13.7 ± 8.92 (N = 21)	−15.8 ± 14.79 (N = 24)
LDL cholesterol (mg/dL)	Baseline	113.2 ± 33.29 (N = 573)	113.3 ± 32.30 (N = 584)	116.3 ± 32.83 (N = 574)	114.0 ± 32.66 (N = 582)	125.3 ± 26.61 (N = 24)	119.5 ± 27.82 (N = 23)	121.1 ± 21.88 (N = 21)	129.4 ± 34.32 (N = 27)
	Percentage change at Week 72 (%)	3.05 ± 28.63 (N = 456)	−1.70 ± 26.60 (N = 514)	−3.55 ± 26.37 (N = 511)	−5.97 ± 24.89 (N = 515)	3.5 ± 16.48 (N = 22)	−9.4 ± 16.41 (N = 23)	−20.1 ± 13.83 (N = 21)	−19.2 ± 25.40 (N = 24)
HDL cholesterol (mg/dL)	Baseline	48.0 ± 12.61 (N = 576)	49.2 ± 13.14 (N = 589)	48.9 ± 12.73 (N = 577)	49.0 ± 12.62 (N = 584)	52.1 ± 13.88 (N = 24)	53.0 ± 10.93 (N = 23)	52.2 ± 9.81 (N = 21)	57.7 ± 14.05 (N = 27)
	Percentage change at Week 72 (%)	2.82 ± 17.42 (N = 458)	8.68 ± 20.19 (N = 518)	10.13 ± 20.77 (N = 515)	9.96 ± 20.65 (N = 519)	0.17 ± 13.74 (N = 22)	3.92 ± 14.99 (N = 23)	11.76 ± 15.46 (N = 21)	13.11 ± 22.07 (N = 24)
Triglycerides (mg/dL)[a)]	Baseline	146.4 ± 82.81 (N = 606)	150.1 ± 151.96 (N = 603)	144.0 ± 87.89 (N = 599)	142.6 ± 82.01 (N = 606)	151.4 ± 77.24 (N = 26)	157.8 ± 70.55 (N = 24)	121.5 ± 52.48 (N = 21)	153.4 ± 64.20 (N = 27)
	Percentage change at Week 72 (%)	0.5 ± 44.65 (N = 457)	−18.4 ± 34.76 (N = 522)	−19.2 ± 38.52 (N = 515)	−24.8 ± 37.73 (N = 518)	7.6 ± 49.57 (N = 22)	−28.9 ± 31.67 (N = 23)	−30.5 ± 22.83 (N = 21)	−44.2 ± 24.93 (N = 24)

Mean ± SD (number of subjects evaluated)
a) Fasting

Tables 17 and 18 show the incidence of adverse events and adverse drug reactions occurring in ≥5% of subjects in any treatment group in the entire population and the Japanese subpopulation, respectively.

Table 17. Incidence of adverse events and adverse drug reactions occurring in ≥5% of subjects in any treatment group (Study GPHK [entire population], safety analysis population)

Event	Placebo (N = 637)		Tirzepatide 5 mg (N = 624)		Tirzepatide 10 mg (N = 628)		Tirzepatide 15 mg (N = 628)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	71.9 (458)	30.5 (194)	80.9 (505)	55.6 (347)	81.8 (514)	62.3 (391)	78.8 (495)	61.1 (384)
Nausea	9.6 (61)	8.0 (51)	24.7 (154)	21.0 (131)	33.4 (210)	30.7 (193)	31.1 (195)	28.5 (179)
Diarrhoea	7.2 (46)	5.7 (36)	18.9 (118)	15.4 (96)	21.3 (134)	17.8 (112)	22.9 (144)	19.1 (120)
COVID-19	14.1 (90)	0 (0)	15.1 (94)	0 (0)	15.6 (98)	0 (0)	13.1 (82)	0 (0)
Vomiting	1.7 (11)	0.8 (5)	8.3 (52)	6.7 (42)	10.8 (68)	10.0 (63)	12.3 (77)	10.7 (67)
Constipation	5.8 (37)	4.1 (26)	16.7 (104)	13.5 (84)	17.4 (109)	14.0 (88)	11.8 (74)	10.0 (63)
Dyspepsia	4.1 (26)	3.1 (20)	9.0 (56)	7.9 (49)	9.7 (61)	8.1 (51)	11.1 (70)	9.9 (62)
Decreased appetite	3.3 (21)	3.0 (19)	9.5 (59)	8.8 (55)	11.6 (73)	11.0 (69)	8.6 (54)	7.3 (46)
Headache	6.6 (42)	1.6 (10)	6.6 (41)	3.4 (21)	6.8 (43)	3.2 (20)	6.5 (41)	3.5 (22)
Alopecia	0.9 (6)	0.3 (2)	5.1 (32)	1.3 (8)	4.9 (31)	1.3 (8)	5.7 (36)	1.1 (7)
Eructation	0.6 (4)	0.6 (4)	3.8 (24)	3.8 (24)	5.3 (33)	4.9 (31)	5.6 (35)	5.1 (32)
Abdominal pain	3.3 (21)	2.4 (15)	5.0 (31)	3.5 (22)	5.3 (33)	4.8 (30)	4.9 (31)	4.0 (25)
Injection site reaction	0.3 (2)	0.3 (2)	2.9 (18)	2.7 (17)	5.7 (36)	5.6 (35)	4.6 (29)	4.5 (28)
Dizziness	2.4 (15)	0.5 (3)	4.2 (26)	2.1 (13)	5.6 (35)	2.2 (14)	4.1 (26)	1.8 (11)

Incidence % (number of subjects with events), MedDRA/J ver.24.1

Table 18. Incidence of adverse events and adverse drug reactions occurring in ≥5% of subjects in any treatment group (Study GPHK [Japanese subpopulation], safety analysis population)

Event	Placebo (N = 27)		Tirzepatide 5 mg (N = 24)		Tirzepatide 10 mg (N = 22)		Tirzepatide 15 mg (N = 29)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	59.3 (16)	11.1 (3)	75.0 (18)	41.7 (10)	63.6 (14)	54.5 (12)	75.9 (22)	51.7 (15)
Nausea	3.7 (1)	0 (0)	4.2 (1)	4.2 (1)	13.6 (3)	13.6 (3)	20.7 (6)	17.2 (5)
Decreased appetite	0 (0)	0 (0)	12.5 (3)	8.3 (2)	4.5 (1)	4.5 (1)	17.2 (5)	17.2 (5)
Constipation	7.4 (2)	3.7 (1)	25.0 (6)	20.8 (5)	18.2 (4)	18.2 (4)	13.8 (4)	13.8 (4)
Pyrexia	11.1 (3)	0 (0)	8.3 (2)	0 (0)	13.6 (3)	0 (0)	13.8 (4)	0 (0)
Diarrhoea	0 (0)	0 (0)	4.2 (1)	0 (0)	4.5 (1)	4.5 (1)	13.8 (4)	6.9 (2)
Abdominal discomfort	0 (0)	0 (0)	0 (0)	0 (0)	4.5 (1)	4.5 (1)	13.8 (4)	13.8 (4)
Headache	0 (0)	0 (0)	4.2 (1)	0 (0)	0 (0)	0 (0)	10.3 (3)	3.4 (1)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	9.1 (2)	9.1 (2)	6.9 (2)	6.9 (2)
Weight decreased	0 (0)	0 (0)	0 (0)	0 (0)	4.5 (1)	4.5 (1)	6.9 (2)	6.9 (2)
Injection site reaction	0 (0)	0 (0)	4.2 (1)	4.2 (1)	22.7 (5)	22.7 (5)	3.4 (1)	3.4 (1)
Dental caries	7.4 (2)	0 (0)	4.2 (1)	0 (0)	9.1 (2)	0 (0)	3.4 (1)	0 (0)
Back pain	3.7 (1)	0 (0)	8.3 (2)	0 (0)	4.5 (1)	0 (0)	3.4 (1)	0 (0)
Gastrooesophageal reflux disease	3.7 (1)	0 (0)	8.3 (2)	4.2 (1)	0 (0)	0 (0)	3.4 (1)	3.4 (1)
Gastroenteritis	3.7 (1)	0 (0)	4.2 (1)	0 (0)	9.1 (2)	0 (0)	0 (0)	0 (0)
Dermatitis contact	0 (0)	0 (0)	0 (0)	0 (0)	9.1 (2)	0 (0)	0 (0)	0 (0)
Abdominal distension	0 (0)	0 (0)	8.3 (2)	8.3 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Nasopharyngitis	7.4 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence % (number of subjects with events), MedDRA/J ver.24.1

Deaths were observed in 4 subjects in the placebo group (pulmonary embolism, cardiac failure acute, intestinal obstruction, ischaemic stroke in 1 subject each), 4 subjects in the tirzepatide 5 mg group (COVID-19 pneumonia in 2 subjects, and hepatic failure and multiple injuries in 1 subject each), 1 subject in the tirzepatide 10 mg group (homicide), and 1 subject in the tirzepatide 15 mg group (severe acute respiratory syndrome-coronavirus 2 [SARS-CoV-2] test positive). Among them, hepatic failure (1 subject)[14)] in the tirzepatide 5 mg group was considered an adverse drug reaction.

[14)] A 4[redacted]-year-old Black or African American female with a history of hypertension and impaired glucose tolerance was found unconscious at home at Week 45 and was admitted to the intensive care unit on the same day. During hospitalization, she had severe hypoglycaemia and was diagnosed with acute hepatic failure accompanied by hepatic encephalopathy, shock, and acute kidney injury. Clinical laboratory tests detected ethanol in the blood, and urine drug screening was positive for cocaine and opiates. An SARS-CoV-2 test was positive. Her death was confirmed 3 days after admission.

Tables 19 and 20 show the incidence of serious adverse events and adverse events leading to treatment discontinuation.

Table 19. Incidence of serious adverse events (Study GPHK, safety analysis population)

Group	Incidence	Breakdown
Placebo	6.9 (44/637)	COVID-19 in 6 subjects; COVID-19 pneumonia in 4 subjects; appendicitis in 3 subjects; pulmonary embolism and osteoarthritis in 2 subjects each; and obstructive pancreatitis[a)]/cholelithiasis,[a)] renal cancer,[a)] dizziness,[b)] hypertension/pulmonary embolism,[c)] cardiac failure acute,[c)] vaginal haemorrhage/adenocarcinoma of the cervix/acute kidney injury/intestinal obstruction,[c)] wound, ischaemic stroke,[c)] cholecystitis chronic, cholecystitis chronic/cholelithiasis, ovarian cancer, meningioma, retroperitoneal haematoma, vertebral foraminal stenosis, hypoaesthesia, papillary thyroid cancer/duodenal ulcer/pancreatic carcinoma metastatic, diverticulitis, cholelithiasis, coronary artery disease, idiopathic generalised epilepsy, atrial fibrillation/plasma cell myeloma, hypertension, cholecystitis chronic, prostate cancer, intraductal proliferative breast lesion, thrombophlebitis, and non-cardiac chest pain in 1 subject each
Tirzepatide 5 mg	6.3 (39/624)	COVID-19 pneumonia[c)] in 6 subjects; cholelithiasis[a)] and appendicitis[b)] in 3 subjects each; and aspiration/acute respiratory failure/SARS-CoV-2 test positive/substance abuse/acute kidney injury/hepatic failure[a) c)]/brain oedema, pancreatitis acute[a)]/acute kidney injury/pneumonia, ileus paralytic,[a)] prostate cancer,[b)] road traffic accident/multiple injuries,[c)] facial bones fracture, bacterial colitis, ectopic pregnancy, peritonsillar abscess, angina unstable, abortion spontaneous, appendicitis/abdominal abscess, pneumonia, asthma, endometrial cancer/ovarian germ cell endodermal sinus tumour stage I, cholecystitis, major depression/non-cardiac chest pain/contusion, malignant melanoma, chronic obstructive pulmonary disease, chest pain, vertebrobasilar stroke, acute myocardial infarction, urinary tract infection, cholecystitis acute, pneumonia/coronavirus infection, COVID-19, and thalamus haemorrhage in 1 subject each
Tirzepatide 10 mg	6.7 (42/628)	COVID-19 and cholelithiasis in 3 subjects each; COVID-19 pneumonia, cholecystitis,[a)] and cholecystitis acute in 2 subjects each; cholelithiasis[a)]/cholecystitis chronic,[a)] gastroenteritis/anxiety disorder/bulimia nervosa[a)]/COVID-19, hypotension/acute respiratory failure/acute kidney injury/colitis ulcerative[a)]/septic shock, suicide attempt,[a)] vomiting,[a)] osteoarthritis, enteritis, ischaemic stroke, COVID-19/pneumonitis, procedural pain/constipation, sphincter of Oddi dysfunction, meningioma, renal failure, diverticulitis, homicide,[c)] urinary tract infection, tibia fracture/ankle fracture/foot fracture/rectocele/cystocele/uterine prolapse, pyelonephritis, vertigo, adjustment disorder with mixed anxiety and depressed mood, lumbar vertebral fracture, myocardial infarction/coronavirus pneumonia/proctitis, acute coronary syndrome, peritoneal tuberculosis, malignant melanoma, influenza, COVID-19/deep vein thrombosis, dyspnoea, endometrial hyperplasia, and COVID-19 pneumonia/pneumonia bacterial/pulmonary embolism in 1 subject each
Tirzepatide 15 mg	5.1 (32/628)	COVID-19 pneumonia in 3 subjects; appendicitis in 2 subjects; and chronic gastritis,[a)] colitis[a)]/pancreatitis,[a)] vomiting,[a)] cholecystitis acute,[a)] uterine leiomyoma,[b)] SARS-CoV-2 test positive,[c)] thyroidectomy, breast cancer/cellulitis, multiple sclerosis relapse, biliary obstruction/bile duct stone, suicide attempt, oesophagitis ulcerative/cholelithiasis/gastric antral vascular ectasia/pneumonia aspiration, nephrolithiasis, hypotension, cholelithiasis/cholecystitis chronic, hypertensive urgency/encephalopathy, leiomyoma, pelvic inflammatory disease, cholelithiasis, anal abscess, pyelonephritis, lung adenocarcinoma, renal mass, cholangitis acute, adenosquamous carcinoma of the cervix, meningioma, and COVID-19 in 1 subject each

The occurrence is presented as the incidence % (number of subjects with events/number of subjects evaluated). MedDRA/J ver. 24.1

a) Events assessed as adverse drug reactions. Of them, 1 of the 3 cases of cholelithiasis in the placebo group, 2 of the 3 cases in the tirzepatide 5 mg group, 1 of the 4 cases in the tirzepatide 10 mg group, and 1 of the 2 cases of cholecystitis were considered adverse drug reactions.

b) Events that occurred in Japanese subjects. Of them, 1 of the 4 cases of appendicitis in the tirzepatide 5 mg group occurred in a Japanese subject.

c) Events with a fatal outcome. Of them, 1 of the 3 cases of pulmonary embolism in the placebo group, and 2 of the 6 cases of COVID-19 pneumonia in the tirzepatide 5 mg group, had a fatal outcome.

Table 20. Incidence of adverse events leading to treatment discontinuation (Study GPHK, safety analysis population)

Group	Incidence	Breakdown
Placebo	3.1 (20/637)	Nausea[a)] and pulmonary embolism in 2 subjects each; and obstructive pancreatitis,[a)] asthenia,[a)] migraine,[a)] renal cancer,[a)] cardiac failure acute, hepatic steatosis, COVID-19 pneumonia, blood potassium decreased, hepatic enzyme increased, adenocarcinoma of the cervix, pancreatic carcinoma metastatic, plasma cell myeloma, ischaemic stroke, anxiety, alopecia, and peritoneal formation in 1 subject each
Tirzepatide 5 mg	4.5 (28/624)	Nausea[a) b)] in 5 subjects; diarrhoea[a)] and COVID-19 pneumonia in 2 subjects each; and gastrooesophageal reflux disease,[a)] constipation,[a)] pancreatitis acute,[a)] malaise,[a)] cholelithiasis,[a)] hepatic failure,[a)] lipase increased,[a)] headache,[a)] hiccups,[a)] orthostatic hypotension,[a)] vision blurred, dyspepsia, multiple injuries, prostate cancer, malignant melanoma, invasive ductal breast carcinoma, resting tremor, thalamus haemorrhage, and dyspnoea[a)] in 1 subject each
Tirzepatide 10 mg	7.0 (44/628)	Nausea[a)] in 6 subjects; diarrhoea[a)] in 5 subjects; vomiting[a)] in 4 subjects; abdominal pain,[a)] constipation,[a)] gastrointestinal disorders,[a)] abdominal distension,[a)] blood calcitonin increased,[a)] and rash[a)] in 2 subjects each; and gastrooesophageal reflux disease,[a)] dyspepsia,[a)] abdominal pain upper,[a)] injection site rash,[a)] liver function test increased,[a)] decreased appetite,[a)] musculoskeletal pain,[a)] suicide attempt,[a)] vertigo, diverticulitis, peritoneal tuberculosis, malignant melanoma, dizziness, mania, homicide, abortion induced, and deep vein thrombosis in 1 subject each
Tirzepatide 15 mg	6.4 (40/628)	Nausea[a) b)] in 12 subjects; diarrhoea[a)] and abdominal pain[a)] in 3 subjects each; gastrooesophageal reflux disease[a) b)] and flatulence[a)] in 2 subjects each; and dyspepsia,[a)] gastrointestinal disorders,[a)] colitis,[a)] drug intolerance,[a)] injection site reaction,[a)] gamma-glutamyltransferase increased,[a)] decreased appetite,[a)] myalgia,[a)] depression,[a)] oesophagitis ulcerative, fatigue, SARS-CoV-2 test positive, adenosquamous carcinoma of the cervix, breast cancer, lung adenocarcinoma, renal mass, dermatitis, and orthostatic hypotension in 1 subject each

The occurrence is presented as the incidence % (number of subjects with events/number of subjects evaluated). MedDRA/J ver. 24.1

a) Events assessed as adverse drug reactions. Of them, 4 (including 1 Japanese subject) of 5 cases of nausea in the tirzepatide 5 mg group, 5 of 6 cases of nausea in the tirzepatide 10 mg group, and 11 (including 1 Japanese subject) of 12 cases of nausea in the tirzepatide 15 mg group, as well as 2 of 3 cases of abdominal pain and 1 of 2 cases of flatulence, both in the tirzepatide 15 mg group, were considered adverse drug reactions.

b) Events that occurred in Japanese subjects. Of them, 1 of 5 cases of nausea in the tirzepatide 5 mg group, 1 of 12 cases of nausea in the tirzepatide 15 mg group, and 1 of 2 cases of gastrooesophageal reflux disease were observed in Japanese subjects.

Among the 22 randomized subjects excluded from the mITT population, death (suspected stroke) was observed in 1 subject in the tirzepatide 10 mg group, but this event was not considered an adverse drug reaction. Serious adverse events were observed in 1 subject in the tirzepatide 5 mg group (intraductal proliferative breast lesion) and 2 subjects in the tirzepatide 10 mg group (device dislocation and cerebrovascular accident in 1 subject each). Among them, the intraductal proliferative breast lesion (1 subject) in the tirzepatide 5 mg group was considered an adverse drug reaction. Adverse events leading to treatment discontinuation were observed in 1 subject in the placebo group (hepatitis A), 2 subjects in the tirzepatide 5 mg group (nausea and intraductal proliferative breast lesion in 1 subject each), and 2 subjects in the tirzepatide 10 mg group (nausea and gastrooesophageal reflux disease in 1 subject each). Among them, nausea and intraductal proliferative breast lesion (1 subject each) in the tirzepatide 5 mg group, as well as nausea and gastrooesophageal reflux disease (1 subject each) in the tirzepatide 10 mg group, were considered adverse drug reactions.

7.3 Global phase III study in patients with overweight or obesity with type 2 diabetes mellitus (CTD 5.3.5.1.4, Study GPHL [March 2021 to April 2023])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of tirzepatide as an adjunct to diet and exercise therapy in patients with overweight or obesity with type 2 diabetes mellitus, including Japanese subjects[15)] (target sample size, 900 subjects[16)]; 300 per group).

The main inclusion criteria were patients aged ≥18 years with overweight or obesity who met all of the following criteria: (1) BMI ≥27 kg/m^2; (2) diagnosed with type 2 diabetes mellitus,[17)] with HbA1c between ≥7% and ≤10% at screening; and (3) failed at least once in dietary efforts to reduce weight. Patients with type 1 diabetes mellitus or those who had undergone or were scheduled to undergo bariatric surgery were excluded.

This study consisted of a screening period (3 weeks), a treatment period (72 weeks), and a follow-up period (4 weeks).

Placebo, tirzepatide 10 mg, or tirzepatide 15 mg was administered subcutaneously (self-injection) once weekly[6)] in the abdomen or thigh. The starting dose of tirzepatide was 2.5 mg, with dose escalation by 2.5 mg every 4 weeks until reaching the maintenance dose (10 mg or 15 mg).[18)]

All of 938 randomized subjects (315 in the placebo group [21 Japanese subjects], 312 in the tirzepatide 10 mg group [24 Japanese subjects], 311 in the tirzepatide 15 mg group [22 Japanese subjects]) received at least 1 dose of the study drug. After excluding 26 subjects enrolled at study sites involving a SMO where GCP violations were identified,[8)] 912 subjects (307 in the placebo group [13 Japanese subjects], 302 in the tirzepatide 10 mg group [14 Japanese subjects], 303 in the tirzepatide 15 mg group [14 Japanese subjects]) were included in the mITT and safety analysis populations, and the mITT population was used for primary efficacy analyses. A total of 78 subjects (34 in the placebo group, 16 in the tirzepatide 10 mg group, 28 in the tirzepatide 15 mg group [2 Japanese subjects]) discontinued the study. Reasons for discontinuation were as follows: Consent withdrawal in 32 subjects (16 in the placebo group, 7 in the tirzepatide 10 mg group, 9 in the tirzepatide 15 mg group [1 Japanese subject]); lost to follow-up in 22 subjects (8 in the placebo group, 4 in the tirzepatide 10 mg group, 10 in the tirzepatide 15 mg group); adverse events in 11 subjects (5 in the placebo group, 1 in the tirzepatide 10 mg group, 5 in the tirzepatide 15 mg group [1 Japanese subject]); pregnancy in 4 subjects (2 in the placebo group, 2 in the tirzepatide 15 mg group); death in 2 subjects (2 in the tirzepatide 10 mg group); and other reasons in 7 subjects (3 in the placebo group, 2 in the tirzepatide 10 mg group, 2 in the tirzepatide 15 mg group).

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15) Japan, Argentina, Brazil, India, Russia, Taiwan, and the US (including Puerto Rico)

16) For the percentage change in body weight from baseline to Week 72, which was one of the co-primary endpoints,, the target sample size was 300 subjects per group (total of 900 subjects) to ensure a statistical power of >90% under the assumptions of an mean group difference of 11%, a common SD of 10%, and a dropout rate of 25% for comparisons between the tirzepatide 10 mg and placebo groups, as well as the tirzepatide 15 mg and placebo groups, with a two-sided significance level of 2.5% for each hypothesis test using a t-test. With 300 subjects per group, sufficient statistical power of >90% was also ensured for another co-primary efficacy endpoint, which was the proportion of subjects achieving ≥5% body weight reduction at Week 72, when applying a chi-square test under the assumptions of an achievement rate of 90% for the tirzepatide 10 mg and 15 mg groups, 25% for the placebo group, a dropout rate of 25%, and a two-sided significance level of 2.5% for comparisons between the tirzepatide 10 mg and placebo groups, as well as the tirzepatide 15 mg and placebo groups.

17) Subjects were required to have received stable treatment for at least 3 months before screening, which could include diet/exercise therapy alone or oral hypoglycemic drugs excluding dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists.

18) Subjects experiencing intolerable gastrointestinal symptoms were allowed a one-time dose reduction (from 15 mg to 10 mg, or from 10 mg to placebo). If intolerable gastrointestinal symptoms persisted despite dose reduction, treatment was discontinued.

Regarding efficacy, the success criteria for the study were demonstrating the superiority over placebo for both co-primary endpoints, i.e., percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% body weight loss at Week 72. The results are shown in Table 21, demonstrating the superiority of tirzepatide 10 mg and tirzepatide 15 mg over placebo.

Table 21. Percentage change in body weight from baseline to Week 72 and proportion of subjects achieving ≥5% weight reduction at Week 72 (Study GPHL, mITT population)

Endpoint	Entire population			Japanese subpopulation		
	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
Baseline body weight (kg)	102.1 ± 22.27 (N = 303)	101.7 ± 20.84 (N = 299)	99.8 ± 20.10 (N = 301)	86.5 ± 7.24 (N = 13)	89.0 ± 15.78 (N = 14)	88.5 ± 10.40 (N = 14)
Body weight at Week 72 (kg)	97.3 ± 22.49 (N = 256)	88.5 ± 20.36 (N = 274)	84.1 ± 19.51 (N = 259)	83.7 ± 9.91 (N = 13)	78.1 ± 16.57 (N = 14)	80.0 ± 13.74 (N = 12)
Body weight change (%) at Week 72	−3.5 ± 5.87 (N = 256)	−13.3 ± 8.38 (N = 274)	−16.0 ± 9.70 (N = 259)	−3.5 ± 4.93 (N = 13)	−12.4 ± 7.96 (N = 14)	−10.0 ± 6.93 (N = 12)
Difference from placebo[a] [95% CI]	-	−10.3[c] [−11.7, −8.9]	−12.4[c] [−13.8, −11.1]	-	−8.9 [−14.1, −3.8]	−6.7 [−11.9, −1.5]
% of subjects achieving ≥5% reduction in body weight at Week 72	33.6 (86/256)	82.1 (225/274)	87.6 (227/259)	46.2 (6/13)	85.7 (12/14)	75.0 (9/12)
Odds ratio compared to placebo[b] [95% CI]	-	11.03[c] [7.42, 16.39]	14.92[c] [9.80, 22.71]	-	5.12 [0.84, 31.10]	3.65 [0.70, 19.18]

Mean ± SD (number of subjects evaluated) or percentage (number of applicable subjects/number of subjects evaluated); inter-group differences are expressed as least-squares mean difference [95% CI]; -, not applicable

a) For the entire population, calculated using a MMRM, with treatment group, time point, treatment group-by-time point interaction, baseline body weight, type of hypoglycemic drug(s) used at randomization, region, and sex as explanatory variables, assuming an unstructured covariance matrix for within-subject errors. For the Japanese subpopulation, calculated using a MMRM, with treatment group, time point, treatment group-by-time point interaction, baseline body weight, type of hypoglycemic drug(s) used at randomization, and sex as explanatory variables, assuming an unstructured covariance matrix for within-subject errors.

b) For the entire population, after imputing missing data using predicted values for the percentage change in body weight as calculated by the MMRM described in footnote a) for the entire population, calculated using Firth's penalized logistic regression with treatment group, baseline body weight, type of hypoglycemic drug(s) used at randomization, region, and sex as explanatory variables. For the Japanese subpopulation, after imputing missing data using predicted values for the percentage change in body weight as calculated by the MMRM described in footnote a) for the Japanese subpopulation, calculated using Firth's penalized logistic regression with treatment group, baseline body weight, type of hypoglycemic drug(s) used at randomization, and sex as explanatory variables.

c) $P < 0.001$. To control the overall type I error rate at 5% across the study, a graphical approach that included secondary endpoints was employed, using a two-sided significance level of 2.5% for each comparison of between the tirzepatide 10 mg group and the placebo group, and between the tirzepatide 15 mg group and the placebo group.

Figure 3 shows the time course of percentage change in body weight from baseline to Week 72. Tables 22 and 23 show the results of the main secondary endpoints.

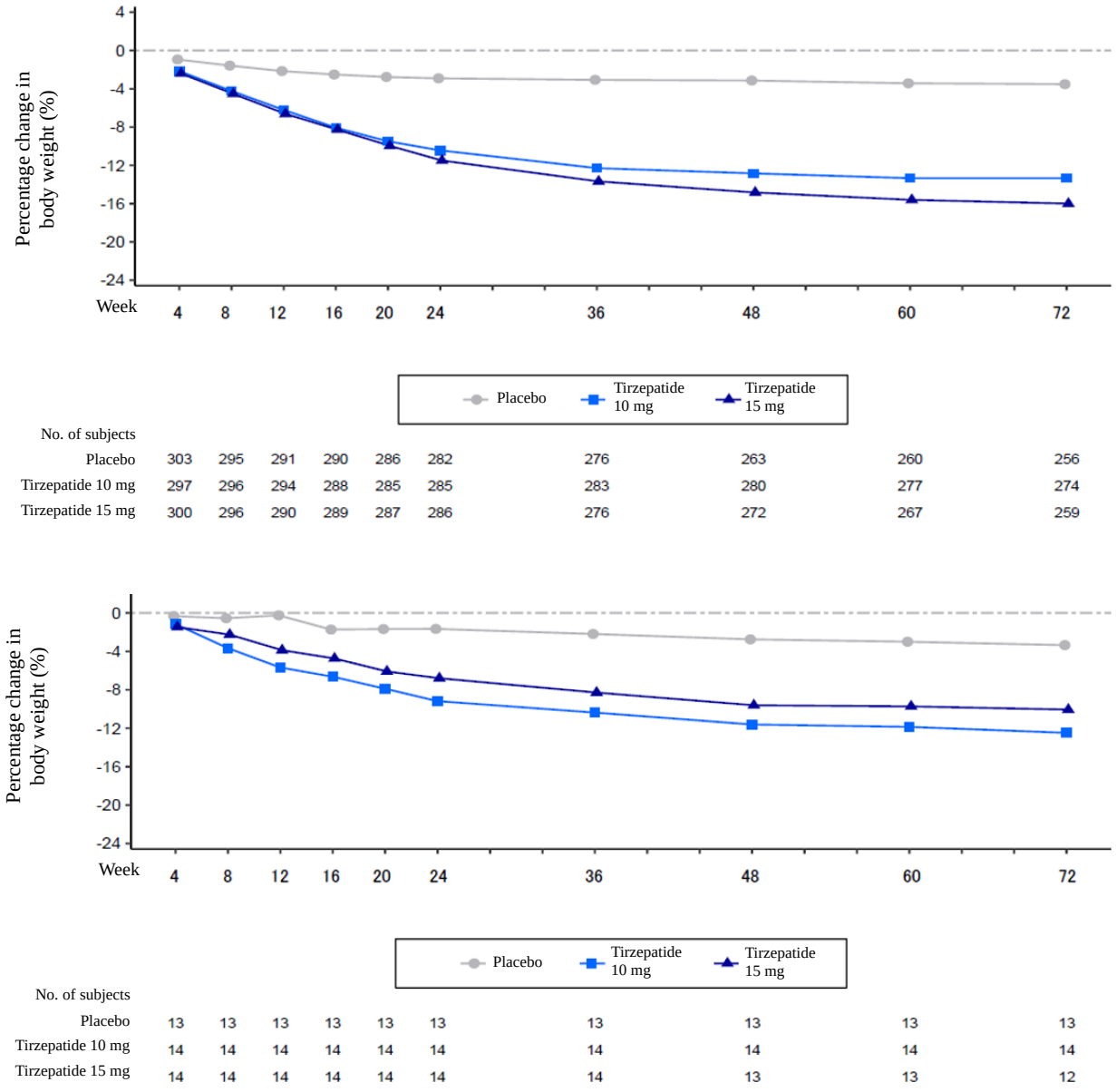

Figure 3. Time course of percentage change in body weight from baseline to Week 72
(Upper, entire population; Lower, Japanese subpopulation)
(Mean values, Study GPHL, mITT population)

Table 22. Results of main secondary endpoints related to body weight (Study GPHL, mITT population)

Endpoint		Entire population			Japanese subpopulation		
		Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
% of subjects achieving body weight loss[a)]	≥10%	10.2 (26/256)	63.1 (173/274)	71.0 (184/259)	7.7 (1/13)	57.1 (8/14)	50.0 (6/12)
	≥15%	3.1 (8/256)	41.2 (113/274)	54.1 (140/259)	0.0 (0/13)	35.7 (5/14)	16.7 (2/12)
	≥20%	1.2 (3/256)	21.9 (60/274)	34.4 (89/259)	0.0 (0/13)	21.4 (3/14)	16.7 (2/12)
	≥25%	0.4 (1/256)	8.8 (24/274)	17.4 (45/259)	0.0 (0/13)	7.1 (1/14)	0.0 (0/12)
BMI (kg/m^2)	Baseline	36.8 ± 7.26 (N = 303)	36.2 ± 6.41 (N = 299)	35.8 ± 6.11 (N = 301)	30.8 ± 2.54 (N = 13)	32.0 ± 4.00 (N = 14)	31.9 ± 4.29 (N = 14)
	Change at Week 72	−1.3 ± 2.17 (N = 256)	−4.9 ± 3.29 (N = 274)	−5.8 ± 3.70 (N = 259)	−1.0 ± 1.51 (N = 13)	−4.0 ± 2.75 (N = 14)	−3.2 ± 2.16 (N = 12)
Waist circumference[b] (cm)	Baseline	116.4 ± 15.59 (N = 303)	114.8 ± 13.96 (N = 299)	114.9 ± 13.12 (N = 301)	104.5 ± 7.71 (N = 13)	104.8 ± 10.33 (N = 14)	104.4 ± 6.86 (N = 14)
	Change at Week 72	−3.8 ± 7.32 (N = 256)	−11.2 ± 9.09 (N = 274)	−14.1 ± 10.11 (N = 259)	−3.7 ± 4.47 (N = 13)	−9.3 ± 9.49 (N = 14)	−9.8 ± 4.74 (N = 12)

Percentage (number of applicable subjects/number of subjects evaluated) or mean ± SD (number of subjects evaluated)
a) Percentage of subjects who achieved ≥10%, ≥15%, ≥20%, or ≥25% weight loss from baseline to Week 72.
b) Measured at the midpoint between the lower margin of the rib cage and the upper margin of the iliac crest.

Table 23. Results of main secondary endpoints related to blood glucose, blood pressure, and lipid parameters (Study GPHL, mITT population)

Endpoint		Entire population			Japanese subpopulation		
		Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
HbA1c (%)	Baseline	7.96 ± 0.84 (N = 282)	8.02 ± 0.83 (N = 291)	8.07 ± 1.00 (N = 293)	7.99 ± 0.85 (N = 13)	7.62 ± 0.65 (N = 14)	7.99 ± 0.59 (N = 14)
	Change at Week 72	−0.59 ± 1.04 (N = 165)	−2.22 ± 1.00 (N = 265)	−2.29 ± 1.12 (N = 249)	−0.52 ± 0.83 (N = 11)	−1.96 ± 0.78 (N = 14)	−2.21 ± 0.62 (N = 12)
Fasting plasma glucose (mg/dL)	Baseline	157.41 ± 45.61 (N = 282)	158.23 ± 42.52 (N = 290)	161.87 ± 50.20 (N = 293)	143.29 ± 28.62 (N = 13)	128.42 ± 11.73 (N = 1)	147.85 ± 23.13 (N = 14)
	Change at Week 72	−9.34 ± 39.89 (N = 162)	−50.24 ± 44.36 (N = 264)	−53.22 ± 44.93 (N = 250)	−12.61 ± 18.93 (N = 11)	−35.77 ± 15.46 (N = 14)	−44.14 ± 16.94 (N = 12)
Systolic blood pressure (mmHg)	Baseline	131.3 ± 11.77 (N = 303)	130.6 ± 12.19 (N = 299)	130.2 ± 12.23 (N = 301)	125.7 ± 8.20 (N = 13)	128.2 ± 10.49 (N = 14)	130.1 ± 10.42 (N = 14)
	Change at Week 72	−1.2 ± 13.65 (N = 256)	−6.0 ± 14.55 (N = 274)	−7.9 ± 13.25 (N = 259)	7.3 ± 15.65 (N = 13)	−8.9 ± 10.82 (N = 14)	−2.7 ± 8.90 (N = 12)
Diastolic blood pressure (mmHg)	Baseline	79.5 ± 8.39 (N = 303)	80.1 ± 8.14 (N = 299)	79.8 ± 8.67 (N = 301)	81.8 ± 6.96 (N = 13)	83.9 ± 8.22 (N = 14)	84.4 ± 7.85 (N = 14)
	Change at Week 72	−0.2 ± 7.75 (N = 256)	−2.4 ± 8.67 (N = 274)	−2.9 ± 9.78 (N = 259)	−0.7 ± 7.33 (N = 13)	−6.0 ± 8.42 (N = 14)	−2.7 ± 7.19 (N = 12)
Total cholesterol (mg/dL)	Baseline	179.3 ± 41.86 (N = 284)	177.5 ± 43.23 (N = 286)	170.9 ± 42.01 (N = 286)	182.6 ± 38.34 (N = 13)	186.3 ± 30.05 (N = 14)	178.4 ± 37.05 (N = 14)
	Percentage change at Week 72 (%)	3.31 ± 20.73 (N = 255)	−1.33 ± 21.65 (N = 272)	1.47 ± 23.73 (N = 257)	−7.1 ± 10.37 (N = 13)	−13.0 ± 12.38 (N = 14)	−7.9 ± 17.68 (N = 12)
LDL cholesterol (mg/dL)	Baseline	97.9 ± 33.72 (N = 284)	96.0 ± 35.20 (N = 286)	92.3 ± 35.23 (N = 286)	96.5 ± 28.79 (N = 13)	104.1 ± 31.74 (N = 14)	102.5 ± 36.30 (N = 14)
	Percentage change at Week 72 (%)	10.80 ± 39.07 (N = 255)	10.57 ± 75.67 (N = 272)	12.45 ± 48.15 (N = 256)	−8.4 ± 22.90 (N = 13)	−16.0 ± 17.47 (N = 14)	−9.5 ± 24.76 (N = 12)
HDL cholesterol (mg/dL)	Baseline	43.9 ± 11.42 (N = 284)	45.2 ± 12.42 (N = 286)	42.9 ± 10.31 (N = 286)	54.4 ± 12.98 (N = 13)	56.5 ± 13.73 (N = 14)	50.0 ± 8.36 (N = 14)
	Percentage change at Week 72 (%)	2.58 ± 18.24 (N = 255)	8.04 ± 18.96 (N = 272)	12.78 ± 25.76 (N = 257)	5.51 ± 13.29 (N = 13)	2.63 ± 13.18 (N = 14)	10.26 ± 15.85 (N = 12)
Triglycerides (mg/dL)[a)]	Baseline	191.4 ± 117.88 (N = 284)	187.0 ± 143.42 (N = 286)	182.5 ± 131.03 (N = 286)	158.7 ± 72.20 (N = 13)	128.7 ± 44.38 (N = 14)	129.8 ± 44.35 (N = 14)
	Percentage change at Week 72 (%)	1.0 ± 43.14 (N = 255)	−19.8 ± 36.77 (N = 272)	−21.7 ± 40.79 (N = 257)	−13.0 ± 34.19 (N = 13)	−23.4 ± 30.08 (N = 14)	−33.4 ± 12.43 (N = 12)

Mean ± SD (number of subjects evaluated)
a) Fasting

Table 24 shows the incidence of adverse events and adverse drug reactions that occurred in ≥5% of subjects in any treatment group in the entire population. Table 25 shows the incidence of adverse events and adverse drug reactions that occurred in ≥2 subjects in any treatment group in the Japanese subpopulation.

Table 24. Incidence of adverse events and adverse drug reactions occurring in ≥5% of any treatment group (Study GPHL [entire population], safety analysis population)

Event	Placebo (N = 307)		Tirzepatide 10 mg (N = 302)		Tirzepatide 15 mg (N = 303)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	75.6 (232)	27.0 (83)	76.8 (232)	48.7 (147)	71.3 (216)	47.2 (143)
Nausea	6.5 (20)	5.2 (16)	19.9 (60)	17.5 (53)	21.5 (65)	19.5 (59)
Diarrhoea	8.8 (27)	6.8 (21)	19.5 (59)	14.9 (45)	21.5 (65)	17.2 (52)
Vomiting	3.3 (10)	2.6 (8)	10.6 (32)	8.3 (25)	12.9 (39)	11.2 (34)
COVID-19	16.9 (52)	0 (0)	17.2 (52)	0 (0)	10.9 (33)	0 (0)
Decreased appetite	2.3 (7)	2.3 (7)	9.6 (29)	9.3 (28)	9.9 (30)	8.9 (27)
Constipation	3.9 (12)	2.0 (6)	7.9 (24)	6.6 (20)	8.9 (27)	5.9 (18)
Dyspepsia	2.9 (9)	2.9 (9)	7.3 (22)	6.3 (19)	7.3 (22)	6.3 (19)
Abdominal pain	2.3 (7)	2.0 (6)	4.0 (12)	2.6 (8)	7.3 (22)	6.3 (19)
Eructation	0.7 (2)	0.7 (2)	6.3 (19)	5.6 (17)	4.3 (13)	4.3 (13)
Upper respiratory tract infection	6.8 (21)	0 (0)	3.3 (10)	0 (0)	4.0 (12)	0 (0)
Nasopharyngitis	5.5 (17)	0 (0)	2.6 (8)	0 (0)	3.0 (9)	0 (0)
Dizziness	1.6 (5)	0.3 (1)	5.6 (17)	2.3 (7)	2.6 (8)	1.7 (5)
Hyperglycaemia	14.3 (44)	0 (0)	2.0 (6)	0 (0)	1.3 (4)	0 (0)

Incidence % (number of subjects with events), MedDRA/J ver.25.1

Table 25. Incidence of adverse events and adverse drug reactions occurring in ≥2 subjects in any treatment group (Study GPHL [Japanese subpopulation], safety analysis population)

Event	Placebo (N = 13)		Tirzepatide 10 mg (N = 14)		Tirzepatide 15 mg (N = 14)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Any event	92.3 (12)	7.7 (1)	92.9 (13)	50.0 (7)	92.9 (13)	35.7 (5)
Myalgia	15.4 (2)	0 (0)	14.3 (2)	0 (0)	21.4 (3)	0 (0)
Constipation	0 (0)	0 (0)	7.1 (1)	7.1 (1)	21.4 (3)	14.3 (2)
Gastroenteritis	15.4 (2)	0 (0)	0 (0)	0 (0)	21.4 (3)	7.1 (1)
Diarrhoea	0 (0)	0 (0)	35.7 (5)	35.7 (5)	14.3 (2)	7.1 (1)
COVID-19	0 (0)	0 (0)	21.4 (3)	0 (0)	14.3 (2)	0 (0)
Pyrexia	23.1 (3)	0 (0)	14.3 (2)	0 (0)	14.3 (2)	0 (0)
Nasopharyngitis	7.7 (1)	0 (0)	14.3 (2)	0 (0)	14.3 (2)	0 (0)
Tooth extraction	7.7 (1)	0 (0)	7.1 (1)	0 (0)	14.3 (2)	0 (0)
Nausea	0 (0)	0 (0)	7.1 (1)	7.1 (1)	14.3 (2)	14.3 (2)
Vomiting	0 (0)	0 (0)	7.1 (1)	7.1 (1)	14.3 (2)	14.3 (2)
Injection site reaction	0 (0)	0 (0)	7.1 (1)	7.1 (1)	14.3 (2)	14.3 (2)
Cataract	0 (0)	0 (0)	0 (0)	0 (0)	14.3 (2)	0 (0)
Blood creatine phosphokinase increased	0 (0)	0 (0)	0 (0)	0 (0)	14.3 (2)	0 (0)
Oropharyngeal pain	0 (0)	0 (0)	14.3 (2)	0 (0)	7.1 (1)	0 (0)
Arthralgia	15.4 (2)	0 (0)	7.1 (1)	0 (0)	7.1 (1)	0 (0)
Lipase increased	0 (0)	0 (0)	14.3 (2)	14.3 (2)	0 (0)	0 (0)
Abdominal discomfort	0 (0)	0 (0)	14.3 (2)	14.3 (2)	0 (0)	0 (0)
Dizziness	0 (0)	0 (0)	14.3 (2)	7.1 (1)	0 (0)	0 (0)

Incidence % (number of subjects with events), MedDRA/J ver.25.1

Deaths were reported in 2 subjects in the tirzepatide 10 mg group (respiratory fume inhalation disorder and cardio-respiratory arrest in 1 subject each); neither was determined to be an adverse drug reaction.

Tables 26 and 27 show the incidences of serious adverse events and adverse events leading to treatment discontinuation, respectively.

Table 26. Incidence of serious adverse events (Study GPHL, safety analysis population)

Group	Incidence	Breakdown
Placebo	7.5 (23/307)	Diverticulum intestinal haemorrhagic,[a)b)] cardiac failure congestive,[a)] obstructive pancreatitis[a)]/cholecystitis acute,[a)] acute myocardial infarction, coronary artery disease, upper gastrointestinal haemorrhage, cholecystitis acute, cholelithiasis, COVID-19 pneumonia, appendicitis perforated, gangrene, osteomyelitis, ankle fracture, calculus bladder/post procedural haematuria/pyrexia, osteoarthritis, spondylolisthesis, adenocarcinoma of colon, anaemia/colon cancer, invasive breast carcinoma, leukaemia, mantle cell lymphoma, COVID-19 pneumonia/transient ischaemic attack/acute kidney injury, and diabetic foot in 1 subject each
Tirzepatide 10 mg	5.6 (17/302)	Ventricular extrasystoles,[a)] hyponatraemia[a)]/acute kidney injury, acute kidney injury,[a)] cardio-respiratory arrest[c), r]espiratory fume inhalation disorder,[c)] angina unstable/vascular pseudoaneurysm, atrial fibrillation/atrial flutter, cholecystitis acute/biliary colic, gastroenteritis/transient ischaemic attack, COVID-19, limb traumatic amputation, gastroenteritis/dehydration/acute kidney injury, haemorrhagic stroke, nephrolithiasis/inguinal hernia strangulated, adenomyosis, hypotension, and peripheral venous disease in 1 subject each
Tirzepatide 15 mg	8.6 (26/303)	Cholecystitis acute,[a)] cellulitis, and pancreatitis acute/cholelithiasis in 2 subjects each; and diarrhoea[a)]/vomiting,[a)] clavicle fracture,[a)] dehydration,[a)] angina unstable/coronary artery occlusion, cardiac failure, ventricular arrhythmia, upper gastrointestinal haemorrhage, hernial eventration, non-cardiac chest pain, appendicitis, shunt thrombosis, tendon rupture, hyponatraemia, prostate cancer, adenocarcinoma of colon, endometrial cancer, gastric neoplasm, ischaemic stroke, haematoma, and ischaemic stroke/femur fracture in 1 subject each

The occurrence is presented as the incidence % (number of subjects with events/number of subjects evaluated). MedDRA/J ver. 25.1

a) Events assessed as adverse drug reactions. Of them, 1 of the 2 cases of cholecystitis acute in the placebo group, 1 of the 3 cases of acute kidney injury in the tirzepatide 10 mg group, and 1 of the 2 cases of cholecystitis acute in the tirzepatide 15 mg group were considered adverse drug reactions.
b) Event that occurred in Japanese subjects.
c) Event with a fatal outcome

Table 27. Incidence of adverse events leading to treatment discontinuation (Study GPHL, safety analysis population)

Group	Incidence	Breakdown
Placebo	3.9 (12/307)	Abdominal pain,[a)] obstructive pancreatitis,[a)] hypersensitivity,[a)] headache,[a)] insomnia,[a)] diabetes mellitus inadequate control, hyperglycaemia, adenocarcinoma of colon, colon cancer, invasive breast carcinoma, leukaemia, and mantle cell lymphoma in 1 subject each
Tirzepatide 10 mg	4.0 (12/302)	Vomiting[a)] and blood calcitonin increased[a)] in 2 subjects each; nausea,[a)] hyponatraemia,[a)] cardio-respiratory arrest, diabetic retinopathy, respiratory fume inhalation disorder, arthralgia, depression, and gastric bypass in 1 subject each
Tirzepatide 15 mg	7.3 (22/303)	Diarrhoea[a)] in 5 subjects; nausea[a)] in 3 subjects; and gastroenteritis,[a)b)] abdominal pain,[a)] constipation,[a)] diabetic gastroparesis,[a)] cholecystitis acute,[a)] blood pressure increased,[a)] weight decreased,[a)] somnolence,[a)] pancreatic cyst, pancreatitis acute, asthenia, adenocarcinoma of colon, gastric neoplasm, and prostate cancer in 1 subject each

The occurrence is presented as the incidence % (number of subjects with events/number of subjects evaluated). MedDRA/J ver. 25.1

a) Events assessed as adverse drug reactions. Of them, 1 of the 2 cases of vomiting and 1 of the 2 cases of blood calcitonin increased in the tirzepatide 10 mg group were considered adverse drug reactions.
b) Event that occurred in Japanese subjects.

Among the 26 subjects excluded from the mITT population after randomization, no deaths were reported. Serious adverse events were observed in 1 subject in the tirzepatide 10 mg group (contusion/renal injury) and 1 subject in the tirzepatide 15 mg group (COVID-19 pneumonia); none were determined to be adverse drug reactions. Adverse events leading to treatment discontinuation were reported in 2 subjects in the tirzepatide 10 mg group (pancreatic enzymes increased in 2 subjects) and 1 subject in the tirzepatide 15 mg group (nausea), all of which were determined to be adverse drug reactions.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Effect on weight reduction

The applicant's explanation:

In all clinical studies, including the Japanese phase III study (Study GPHZ) in patients with obesity disease, the global phase III study (Study GPHK) in patients with overweight or obesity without type 2 diabetes mellitus, and the global phase III study (Study GPHL) in patients with overweight or obesity with type 2 diabetes mellitus, the superiority of tirzepatide 10 mg and tirzepatide 15 mg over placebo was demonstrated for the co-primary endpoints, i.e., the percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% weight reduction at Week 72 (Tables 9, 14, and 21). As for the comparison between doses of tirzepatide, Study GPHK showed similar results between the tirzepatide 10 mg and tirzepatide 15 mg groups for each co-primary endpoint. In the other 2 studies, the tirzepatide 15 mg group exhibited greater improvement than the tirzepatide 10 mg group. For the main secondary endpoints related to body weight, all 3 studies (Studies GPHZ, GPHK, and GPHL) showed a higher proportion of subjects achieving weight loss and greater reductions in BMI and waist circumference in the tirzepatide groups compared with the placebo groups (Tables 10, 15, and 22). As for the comparison between doses of tirzepatide, in Study GPHK, changes from baseline in BMI and waist circumference were similar between the tirzepatide 10 mg and tirzepatide 15 mg groups; in contrast, the proportion of subjects achieving weight loss tended to be higher in the tirzepatide 15 mg group compared with the tirzepatide 10 mg group. In Studies GPHZ and GPHL, all evaluated parameters showed a tendency for greater improvement in the tirzepatide 15 mg group than in the tirzepatide 10 mg group. In Study GPHZ, the effect on visceral adipose tissue area was also evaluated. The reduction in visceral adipose tissue area from baseline to Week 72 was greater in the tirzepatide groups compared with the placebo group, with a larger reduction observed in the tirzepatide 15 mg group than in the tirzepatide 10 mg group (Table 10). The percentage change in body weight from baseline to Week 72 tended to be smaller in Study GPHL, which included patients with type 2 diabetes mellitus, compared with Studies GPHZ and GPHK, which excluded patients with diabetes mellitus. A similar trend was observed in clinical studies of other GLP-1 receptor agonists in patients with overweight or obesity (*Lancet.* 2021;397:971-84, *N Engl J Med.* 2021;384:989-1002, etc.).

The efficacy of tirzepatide in the Japanese subpopulation of the global phase III studies (Studies GPHK and GPHL) was evaluated as follows: For extrinsic ethnic factors, while the diagnostic criteria for obesity disease, or obesity or overweight in guidelines vary across countries and the types of approved treatments differ, the concept of obesity does not show significant ethnic differences. Furthermore, body weight loss rate is commonly recognized as an evaluation parameter for treatment efficacy in both Japanese and non-Japanese patients. As for intrinsic ethnic factors, the pharmacokinetics of tirzepatide showed a higher exposure in Japanese patients than in non-Japanese patients, which was attributed to differences in body weight [see Section "6.R.1 Comparison of pharmacokinetics between Japanese and non-Japanese populations"].

Tables 28 and 29 show baseline subject characteristics in the entire population and Japanese subpopulation of Studies GPHK and GPHL. Compared with the entire population, the Japanese subpopulation had a lower proportion of female subjects, a lower proportion of subjects with hypo high-

density lipoprotein (HDL) cholesterolaemia, and lower mean body weight and BMI. The Japanese subpopulation in Studies GPHK and GPHL had similar baseline subject characteristics to those in the Japanese phase III study (Study GPHZ) (Table 30).

Table 28. Baseline characteristics of subjects (Study GPHK, mITT population)

Parameter		Entire population (N = 2517)				Japanese subpopulation (N = 102)			
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
Age (years)	Mean ± SD	44.4 ± 12.6	45.5 ± 12.7	44.5 ± 12.3	44.8 ± 12.3	43.9 ± 11.0	47.7 ± 10.8	45.5 ± 13.7	47.8 ± 10.8
	<65[a)]	94.7 (603)	91.8 (573)	95.4 (599)	94.4 (593)	100.0 (27)	95.8 (23)	90.9 (20)	89.7 (26)
	≥65[a)]	5.3 (34)	8.2 (51)	4.6 (29)	5.6 (35)	0 (0)	4.2 (1)	9.1 (2)	10.3 (3)
Sex[a)]	Male	31.9 (203)	32.2 (201)	32.6 (205)	32.3 (203)	63.0 (17)	62.5 (15)	68.2 (15)	65.5 (19)
	Female	68.1 (434)	67.8 (423)	67.4 (423)	67.7 (425)	37.0 (10)	37.5 (9)	31.8 (7)	34.5 (10)
Body weight (kg)		104.9 ± 21.41	103.1 ± 20.64	106.1 ± 23.28	105.6 ± 22.94	87.4 ± 10.76	89.0 ± 11.12	86.2 ± 13.37	86.6 ± 9.74
BMI (kg/m^2)	Mean ± SD	38.2 ± 6.89	37.5 ± 6.62	38.3 ± 7.00	38.1 ± 6.70	31.9 ± 3.38	32.5 ± 4.61	31.6 ± 3.42	31.3 ± 2.88
	<30[a)]	3.6 (23)	5.4 (34)	5.6 (35)	6.4 (40)	37.0 (10)	29.2 (7)	36.4 (8)	34.5 (10)
	≥30 and <35[a)]	35.0 (223)	38.5 (240)	32.8 (206)	31.5 (198)	44.4 (12)	50.0 (12)	54.5 (12)	55.2 (16)
	≥35 and <40[a)]	28.1 (179)	27.7 (173)	29.5 (185)	28.3 (178)	14.8 (4)	16.7 (4)	9.1 (2)	10.3 (3)
	≥40[a)]	33.3 (212)	28.4 (177)	32.2 (202)	33.8 (212)	3.7 (1)	4.2 (1)	0 (0)	0 (0)
Hypertriglyceridaemia[a)b)]		36.4 (232)	34.6 (216)	32.6 (205)	34.6 (217)	44.4 (12)	45.8 (11)	22.7 (5)	41.4 (12)
Hyper-LDL-cholesterolaemia[a)c)]		18.9 (120)	17.9 (111)	22.2 (139)	18.2 (114)	25.9 (7)	20.8 (5)	31.8 (7)	37.9 (11)
Hypo HDL cholesterolaemia[a)d)]		27.6 (176)	25.2 (157)	26.8 (168)	25.0 (157)	7.4 (2)	8.3 (2)	9.1 (2)	6.9 (2)
Hypertension[a)e)]		30.6 (195)	32.2 (201)	32.2 (202)	33.0 (207)	22.2 (6)	45.8 (11)	50.0 (11)	48.3 (14)

Mean ± SD
a) Percentage of applicable subjects (%) (number of applicable subjects)
b) Defined as fasting triglycerides ≥150 mg/dL
c) Defined as low-density lipoprotein (LDL) cholesterol ≥140 mg/dL
d) Defined as HDL cholesterol <40 mg/dL
e) Hypertension as defined by the inclusion criteria of Study GPHK

Table 29. Baseline characteristics of subjects (Study GPHL, mITT population)

Parameter		Entire population (N = 912)			Japanese subpopulation (N = 41)		
		Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
Age (years)	Mean ± SD	54.8 ± 10.5	54.3 ± 10.8	53.8 ± 10.7	55.7 ± 9.5	52.6 ± 10.1	52.5 ± 10.7
	<65[a)]	82.1 (252)	82.5 (249)	82.2 (249)	84.6 (11)	85.7 (12)	85.7 (12)
	≥65[a)]	17.9 (55)	17.5 (53)	17.8 (54)	15.4 (2)	14.3 (2)	14.3 (2)
Sex[a)]	Male	48.5 (149)	48.3 (146)	48.2 (146)	69.2 (9)	71.4 (10)	78.6 (11)
	Female	51.5 (158)	51.7 (156)	51.8 (157)	30.8 (4)	28.6 (4)	21.4 (3)
Body weight (kg)		102.0 ± 22.27	101.5 ± 20.86	99.9 ± 20.10	86.5 ± 7.24	89.0 ± 15.78	88.5 ± 10.40
BMI (kg/m^2)	Mean ± SD	36.8 ± 7.25	36.2 ± 6.39	35.8 ± 6.09	30.8 ± 2.54	32.0 ± 4.00	31.9 ± 4.29
	<30[a)]	15.0 (46)	17.2 (52)	15.8 (48)	46.2 (6)	28.6 (4)	28.6 (4)
	≥30 and <35[a)]	33.9 (104)	29.8 (90)	36.6 (111)	46.2 (6)	50.0 (7)	50.0 (7)
	≥35 and <40[a)]	23.1 (71)	31.1 (94)	27.4 (83)	7.7 (1)	14.3 (2)	14.3 (2)
	≥40[a)]	28.0 (86)	21.9 (66)	20.1 (61)	0 (0)	7.1 (1)	7.1 (1)
HbA1c (%)		7.99 ± 0.84	8.00 ± 0.84	8.06 ± 1.00	7.99 ± 0.85	7.62 ± 0.65	7.99 ± 0.59
Hypertriglyceridaemia[a)b)]		58.0 (178)	48.7 (147)	54.1 (164)	53.8 (7)	35.7 (5)	21.4 (3)
Hyper-LDL-cholesterolaemia[a)c)]		9.8 (30)	8.9 (27)	9.6 (29)	7.7 (1)	14.3 (2)	21.4 (3)
Hypo HDL cholesterolaemia[a)d)]		42.0 (129)	38.4 (116)	42.2 (128)	7.7 (1)	7.1 (1)	14.3 (2)
Hypertension[a)]		69.1 (212)	64.9 (196)	65.7 (199)	61.5 (8)	50.0 (7)	64.3 (9)

Mean ± SD
a) Percentage of applicable subjects (%) (number of applicable subjects)
b) Defined as fasting triglycerides ≥150 mg/dL
c) Defined as LDL cholesterol ≥140 mg/dL
d) Defined as HDL cholesterol <40 mg/dL

Table 30. Baseline characteristics of subjects (Study GPHZ, mITT population)

Parameter		Entire population (N = 225)		
		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Age (years)	Mean ± SD	52.3 ± 10.9	49.0 ± 10.9	51.1 ± 10.3
	<65[a)]	86.7 (65)	93.2 (68)	90.9 (70)
	≥65[a)]	13.3 (10)	6.8 (5)	9.1 (7)
Sex [a)]	Male	60.0 (45)	58.9 (43)	58.4 (45)
	Female	40.0 (30)	41.1 (30)	41.6 (32)
Body weight (kg)		92.0 ± 15.25	92.4 ± 14.99	91.7 ± 14.78
BMI (kg/m^2)	Mean ± SD	33.7 ± 4.88	33.2 ± 4.12	33.6 ± 4.31
	<30[a)]	32.0 (24)	27.4 (20)	26.0 (20)
	≥30 and <35[a)]	33.3 (25)	39.7 (29)	39.0 (30)
	≥35 and <40[a)]	22.7 (17)	27.4 (20)	27.3 (21)
	≥40[a)]	12.0 (9)	5.5 (4)	7.8 (6)
HbA1c (%)		5.67 ± 0.32	5.65 ± 0.33	5.66 ± 0.36
Hypertriglyceridaemia[a)b)]		54.7 (41)	54.8 (40)	57.1 (44)
Hyper LDL cholesterolaemia[a)c)]		36.0 (27)	37.0 (27)	42.9 (33)
Hypo HDL cholesterolaemia[a)d)]		24.0 (18)	24.7 (18)	18.2 (14)
Hypertension[a)]		54.7 (41)	53.4 (39)	51.9 (40)

Mean ± SD
a) Percentage of applicable subjects (%) (number of applicable subjects)
b) Defined as fasting triglycerides ≥150 mg/dL
c) Defined as LDL cholesterol ≥140 mg/dL
d) Defined as HDL cholesterol <40 mg/dL

As for the co-primary endpoints, namely the percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% weight reduction at Week 72, the results for the Japanese subpopulation in both Study GPHK and Study GPHL exhibited a similar trend to those observed in the entire population (Tables 14 and 21).

For baseline characteristics such as sex, body weight, and BMI, where differences in distribution were observed between the Japanese subpopulation and the entire population in Studies GPHK and GPHL, an analysis was conducted to evaluate the percentage change in body weight from baseline to Week 72 by subgrouping based on these factors. The results showed a trend indicating a greater percentage change in body weight in females compared to males. This trend remained consistent between the Japanese subpopulation and the entire population. For other characteristics, no substantial differences were observed between the Japanese subpopulation and the entire population, although the number of subjects in some subgroups was very small (Tables 31 and 32).

Table 31. Comparison of percentage change in body weight from baseline to Week 72 by subject characteristics (Study GPHK, mITT population)

Parameter		Entire population				Japanese subpopulation			
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
Sex	Male	−2.4 ± 6.39 (N = 159)	−12.7 ± 7.72 (N = 173)	−17.8 ± 9.02 (N = 168)	−18.3 ± 9.12 (N = 173)	−1.5 ± 7.87 (N = 16)	−14.5 ± 7.24 (N = 15)	−19.6 ± 6.83 (N = 15)	−19.7 ± 8.45 (N = 16)
	Female	−3.8 ± 7.19 (N = 307)	−18.3 ± 9.21 (N = 362)	−23.7 ± 10.12 (N = 358)	−25.2 ± 9.89 (N = 360)	2.2 ± 5.35 (N = 6)	−8.2 ± 5.61 (N = 8)	−29.7 ± 8.14 (N = 6)	−27.2 ± 9.75 (N = 8)
Body weight (kg)	<85	−3.9 ± 7.34 (N = 86)	−18.4 ± 8.92 (N = 97)	−22.0 ± 9.48 (N = 90)	−22.0 ± 10.09 (N = 95)	−0.7 ± 6.15 (N = 11)	−11.6 ± 6.19 (N = 10)	−25.2 ± 8.06 (N = 10)	−22.8 ± 9.80 (N = 11)
	≥85 and <100	−3.6 ± 6.84 (N = 135)	−17.2 ± 9.10 (N = 191)	−23.0 ± 9.54 (N = 159)	−23.6 ± 10.02 (N = 142)	−2.7 ± 8.99 (N = 7)	−12.2 ± 9.07 (N = 10)	−18.8 ± 8.63 (N = 8)	−19.6 ± 9.46 (N = 10)
	≥100 and <115	−2.7 ± 7.14 (N = 114)	−16.1 ± 9.21 (N = 128)	−24.0 ± 10.04 (N = 119)	−24.5 ± 9.90 (N = 139)	4.0 ± 7.08 (N = 4)	−13.0 ± 3.71 (N = 2)	−20.1 ± 7.56 (N = 2)	−28.4 ± 6.55 (N = 3)
	≥115	−3.1 ± 6.68 (N = 131)	−14.2 ± 8.87 (N = 119)	−19.1 ± 10.68 (N = 158)	−21.5 ± 10.40 (N = 157)	- (N = 0)	−19.6 (N = 1)	−30.3 (N = 1)	- (N = 0)
BMI (kg/m^2)	<30	−3.6 ± 6.99 (N = 18)	−15.7 ± 7.11 (N = 28)	−17.8 ± 9.38 (N = 30)	−18.4 ± 6.70 (N = 26)	−5.6 ± 7.23 (N = 9)	−13.0 ± 6.54 (N = 7)	−22.1 ± 6.18 (N = 8)	−17.7 ± 4.86 (N = 5)
	≥30 and <35	−3.6 ± 7.03 (N = 170)	−17.1 ± 9.07 (N = 207)	−21.9 ± 9.31 (N = 173)	−21.4 ± 10.71 (N = 175)	2.0 ± 4.40 (N = 8)	−13.0 ± 8.00 (N = 11)	−21.8 ± 10.36 (N = 11)	−22.0 ± 10.14 (N = 16)
	≥35 and <40	−2.7 ± 6.55 (N = 122)	−15.8 ± 9.54 (N = 155)	−22.7 ± 9.52 (N = 149)	−25.0 ± 9.78 (N = 151)	4.1 ± 6.99 (N = 4)	−7.4 ± 5.89 (N = 4)	−27.9 ± 3.40 (N = 2)	−30.5 ± 6.59 (N = 3)
	≥40	−3.5 ± 7.21 (N = 156)	−16.5 ± 9.13 (N = 145)	−21.8 ± 11.46 (N = 174)	−23.3 ± 9.97 (N = 181)	7.2 (N = 1)	−19.6 (N = 1)	- (N = 0)	- (N = 0)

Unit, %; Mean ± SD (number of subjects evaluated); -, not applicable

Table 32. Comparison of percentage change in body weight from baseline to Week 72 by subject characteristics (Study GPHL, mITT population)

Parameter		Entire population			Japanese subpopulation		
		Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
Sex	Male	−2.9 ± 5.49 (N = 124)	−11.8 ± 7.77 (N = 134)	−14.0 ± 9.37 (N = 127)	−3.1 ± 5.23 (N = 9)	−11.0 ± 5.95 (N = 10)	−8.5 ± 5.98 (N = 10)
	Female	−4.1 ± 6.17 (N = 132)	−14.8 ± 8.71 (N = 140)	−17.9 ± 9.67 (N = 132)	−4.2 ± 4.84 (N = 4)	−16.0 ± 12.03 (N = 4)	−18.0 ± 7.48 (N = 2)
Body weight (kg)	<85	−3.5 ± 6.23 (N = 61)	−13.8 ± 7.01 (N = 49)	−16.4 ± 10.25 (N = 51)	−7.0 ± 4.29 (N = 4)	−13.4 ± 7.60 (N = 6)	−15.5 ± 7.72 (N = 4)
	≥85 and <100	−3.4 ± 4.78 (N = 85)	−12.3 ± 8.19 (N = 100)	−16.3 ± 10.40 (N = 98)	−1.9 ± 4.52 (N = 9)	−12.7 ± 9.92 (N = 6)	−7.3 ± 5.07 (N = 6)
	≥100 and <115	−4.4 ± 7.46 (N = 51)	−13.3 ± 8.23 (N = 69)	−12.6 ± 8.31 (N = 51)	- (N = 0)	−6.8 (N = 1)	−7.2 ± 6.40 (N = 2)
	≥115	−2.9 ± 5.42 (N = 59)	−14.8 ± 9.86 (N = 56)	−18.2 ± 8.54 (N = 59)	- (N = 0)	−10.3 (N = 1)	- (N = 0)
BMI (kg/m^2)	<30	−4.3 ± 6.30 (N = 38)	−11.3 ± 7.35 (N = 43)	−14.9 ± 8.29 (N = 38)	−5.8 ± 4.15 (N = 6)	−13.5 ± 6.98 (N = 4)	−11.6 ± 9.02 (N = 3)
	≥30 and <35	−2.8 ± 5.48 (N = 93)	−12.5 ± 8.11 (N = 83)	−14.1 ± 10.52 (N = 95)	−0.1 ± 3.72 (N = 6)	−10.4 ± 7.03 (N = 7)	−8.7 ± 7.49 (N = 7)
	≥35 and <40	−4.6 ± 6.53 (N = 58)	−13.8 ± 7.95 (N = 87)	−18.3 ± 10.02 (N = 73)	−9.3 (N = 1)	−20.2 ± 13.97 (N = 2)	−11.8 (N = 1)
	≥40	−3.2 ± 5.50 (N = 67)	−15.3 ± 9.65 (N = 61)	−16.9 ± 7.98 (N = 53)	- (N = 0)	−6.8 (N = 1)	−12.7 (N = 1)

Unit, %; Mean ± SD (number of subjects evaluated); -, not applicable

Table 33 shows the percentage change in body weight from baseline to Week 72 by sex, body weight, and BMI in the Japanese phase III study (Study GPHZ). Similar to Studies GPHK and GPHL (Tables 31 and 32), a tendency was observed where the percentage change in body weight was greater in females than in males. No significant differences were observed among subgroups with regard to other characteristics.

Table 33. Percentage change in body weight from baseline to Week 72 by subject characteristics (Study GPHZ, mITT population)

Parameter		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Sex	Male	−1.7 ± 4.68 (N = 40)	−17.6 ± 7.83 (N = 32)	−19.8 ± 8.00 (N = 38)
	Female	−2.1 ± 5.39 (N = 26)	−19.3 ± 7.39 (N = 27)	−26.6 ± 8.72 (N = 27)
Body weight (kg)	<85	−2.7 ± 5.13 (N = 23)	−21.9 ± 5.58 (N = 20)	−23.1 ± 8.92 (N = 19)
	≥85 and <100	−1.0 ± 4.72 (N = 23)	−19.1 ± 8.19 (N = 22)	−23.0 ± 10.08 (N = 28)
	≥100 and <115	−1.7 ± 5.38 (N = 13)	−11.5 ± 5.94 (N = 12)	−20.3 ± 7.52 (N = 13)
	≥115	−1.9 ± 4.76 (N = 7)	−17.4 ± 5.87 (N = 5)	−24.6 ± 5.25 (N = 5)
BMI (kg/m^2)	<30	−2.0 ± 5.15 (N = 21)	−22.3 ± 4.75 (N = 14)	−18.6 ± 7.70 (N = 15)
	≥30 and <35	−1.8 ± 5.34 (N = 21)	−19.5 ± 9.31 (N = 24)	−23.7 ± 9.71 (N = 25)
	≥35 and <40	−2.0 ± 5.09 (N = 16)	−13.7 ± 4.73 (N = 18)	−23.9 ± 9.15 (N = 19)
	≥40	−1.2 ± 3.64 (N = 8)	−18.7 ± 4.97 (N = 3)	−23.9 ± 5.52 (N = 6)

Unit, %; Mean ± SD (number of subjects evaluated)

Regarding the efficacy of body weight loss in relation to obesity-related health disorders, Tables 34 and 35 show the percentage change in body weight from baseline to Week 72 by the status of each disorder at baseline. As for glucose metabolism, as mentioned earlier, in Study GPHL, which included patients with type 2 diabetes mellitus, the percentage change in body weight was smaller compared to Studies GPHZ and GPHK, which excluded patients with diabetes mellitus. No substantial differences in the percentage change in body weight were observed among subgroups classified by glucose metabolism status in Studies GPHZ and GPHK. For hypertension and dyslipidaemia, no significant differences were observed in the percentage change in body weight by these conditions.

Table 34. Percentage change in body weight from baseline to Week 72 by obesity-related health disorders (Study GPHZ, mITT population)

Parameter			Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Glucose metabolism	IGT		−2.4 ± 5.02 (N = 47)	−19.7 ± 6.88 (N = 35)	−22.2 ± 9.27 (N = 40)
	Normal		−0.4 ± 4.55 (N = 19)	−16.5 ± 8.36 (N = 24)	−23.2 ± 8.42 (N = 25)
Hypertension	Yes		−2.0 ± 5.00 (N = 35)	−18.6 ± 6.27 (N = 29)	−20.9 ± 8.38 (N = 32)
	No		−1.7 ± 4.94 (N = 31)	−18.1 ± 8.82 (N = 30)	−24.2 ± 9.21 (N = 33)
Dyslipidaemia	Triglycerides[a)]	≥150 mg/dL	−1.6 ± 5.20 (N = 36)	−18.4 ± 8.11 (N = 29)	−21.7 ± 8.88 (N = 37)
		<150 mg/dL	−2.1 ± 4.67 (N = 30)	−18.3 ± 7.24 (N = 30)	−23.8 ± 8.93 (N = 28)
	LDL cholesterol	≥140 mg/dL	−1.4 ± 5.52 (N = 21)	−19.1 ± 8.96 (N = 24)	−24.1 ± 7.74 (N = 27)
		<140 mg/dL	−2.1 ± 4.69 (N = 45)	−17.9 ± 6.62 (N = 35)	−21.5 ± 9.59 (N = 38)
	HDL cholesterol	<40 mg/dL	−1.7 ± 4.34 (N = 15)	−14.4 ± 7.61 (N = 13)	−18.8 ± 8.34 (N = 13)
		≥40 mg/dL	−1.9 ± 5.14 (N = 51)	−19.5 ± 7.30 (N = 46)	−23.5 ± 8.85 (N = 52)

Unit, %; Mean ± SD (number of subjects evaluated)
a) Fasting

Table 35. Percentage change in body weight from baseline to Week 72 by obesity-related disorders (Studies GPHK and GPHL, mITT population)

Parameter			Study GPHK				Study GPHL		
			Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
Glucose metabolism	Type 2 diabetes mellitus		-	-	-	-	−3.5 ± 5.87 (N = 256)	−13.3 ± 8.38 (N = 274)	−16.0 ± 9.70 (N = 259)
	Prediabetes[a)]		−4.0 ± 6.72 (N = 194)	−15.5 ± 8.70 (N = 216)	−21.5 ± 10.32 (N = 220)	−23.1 ± 10.03 (N = 215)	-	-	-
	Normal[a)]		−2.8 ± 7.09 (N = 272)	−17.1 ± 9.36 (N = 319)	−22.1 ± 10.05 (N = 306)	−22.8 ± 10.27 (N = 318)	-	-	-
Hyper-tension[b)]	Yes		−3.4 ± 6.86 (N = 145)	−15.0 ± 8.71 (N = 173)	−19.9 ± 9.48 (N = 179)	−21.0 ± 8.30 (N = 177)	−3.6 ± 5.54 (N = 177)	−13.0 ± 8.06 (N = 177)	−16.1 ± 9.65 (N = 176)
	No		−3.3 ± 7.01 (N = 321)	−17.2 ± 9.24 (N = 362)	−22.9 ± 10.36 (N = 347)	−23.9 ± 10.85 (N = 356)	−3.3 ± 6.60 (N = 79)	−13.9 ± 8.95 (N = 97)	−15.7 ± 9.86 (N = 83)
Dyslipidaemia	Triglycerides[c)]	≥150 mg/dL	−2.3 ± 5.92 (N = 163)	−16.0 ± 9.12 (N = 191)	−21.3 ± 9.90 (N = 173)	−23.3 ± 9.91 (N = 178)	−3.4 ± 5.21 (N = 148)	−12.7 ± 8.38 (N = 136)	−16.4 ± 8.73 (N = 143)
		<150 mg/dL	−3.8 ± 7.41 (N = 303)	−16.7 ± 9.14 (N = 344)	−22.1 ± 10.28 (N = 353)	−22.7 ± 10.29 (N = 355)	−3.6 ± 6.70 (N = 108)	−14.0 ± 8.36 (N = 138)	−15.5 ± 10.80 (N = 116)
	LDL cholesterol	≥140 mg/dL	−2.6 ± 6.06 (N = 87)	−16.9 ± 9.23 (N = 95)	−21.5 ± 10.05 (N = 109)	−23.1 ± 8.46 (N = 98)	−4.6 ± 9.86 (N = 27)	−12.9 ± 7.88 (N = 26)	−16.4 ± 10.26 (N = 25)
		<140 mg/dL	−3.5 ± 7.15 (N = 378)	−16.4 ± 9.07 (N = 436)	−21.9 ± 10.21 (N = 414)	−23.0 ± 10.39 (N = 433)	−3.4 ± 5.23 (N = 229)	−13.4 ± 8.45 (N = 248)	−16.0 ± 9.66 (N = 234)
	HDL cholesterol	<40 mg/dL	−2.6 ± 6.97 (N = 136)	−15.1 ± 8.91 (N = 131)	−21.3 ± 9.55 (N = 133)	−21.8 ± 10.50 (N = 132)	−3.5 ± 5.18 (N = 108)	−11.8 ± 7.83 (N = 104)	−15.0 ± 9.44 (N = 110)
		≥40 mg/dL	−3.6 ± 6.94 (N = 330)	−16.9 ± 9.16 (N = 404)	−22.0 ± 10.36 (N = 393)	−23.3 ± 10.03 (N = 401)	−3.5 ± 6.35 (N = 148)	−14.3 ± 8.59 (N = 170)	−16.7 ± 9.86 (N = 149)

Unit, %; Mean ± SD (number of subjects evaluated); -, not applicable
a) Classified according to the definition of American Diabetes Association (ADA)
b) In Study GPHK, hypertension defined by the inclusion criteria
c) Fasting

In Studies GPHZ, GPHK, and GPHL, no trends different from those observed in the mITT population were noted for the results of the primary and secondary endpoints in all randomized cases, along with those deleted due to GCP violations confirmed at SMO.

On the basis of the following study results, etc., PMDA considers that the weight reduction effect of tirzepatide in patients with obesity disease has been demonstrated and that a greater effect can be expected with the tirzepatide 15 mg group compared to the tirzepatide 10 mg group. The clinical significance of the degree of weight reduction observed with tirzepatide administration will be examined in the next section, taking into account the improvement of health disorders associated with obesity.

- In the Japanese phase III study (Study GPHZ), the results demonstrated the superiority of tirzepatide 10 mg and tirzepatide 15 mg over placebo in the co-primary endpoints, i.e., the percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% weight reduction at Week 72. As for the secondary endpoints, the proportion of subjects achieving ≥10% weight reduction was higher in the tirzepatide groups than in the placebo group, and the reductions in BMI, waist circumference, and visceral adipose tissue area were also greater in the tirzepatide groups than in the placebo group.
- In the global phase III studies (Studies GPHK and GPHL), the results demonstrated the superiority of tirzepatide 10 mg and tirzepatide 15 mg over placebo in the co-primary endpoints, i.e., the percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% weight reduction at Week 72. As for the secondary endpoints, the proportion of subjects achieving ≥10% weight reduction was higher in the tirzepatide groups than in the placebo group, and the reductions in BMI and waist circumference were also greater in the tirzepatide groups than in the placebo group.
- In Studies GPHK and GPHL, while some differences in baseline subject characteristics were observed between the Japanese subpopulation and the entire population, the impact of these differences (including body weight difference that were considered a factor for higher exposure levels of tirzepatide in Japanese patients compared to non-Japanese patients) was not significant with respect to the efficacy of tirzepatide. The trends in the percentage change in body weight from baseline to Week 72 and the proportion of subjects achieving ≥5% weight reduction at Week 72, the co-primary endpoints, were consistent between the Japanese subpopulation and the entire population. Thus, the efficacy of tirzepatide in the Japanese subpopulation was considered consistent with that in the entire population, including secondary endpoints.
- In the results of the co-primary and secondary endpoints of Studies GPHZ, GPHK, and GPHL, while some evaluation items in Study GPHK showed similar results between the tirzepatide 10 mg and 15 mg groups, overall, the tirzepatide 15 mg group demonstrated a greater weight reduction effect compared to the tirzepatide 10 mg group.

7.R.1.2 Improvement in health disorders associated with obesity

The applicant's explanation:

Regarding the improvement effects on blood glucose, blood pressure, and lipid parameters with tirzepatide administration, in all phase III studies (Studies GPHZ, GPHK, and GPHL), except for low-density lipoprotein (LDL) cholesterol results in Study GPHL, the tirzepatide groups exhibited a trend toward improvement compared to the placebo group (Tables 11, 16, and 23). As for the comparison

between doses of tirzepatide, the change from baseline in blood glucose parameters showed no significant difference between the tirzepatide 10 mg group and the tirzepatide 15 mg group in Study GPHL, which targeted patients with type 2 diabetes mellitus. The change from baseline in blood pressure parameters was greater in the tirzepatide 15 mg group compared to the tirzepatide 10 mg group in Study GPHL; however, no significant differences between the 2 dose groups were observed in Studies GPHZ and GPHK. The percentage change from baseline in lipid parameters showed a tendency for greater improvement in the tirzepatide 15 mg group compared to the tirzepatide 10 mg group in Study GPHZ. In Study GPHK, total cholesterol, LDL cholesterol, and triglycerides showed greater improvement in the tirzepatide 15 mg group compared to the tirzepatide 10 mg group, but there was no significant difference in HDL cholesterol between the 2 groups. In Study GPHL, HDL cholesterol and triglycerides showed greater improvement in the tirzepatide 15 mg group compared to the tirzepatide 10 mg group, whereas LDL cholesterol and total cholesterol showed no significant differences between the 2 groups.

Regarding the efficacy of tirzepatide according to various health disorders associated with obesity, Tables 36, 37, and 38 show the results of HbA1c by baseline glycemic status, blood pressure by hypertension status, and lipid parameters by dyslipidaemia status in phase III studies (Studies GPHZ, GPHK, and GPHL). Except for the population without hyper LDL cholesterolaemia in Study GPHL, a trend toward improvement was observed in the tirzepatide groups compared to the placebo group across all populations, regardless of each health disorder. In Study GPHL, an improvement in LDL cholesterol levels was observed in the tirzepatide group compared to the placebo group in patients with hyper LDL cholesterolaemia at baseline.

Table 36. Changes in HbA1c, blood pressure, and lipid parameters (% change) from baseline to Week 72 by differences in subject characteristics (Study GPHZ, mITT Population)

Parameter	At baseline	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
HbA1c (%)	Glucose metabolism: IGT	−0.01 ± 0.30 (47)	−0.67 ± 0.35 (35)	−0.67 ± 0.32 (40)
	Glucose metabolism: Normal	0.08 ± 0.17 (19)	−0.35 ± 0.27 (24)	−0.52 ± 0.20 (25)
Systolic blood pressure (mmHg)	With hypertension	3.5 ± 9.27 (35)	−13.3 ± 12.18 (29)	−9.0 ± 12.44 (32)
	Without hypertension	−0.3 ± 8.55 (31)	−9.7 ± 14.42 (30)	−15.0 ± 13.11 (33)
Diastolic blood pressure (mmHg)	With hypertension	1.0 ± 8.46 (35)	−6.8 ± 10.21 (29)	−4.3 ± 8.89 (32)
	Without hypertension	−0.5 ± 8.07 (31)	−5.6 ± 10.62 (30)	−8.3 ± 8.38 (33)
LDL cholesterol (mg/dL)	With hyper LDL cholesterolaemia[b)]	−0.5 ± 9.97 (21)	−19.1 ± 17.16 (24)	−18.6 ± 17.47 (27)
	Without hyper LDL cholesterolaemia[b)]	2.9 ± 16.91 (45)	−1.5 ± 29.51 (35)	−9.5 ± 19.61 (38)
HDL cholesterol (mg/dL)	With hypo HDL cholesterolaemia[c)]	7.9 ± 15.67 (15)	28.0 ± 20.58 (13)	18.4 ± 17.07 (13)
	Without hypo HDL cholesterolaemia[c)]	2.5 ± 11.06 (51)	11.8 ± 15.33 (46)	17.3 ± 22.67 (52)
Triglycerides[a)] (mg/dL)	With hypertriglyceridaemia[d)]	−4.9 ± 38.50 (36)	−43.3 ± 24.54 (29)	−46.7 ± 19.11 (37)
	Without hypertriglyceridaemia[d)]	−2.3 ± 29.30 (30)	−23.3 ± 30.77 (30)	−36.6 ± 28.07 (28)

Mean ± SD (number of subjects evaluated)
a) Fasting
b) Defined as LDL cholesterol ≥140 mg/dL.
c) Defined as HDL cholesterol <40 mg/dL.
d) Defined as fasting triglycerides ≥150 mg/dL.

Table 37. Changes in HbA1c, blood pressure, and lipid parameters (% change) from baseline to Week 72 by differences in subject characteristics (Study GPHK, mITT population)

Parameter	At baseline	Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)
HbA1c (%)	Glucose metabolism: Prediabetes[b)]	−0.1 ± 0.30 (N = 194)	−0.5 ± 0.29 (N = 213)	−0.6 ± 0.32 (N = 218)	−0.6 ± 0.39 (N = 209)
	Glucose metabolism: Normal[b)]	−0.1 ± 0.30 (N = 265)	−0.3 ± 0.29 (N = 314)	−0.4 ± 0.30 (N = 298)	−0.4 ± 0.30 (N = 315)
Systolic blood pressure (mmHg)	With hypertension[c)]	−1.6 ± 13.37 (N = 145)	−5.7 ± 15.02 (N = 173)	−7.6 ± 15.22 (N = 179)	−4.9 ± 14.28 (N = 177)
	Without hypertension[c)]	−0.9 ± 10.88 (N = 321)	−8.4 ± 11.59 (N = 362)	−9.8 ± 11.60 (N = 347)	−9.5 ± 12.10 (N = 356)
Diastolic blood pressure (mmHg)	With hypertension[c)]	−2.1 ± 8.20 (N = 145)	−4.0 ± 9.48 (N = 173)	−4.3 ± 10.03 (N = 179)	−2.4 ± 9.84 (N = 177)
	Without hypertension[c)]	−0.8 ± 8.23 (N = 321)	−5.9 ± 8.34 (N = 362)	−6.8 ± 8.01 (N = 347)	−5.8 ± 8.71 (N = 356)
LDL cholesterol (mg/dL)	With hyper HDL cholesterolaemia[d)]	−9.6 ± 20.72 (N = 85)	−14.5 ± 18.69 (N = 94)	−15.6 ± 18.82 (N = 106)	−17.8 ± 15.79 (N = 97)
	Without hyper HDL cholesterolaemia[d)]	6.0 ± 29.41 (N = 371)	1.2 ± 27.27 (N = 420)	−0.4 ± 27.17 (N = 405)	−3.2 ± 25.81 (N = 418)
HDL cholesterol (mg/dL)	With hypo HDL cholesterolaemia[e)]	9.3 ± 20.01 (N = 134)	19.1 ± 20.30 (N = 129)	19.9 ± 22.15 (N = 132)	19.4 ± 22.60 (N = 128)
	Without hypo HDL cholesterolaemia[e)]	0.1 ± 15.49 (N = 324)	5.2 ± 18.95 (N = 389)	6.8 ± 19.17 (N = 383)	6.9 ± 19.00 (N = 391)
Triglycerides[a)] (mg/dL)	With hypertriglyceridaemia[f)]	−17.1 ± 33.10 (N = 160)	−33.8 ± 31.31 (N = 188)	−38.8 ± 28.66 (N = 171)	−42.4 ± 26.35 (N = 177)
	Without hypertriglyceridaemia[f)]	10.1 ± 47.15 (N = 297)	−9.8 ± 33.65 (N = 334)	−9.5 ± 39.10 (N = 344)	−15.7 ± 39.53 (N = 341)

Mean ± SD (number of subjects evaluated)

a) Fasting
b) Classified by ADA criteria.
c) Defined as hypertension per Study GPHK inclusion criteria.
d) Defined as LDL cholesterol ≥140 mg/dL.
e) Defined as HDL cholesterol <40 mg/dL.
f) Defined as fasting triglycerides ≥150 mg/dL.

Table 38. Changes in HbA1c, blood pressure, and lipid parameters (% change) from baseline to Week 72 by differences in subject characteristics (Study GPHL, mITT population)

Parameter	At baseline	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
HbA1c (%)	Glucose metabolism: Type 2 diabetes mellitus	−0.59 ± 1.04 (N = 165)	−2.22 ± 1.00 (N = 265)	−2.29 ± 1.12 (N = 249)
Systolic blood pressure (mmHg)	With hypertension	−1.4 ± 13.29 (N = 177)	−5.9 ± 15.97 (N = 177)	−7.1 ± 13.11 (N = 176)
	Without hypertension	−0.7 ± 14.50 (N = 79)	−6.1 ± 11.61 (N = 97)	−9.4 ± 13.51 (N = 83)
Diastolic blood pressure (mmHg)	With hypertension	−0.2 ± 7.76 (N = 177)	−2.4 ± 8.51 (N = 177)	−2.3 ± 9.80 (N = 176)
	Without hypertension	−0.4 ± 7.77 (N = 79)	−2.3 ± 8.99 (N = 97)	−4.2 ± 9.65 (N = 83)
LDL cholesterol (mg/dL)	With hyper LDL cholesterolaemia[b)]	−6.5 ± 20.25 (N = 27)	−21.8 ± 21.38 (N = 26)	−17.7 ± 18.58 (N = 25)
	Without hyper LDL cholesterolaemia[b)]	12.9 ± 40.26 (N = 228)	14.0 ± 78.51 (N = 246)	15.7 ± 49.25 (N = 231)
HDL cholesterol (mg/dL)	With hypo HDL cholesterolaemia[c)]	5.5 ± 20.32 (N = 108)	14.8 ± 21.32 (N = 103)	21.7 ± 31.47 (N = 108)
	Without hypo HDL cholesterolaemia[c)]	0.4 ± 16.29 (N = 147)	3.9 ± 16.08 (N = 169)	6.3 ± 18.21 (N = 149)
Triglycerides (mg/dL)[a)]	With hypertriglyceridaemia[d)]	−7.7 ± 43.73 (N = 147)	−28.5 ± 36.06 (N = 135)	−32.3 ± 37.52 (N = 142)
	Without hypertriglyceridaemia[d)]	12.8 ± 39.55 (N = 108)	−11.4 ± 35.59 (N = 137)	−8.6 ± 41.04 (N = 115)

Mean ± SD (number of subjects evaluated)
a) Fasting
b) Defined as LDL cholesterol ≥140 mg/dL.
c) Defined as HDL cholesterol <40 mg/dL.
d) Defined as fasting triglycerides ≥150 mg/dL.

Tables 39 and 40 show the usage status of antihypertensive drugs, lipid-lowering drugs, and hypoglycemic drugs during the study period. With respect to antihypertensive drugs, in all studies, the proportion of subjects in whom the dose was reduced from baseline was higher in the tirzepatide groups than in the placebo group. The proportion of subjects in whom the dose was increased showed no significant difference between treatment groups in Study GPHZ. In Study GPHK, the proportion was lower in the tirzepatide 10 mg and 15 mg groups compared to the placebo group and the tirzepatide 5 mg group. In Study GPHL, the proportion was lower in the tirzepatide group than in the placebo group. For lipid-lowering drugs, the proportion of subjects in whom the dose was reduced from baseline was higher in the tirzepatide groups than in the placebo group in Studies GPHZ and GPHL. In Study GPHK, no significant difference was observed between treatment groups. The proportion of subjects in whom the dose was increased showed no significant difference between treatment groups in any study. Regarding hypoglycemic drugs, in Study GPHL, the proportion of subjects in whom the dose of hypoglycemic drugs was reduced from baseline was higher in the tirzepatide groups than in the placebo group, whereas the proportion of subjects in whom the dose was increased was lower in the tirzepatide groups than in the placebo group.

Table 39. Usage status of medications for health disorders associated with obesity after administration of study drug (Study GPHZ, safety analysis population)[a)]

Comparison to baseline		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Hypotensive drugs	Continued without administration	52.0 (39)	54.8 (40)	61.0 (47)
	Dose increase	2.7 (2)	2.7 (2)	2.6 (2)
	No change	40.0 (30)	26.0 (19)	26.0 (20)
	Dose reduction	1.3 (1)	9.6 (7)	6.5 (5)
	Unknown	4.0 (3)	6.8 (5)	3.9 (3)
Lipid-lowering drugs	Continued without administration	77.3 (58)	72.6 (53)	72.7 (56)
	Dose increase	4.0 (3)	0 (0)	3.9 (3)
	No change	17.3 (13)	21.9 (16)	22.1 (17)
	Dose reduction	0 (0)	5.5 (4)	1.3 (1)
	Unknown	1.3 (1)	0 (0)	0 (0)

Percentage (number of applicable subjects)

a) Subjects receiving hypoglycemic drugs were not enrolled, and no subjects used hypoglycemic drugs during the study period.

Table 40. Usage status of medications for health disorders associated with obesity after administration of study drug (Studies GPHK and GPHL, safety analysis population)

Comparison to baseline		Study GPHK				Study GPHL		
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
Hypotensive drugs	Continued without administration	68.8 (438)	68.6 (428)	69.1 (434)	68.2 (428)	40.7 (125)	42.7 (129)	43.9 (133)
	Dose increase	2.2 (14)	2.2 (14)	1.0 (6)	1.6 (10)	5.2 (16)	3.3 (10)	3.3 (10)
	No change	11.5 (73)	10.6 (66)	9.6 (60)	11.3 (71)	51.1 (157)	44.0 (133)	43.9 (133)
	Dose reduction	2.0 (13)	2.9 (18)	4.8 (30)	4.9 (31)	2.6 (8)	9.6 (29)	7.9 (24)
	Unknown	15.5 (99)	15.7 (98)	15.6 (98)	14.0 (88)	0.3 (1)	0.3 (1)	1.0 (3)
Lipid-lowering drugs	Continued without administration	78.2 (498)	79.5 (496)	83.3 (523)	83.1 (522)	53.1 (163)	58.6 (177)	54.5 (165)
	Dose increase	1.6 (10)	1.3 (8)	1.1 (7)	0.8 (5)	3.9 (12)	3.6 (11)	1.3 (4)
	No change	9.1 (58)	7.4 (46)	4.3 (27)	5.3 (33)	41.0 (126)	35.1 (106)	38.6 (117)
	Dose reduction	1.1 (7)	1.4 (9)	1.6 (10)	1.1 (7)	0.7 (2)	2.6 (8)	3.6 (11)
	Unknown	10.0 (64)	10.4 (65)	9.7 (61)	9.7 (61)	1.3 (4)	0 (0)	2.0 (6)
Hypoglycemic drugs	Continued without administration	-	-	-	-	15.0 (46)	18.2 (55)	21.8 (66)
	Dose increase	-[a)]	-[a)]	-[a)]	[a)]	26.4 (81)	4.0 (12)	5.0 (15)
	No change	-	-	-	-	46.9 (144)	57.3 (173)	53.8 (163)
	Dose reduction	-	-	-	-	10.4 (32)	20.5 (62)	17.2 (52)
	Unknown	-	-	-	-	1.3 (4)	0 (0)	2.3 (7)

Percentage (number of applicable subjects); -, not applicable

a) The proportion of subjects (number of applicable subjects) who had not received hypoglycemic drugs at baseline but used them during the study period was 2.2% (14 subjects) in the placebo group and 0.3% (2 subjects) in each of the tirzepatide 5 mg, 10 mg, and 15 mg groups.

PMDA's view:

In the 3 phase III studies (Studies GPHZ, GPHK, and GPHL), the degree of improvement in HbA1c, blood pressure, and lipid parameters, including LDL cholesterol, was greater in the tirzepatide groups than in the placebo group. In Studies GPHK and GPHL, the results in the Japanese subpopulation were consistent with those in the entire population. Compared to the placebo group, the proportion of subjects in whom the dose of antihypertensive drugs, lipid-lowering drugs, or hypoglycemic drugs was increased from baseline was similar or lower in the tirzepatide groups, whereas the proportion of subjects in whom the dose of these medications was reduced was similar or higher.

From the above results, in patients with obesity disease with health disorders related to obesity, administration of tirzepatide not only led to weight loss but also showed a trend toward improvement in health disorders (hypertension, dyslipidaemia, and type 2 diabetes mellitus). The weight-reducing effect observed in these patients has clinical significance, demonstrating the efficacy of tirzepatide for obesity disease. According to the inclusion criteria of Study GPHZ, patients had to have impaired glucose tolerance (IGT), hypertriglyceridaemia, or non-alcoholic fatty liver disease (NAFLD) as obesity-related

health disorders. The proportion of subjects in whom these health disorders improved tended to be higher in the tirzepatide groups than in the placebo group (Table 12). The significance of the results observed in studies and the appropriateness of defining these health disorders in the indication of tirzepatide taking account of the significance will be further discussed in Section 7.R.3, "Indication and clinical positioning."

7.R.2 Safety

The applicant's explanation:

Tables 41, 42, and 43 show the incidence of adverse events in Studies GPHZ, GPHK, and GPHL, respectively. In Studies GPHZ and GPHK, the incidence of adverse events and adverse drug reactions was higher in the tirzepatide groups than in the placebo group. In Study GPHL, the incidence of adverse events showed no significant difference between the placebo and tirzepatide groups, whereas the incidence of adverse drug reactions was higher in the tirzepatide groups than in the placebo group. The most commonly reported adverse events and adverse drug reactions were gastrointestinal disorders (system organ class [SOC]). No death occurred in Study GPHZ. In Study GPHK, deaths were reported in 4 subjects in the placebo group (pulmonary embolism, cardiac failure acute, intestinal obstruction, and ischaemic stroke in 1 subject each), 4 subjects in the tirzepatide 5 mg group (COVID-19 pneumonia in 2 subjects, and hepatic failure and multiple injuries in 1 subject each), 1 subject in the tirzepatide 10 mg group (homicide), and 1 subject in the tirzepatide 15 mg group (SARS-CoV-2 test positive). In Study GPHL, deaths were reported in 2 subjects in the tirzepatide 10 mg group (respiratory fume inhalation disorder and cardio-respiratory arrest in 1 subject each). Hepatic failure[14)] occurring in 1 subject in Study GPHK was considered an adverse drug reaction. No deaths were reported in the Japanese subpopulations of Studies GPHK and GPHL. The incidence of serious adverse events was comparable between the tirzepatide and placebo groups across Studies GPHZ, GPHK, and GPHL. Most of the events were not considered adverse drug reactions, and their outcomes were reported as resolved or improved. The incidence of adverse events leading to treatment discontinuation tended to be generally higher in the tirzepatide groups than in the placebo group across all studies. Approximately half of the events were gastrointestinal disorders. There was no trend towards a notably higher incidence of specific event.

Comparisons among tirzepatide dose groups showed no clear differences in the incidence of all adverse events, all adverse drug reactions, serious adverse events, or adverse events leading to treatment discontinuation in any of the Studies GPHZ, GPHK, or GPHL.

In the Japanese subpopulations of Studies GPHK and GPHL, the incidence of adverse events and adverse drug reactions showed no notable differences compared to those in the entire population.

Table 41. Incidence of adverse events (Study GPHZ, safety analysis population)

		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
All adverse events		69.3 (52)	83.6 (61)	85.7 (66)
All adverse drug reactions		10.7 (8)	56.2 (41)	63.6 (49)
Serious adverse events		6.7 (5)	11.0 (8)	6.5 (5)
Adverse events leading to treatment discontinuation		6.7 (5)	9.6 (7)	10.4 (8)
Gastrointestinal disorders (SOC)		28.0 (21)	52.1 (38)	61.0 (47)
Hypoglycaemia[a)]		1.3 (1)	5.5 (4)	9.1 (7)
Pancreatitis[b)]		0 (0)	0 (0)	0 (0)
Gallbladder-related events[c)]		0 (0)	0 (0)	1.3 (1)
Hypersensitivity reactions[d)]	Immediate	0 (0)	2.7 (2)	1.3 (1)
	Non-immediate	2.7 (2)	2.7 (2)	7.8 (6)
Injection site reaction[e)]		0 (0)	8.2 (6)	9.1 (7)
Cardiovascular disorders[f)]		1.3 (1)	2.7 (2)	0 (0)
Malignant neoplasm-related events[g)]		2.7 (2)	1.4 (1)	3.9 (3)
Depression and suicide-related events[h)]		0 (0)	0 (0)	0 (0)

Incidence % (number of subjects with events)

a) Hypoglycaemia with blood glucose levels <54 mg/dL or severe hypoglycaemia.

b) Pancreatitis confirmed by the Clinical Events Committee.

c) Events in standardized MedDRA queries (SMQ) for gallbladder-related disorders (narrow), gallstone-related disorders (narrow), and biliary tract disorders (narrow).

d) Events in SMQ for anaphylactic reactions (narrow), angioedema (narrow), severe cutaneous adverse reactions (narrow), hypersensitivity (narrow), and vasculitis (narrow). Events were classified as immediate-type (occurring within 24 hours post-dose of the study drug) or non-immediate-type (occurring between 24 hours post-dose and the next dose of the study drug). Events potentially indicative of immediate-type hypersensitivity reactions included all terms encompassed in the algorithm for anaphylactic reactions in SMQ.

e) Events categorized under high level term (HLT) for injection site reactions, administration site reactions, and infusion site reactions.

f) Major cardiovascular events confirmed by the Clinical Events Committee (all-cause mortality, myocardial infarction, hospitalization for angina unstable, hospitalization for heart failure, coronary artery intervention, cardiovascular events [stroke and transient ischaemic attack]).

g) Events in SMQ for malignant tumours (narrow) and tumours of unspecified malignancy (narrow).

h) Events in SMQ for depression (excl suicide and self-injury) (narrow) and suicide/self-injury (narrow).

Table 42. Incidence of adverse events
(Study GPHK, entire population and Japanese subpopulation, safety analysis population)

		Entire population				Japanese subpopulation			
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
All adverse events		71.9 (458)	80.9 (505)	81.8 (514)	78.8 (495)	59.3 (16)	75.0 (18)	63.6 (14)	75.9 (22)
All adverse drug reactions		30.5 (194)	55.6 (347)	62.3 (391)	61.1 (384)	11.1 (3)	41.7 (10)	54.5 (12)	51.7 (15)
Serious adverse events		6.9 (44)	6.3 (39)	6.7 (42)	5.1 (32)	3.7 (1)	8.3 (2)	0 (0)	3.4 (1)
Adverse events leading to treatment discontinuation		3.1 (20)	4.5 (28)	7.0 (44)	6.4 (40)	0 (0)	4.2 (1)	0 (0)	6.9 (2)
Death		0.6 (4)	0.6 (4)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders (SOC)		30.3 (193)	55.4 (346)	60.8 (382)	59.1 (371)	22.2 (6)	45.8 (11)	40.9 (9)	51.7 (15)
Hypoglycaemia[a)]		0.2 (1)	1.4 (9)	1.6 (10)	1.6 (10)	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatitis[b)]		0.2 (1)	0.2 (1)	0.2 (1)	0.2 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Gallbladder-related events[c)]		1.3 (8)	1.9 (12)	2.7 (17)	1.3 (8)	0 (0)	0 (0)	0 (0)	0 (0)
Hypersensitivity reactions[d)]	Immediate	0.3 (2)	1.8 (11)	3.0 (19)	2.7 (17)	0 (0)	4.2 (1)	13.6 (3)	6.9 (2)
	Non-immediate	2.2 (14)	3.5 (22)	3.5 (22)	4.3 (27)	0 (0)	4.2 (1)	13.6 (3)	3.4 (1)
Injection site reaction[e)]		2.2 (14)	5.8 (36)	9.9 (62)	9.7 (61)	3.7 (1)	4.2 (1)	22.7 (5)	3.4 (1)
Cardiovascular disorders[f)]		0.8 (5)	0.6 (4)	0.5 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Malignant neoplasm-related events[g)]		1.1 (7)	1.3 (8)	0.5 (3)	0.8 (5)	0 (0)	4.2 (1)	4.5 (1)	0 (0)
Depression and suicide-related events[h)]		3.3 (21)	1.6 (10)	3.0 (19)	2.1 (13)	0 (0)	0 (0)	0 (0)	0 (0)

Incidence % (Number of subjects with events)

a)-c), e)-h) Footnotes a)-c) and e)-h) in Table 41

d) Events in SMQ for anaphylactic reactions (narrow), angioedema (narrow), severe cutaneous adverse reactions (narrow), and hypersensitivity (narrow). Events were classified as immediate-type (occurring within 24 hours post-dose *of the study drug) or non-immediate-type (occurring between 24 hours post-dose and the next dose of the study drug). Events potentially indicative of immediate-type hypersensitivity reactions included all terms encompassed in the algorithm for anaphylactic reactions in SMQ.

Table 43. Incidence of adverse events
(Study GPHL, entire population and Japanese subpopulation, safety analysis population)

	Entire population			Japanese subpopulation		
	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
All adverse events	75.6 (232)	76.8 (232)	71.3 (216)	92.3 (12)	92.9 (13)	92.9 (13)
All adverse drug reactions	27.0 (83)	48.7 (147)	47.2 (143)	7.7 (1)	50.0 (7)	35.7 (5)
Serious adverse events	7.5 (23)	5.6 (17)	8.6 (26)	7.7 (1)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	3.9 (12)	4.0 (12)	7.3 (22)	0 (0)	0 (0)	7.1 (1)
Death	0 (0)	0.7 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders (SOC)	28.3 (87)	45.4 (137)	47.9 (145)	15.4 (2)	57.1 (8)	50.0 (7)
Hypoglycaemia[a)]	1.3 (4)	3.6 (11)	5.0 (15)	0 (0)	0 (0)	0 (0)
Pancreatitis[b)]	0.3 (1)	0 (0)	0.7 (2)	0 (0)	0 (0)	0 (0)
Gallbladder-related event[c)]	2.6 (8)	1.3 (4)	2.6 (8)	7.7 (1)	0 (0)	0 (0)
Hypersensitivity reactions[d)] Non-immediate	0.7 (2)	1.3 (4)	1.0 (3)	0 (0)	0 (0)	0 (0)
Hypersensitivity reactions[d)] Immediate	3.6 (11)	2.0 (6)	2.3 (7)	7.7 (1)	7.1 (1)	7.1 (1)
Injection site reaction[e)]	1.0 (3)	5.6 (17)	5.3 (16)	0 (0)	7.1 (1)	14.3 (2)
Cardiovascular disorders[f)]	1.3 (4)	1.3 (4)	1.0 (3)	0 (0)	0 (0)	0 (0)
Malignant neoplasm-related events[g)]	2.3 (7)	0.3 (1)	1.0 (3)	0 (0)	0 (0)	0 (0)
Depression and suicide-related events[h)]	1.3 (4)	1.0 (3)	0.7 (2)	0 (0)	0 (0)	0 (0)

Incidence % (number of subjects with events)
a)-h) Footnotes a)–h) in Table 41

Tables 44 and 45 show the incidence of adverse events by sex, body weight, and BMI, which were subject characteristics identified as differing between the Japanese subpopulation and the entire population in the global phase III studies (Studies GPHK and GPHL). No significant differences in the incidence were observed among subpopulations stratified by these characteristics.

Table 44. Comparison of the incidence of adverse event by subject characteristics
(Study GPHK, entire population and Japanese subpopulation, safety analysis population)

Parameter		Entire population				Japanese subpopulation			
		Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 27)	Tirzepatide 5 mg (N = 24)	Tirzepatide 10 mg (N = 22)	Tirzepatide 15 mg (N = 29)
Sex	Male	64.5 (131/203)	77.6 (156/201)	75.1 (154/205)	71.9 (146/203)	47.1 (8/17)	73.3 (11/15)	53.3 (8/15)	63.2 (12/19)
	Female	75.3 (327/434)	82.5 (349/423)	85.1 (360/423)	82.1 (349/425)	80.0 (8/10)	77.8 (7/9)	85.7 (6/7)	100.0 (10/10)
Body weight (kg)	<85	70.3 (78/111)	79.6 (90/113)	86.8 (92/106)	81.4 (92/113)	53.3 (8/15)	80.0 (8/10)	63.6 (7/11)	78.6 (11/14)
	≥85 and <100	75.3 (143/190)	81.9 (176/215)	81.7 (152/186)	81.3 (139/171)	62.5 (5/8)	63.6 (7/11)	62.5 (5/8)	66.7 (8/12)
	≥100 and <115	70.6 (113/160)	80.8 (122/151)	78.4 (116/148)	82.6 (133/161)	75.0 (3/4)	100.0 (2/2)	50.0 (1/2)	100.0 (3/3)
	≥115	70.5 (124/176)	80.7 (117/145)	81.9 (154/188)	71.6 (131/183)	-	100.0 (1/1)	100.0 (1/1)	-
BMI (kg/m^2)	<30	56.5 (13/23)	73.5 (25/34)	82.9 (29/35)	80.0 (32/40)	50.0 (5/10)	57.1 (4/7)	62.5 (5/8)	80.0 (8/10)
	≥30 and <35	70.4 (157/223)	83.8 (201/240)	81.1 (167/206)	79.3 (157/198)	58.3 (7/12)	91.7 (11/12)	58.3 (7/12)	68.8 (11/16)
	≥35 and <40	77.1 (138/179)	78.6 (136/173)	83.8 (155/185)	82.0 (146/178)	75.0 (3/4)	50.0 (2/4)	100.0 (2/2)	100.0 (3/3)
	≥40	70.8 (150/212)	80.8 (143/177)	80.7 (163/202)	75.5 (160/212)	100.0 (1/1)	100.0 (1/1)	-	-

Incidence % (number of subjects with events/number of subjects evaluated); -, not applicable

Table 45. Comparison of the incidence of adverse event by subject characteristics (Study GPHL, entire population and Japanese subpopulation, safety analysis population)

Parameter		Entire population			Japanese subpopulation		
		Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)	Placebo (N = 13)	Tirzepatide 10 mg (N = 14)	Tirzepatide 15 mg (N = 14)
Sex	Male	70.5 (105/149)	76.0 (111/146)	73.3 (107/146)	88.9 (8/9)	90.0 (9/10)	90.9 (10/11)
	Female	80.4 (127/158)	77.6 (121/156)	69.4 (109/157)	100.0 (4/4)	100.0 (4/4)	100.0 (3/3)
Body weight (kg)	<85	72.5 (50/69)	78.0 (46/59)	75.4 (49/65)	100.0 (4/4)	100.0 (6/6)	100.0 (5/5)
	≥85 and <100	80.6 (79/98)	76.2 (80/105)	72.1 (80/111)	88.9 (8/9)	100.0 (6/6)	85.7 (6/7)
	≥100 and <115	75.8 (47/62)	72.4 (55/76)	72.6 (45/62)	-	100.0 (1/1)	100.0 (2/2)
	≥115	71.8 (56/78)	82.3 (51/62)	64.6 (42/65)	-	0 (0/1)	-
BMI (kg/m^2)	<30	76.1 (35/46)	76.9 (40/52)	72.9 (35/48)	100.0 (6/6)	100.0 (4/4)	100.0 (4/4)
	≥30 and <35	74.0 (77/104)	78.9 (71/90)	76.6 (85/111)	83.3 (5/6)	100.0 (7/7)	85.7 (6/7)
	≥35 and <40	74.6 (53/71)	73.4 (69/94)	71.1 (59/83)	100.0 (1/1)	50.0 (1/2)	100.0 (2/2)
	≥40	77.9 (67/86)	78.8 (52/66)	60.7 (37/61)	-	100.0 (1/1)	100.0 (1/1)

Incidence % (number of subjects with events/number of subjects evaluated); -, not applicable

Table 46 shows the incidence of adverse events by sex, body weight, and BMI in the Japanese phase III study (Study GPHZ). No notable differences in incidence trends were observed among subpopulations stratified by these characteristics.

Table 46. Incidence of adverse events by sex, body weight, and BMI (Study GPHZ, safety analysis population)

Parameter		Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Sex	Male	62.2 (28/45)	86.0 (37/43)	77.8 (35/45)
	Female	80.0 (24/30)	80.0 (24/30)	96.9 (31/32)
Body weight (kg)	<85	81.5 (22/27)	84.0 (21/25)	84.6 (22/26)
	≥85 and <100	59.3 (16/27)	89.3 (25/28)	90.6 (29/32)
	≥100 and <115	84.6 (11/13)	64.3 (9/14)	78.6 (11/14)
	≥115	37.5 (3/8)	100.0 (6/6)	80.0 (4/5)
BMI (kg/m^2)	<30	66.7 (16/24)	95.0 (19/20)	85.0 (17/20)
	≥30 and <35	76.0 (19/25)	75.9 (22/29)	86.7 (26/30)
	≥35 and <40	58.8 (10/17)	85.0 (17/20)	90.5 (19/21)
	≥40	77.8 (7/9)	75.0 (3/4)	66.7 (4/6)

Incidence % (number of subjects with events/number of subjects evaluated)

PMDA's view:

According to the analysis of the incidences of adverse events in the phase III studies, the commonly reported events were gastrointestinal disorders, which, along with other reported events, were generally consistent with those observed in patients treated with the existing tirzepatide formulations for type 2 diabetes mellitus. For the comparison between doses of tirzepatide, as for dose-dependent trends, some studies showed a higher incidence of adverse drug reactions and adverse events leading to treatment discontinuation with increasing doses of tirzepatide. No significant differences in the incidence of serious adverse events were observed among treatment groups, including the placebo group. The applicant's explanation that the there was no trend towards differences in the incidence of adverse events

between the Japanese subpopulation and the entire population in the global studies (Studies GPHK and GPHL) is reasonable.

In addition to the above evaluations, the adverse events of special interest identified from the clinical study results and other data, have been individually examined in Sections "7.R.2.1 Gastrointestinal disorders" to "7.R.2.9 Depression and suicide-related events." The findings indicate that the safety profile observed in the phase III studies did not show any notable differences from that of existing tirzepatide formulations. Given the mechanism of action of tirzepatide and dosage regimen of tirzepatide in the approved indications, the safety of tirzepatide can be managed within the same dosing range as the highest approved dose of existing tirzepatide formulations (15 mg per week), provided that as with existing tirzepatide formulations, appropriate precautionary statements are included in the package insert. Considering the efficacy obtained, the safety of tirzepatide is clinically acceptable.

7.R.2.1 Gastrointestinal disorders

The applicant's explanation:

Table 47 shows the incidence of gastrointestinal disorders (SOC) in the phase III studies (Studies GPHZ, GPHK, and GPHL). In all studies, the incidence of gastrointestinal disorders was higher in the tirzepatide group than in the placebo group; however, no noticeable differences were observed between doses of tirzepatide. The gastrointestinal disorders with high incidence in the tirzepatide group included constipation, nausea, diarrhoea, and vomiting. Most gastrointestinal disorders observed in the tirzepatide groups were non-serious and mild or moderate in severity. No significant differences in the incidence of serious gastrointestinal disorders were observed among the treatment groups, including the placebo group. The incidence of gastrointestinal disorders leading to treatment discontinuation was higher in the tirzepatide group than in the placebo group, showing a tendency of dose-dependent increase. Most of them occurred during the dose-escalation period.

Table 47. Incidence of gastrointestinal disorders (SOC) (safety analysis population)

Event	Study GPHZ		
	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
All gastrointestinal disorders	28.0 (21)	52.1 (38)	61.0 (47)
Serious gastrointestinal disorders	0 (0)	1.4 (1)	0 (0)
Gastrointestinal disorders leading to treatment discontinuation	0 (0)	4.1 (3)	6.5 (5)

Event	Study GPHK				Study GPHL		
	Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
All gastrointestinal disorders	30.3 (193)	55.4 (346)	60.8 (382)	59.1 (371)	28.3 (87)	45.4 (137)	47.9 (145)
Serious gastrointestinal disorders	0.6 (4)	0.3 (2)	0.8 (5)	0.6 (4)	1.0 (3)	0.3 (1)	1.7 (5)
Gastrointestinal disorders leading to treatment discontinuation	0.5 (3)	1.8 (11)	4.1 (26)	4.1 (26)	0.7 (2)	1.0 (3)	4.3 (13)

Incidence % (number of subjects with events)

In the Japanese phase III study (Study GPHZ), constipation, nausea, diarrhoea, and vomiting, which had a high incidence, were primarily observed during the dose-escalation period. Few subjects experienced any of these events for the first time more than 4 weeks after the maintenance dose was reached in each group. Intestinal obstruction, which is a potential risk associated with GLP-1 receptor agonists according to the existing knowledge, occurred in 1 subject each in the placebo group and in the tirzepatide 10 mg group in Study GPHK. The case in the tirzepatide 10 mg group was assessed as an adverse drug reaction.

Based on the results of the above clinical studies, gastrointestinal disorder-related events are considered a risk associated with tirzepatide administration. However, most events were mild or moderate in severity, and the number of events leading to treatment discontinuation was small. The safety profile was similar to that of the existing tirzepatide formulations for type 2 diabetes mellitus.

PMDA's view:
In clinical studies, gastrointestinal disorders that were serious or led to treatment discontinuation were observed and the incidence of such events was higher in the tirzepatide group compared to the placebo group. Therefore, the package insert should include appropriate precautions. Considering the severity and outcomes of each event, and from the applicant's explanation comparing the safety profiles of gastrointestinal disorders between tirzepatide and the existing tirzepatide formulations for type 2 diabetes mellitus, the safety profiles of tirzepatide and the existing tirzepatide formulations are similar. Thus, it is appropriate to provide precautions in the package insert that are consistent with those for the existing tirzepatide formulations.

7.R.2.2 Hypoglycaemia

The applicant's explanation:
Table 48 shows the incidence of hypoglycaemia by baseline glucose metabolism status in Study GPHZ, which targeted patients with obesity disease. In Study GPHZ, no severe hypoglycaemia[19)] was observed. The incidence and rate of hypoglycaemia with blood glucose levels <54 mg/dL showed no difference among treatment groups, including the placebo group, in population with normal baseline glucose metabolism. In the IGT population, however, the incidence was higher in the tirzepatide group than in the placebo group. The incidence and rate of hypoglycaemia with blood glucose levels <70 mg/dL were higher in the tirzepatide group than in the placebo group in both the normal glucose metabolism and IGT populations. All cases of hypoglycaemia with blood glucose levels <54 mg/dL were asymptomatic events observed during the oral glucose tolerance test (OGTT).

[19)] Hypoglycaemia requiring intervention by a third party (ingestion of carbohydrates, administration of glucagon, or other measures).

Table 48. Incidence of hypoglycaemia by baseline glucose metabolism status (Study GPHZ, safety analysis population)

Event	Glucose metabolism	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Hypoglycaemia (blood glucose <54 mg/dL) or severe hypoglycaemia	Normal	4.2 (1/24)	3.6 (1/28)	3.4 (1/29)
		3.1 [1]	2.6 [1]	4.9 [2]
	IGT	0 (0/51)	6.7 (3/45)	12.5 (6/48)
		0 [0]	4.7 [3]	10.1 [7]
Hypoglycaemia (blood glucose <70 mg/dL) or severe hypoglycaemia	Normal	8.3 (2/24)	32.1 (9/28)	51.7 (15/29)
		9.3 [3]	38.6 [15]	55.9 [23]
	IGT	0 (0/51)	28.9 (13/45)	45.8 (22/48)
		0 [0]	28.0 [18]	59.0 [41]

Upper row: Incidence % (number of subjects with events/number of subjects evaluated)
Lower row: Rate of events (number of events/100 person-years) [number of events]

Table 49 shows the incidence of hypoglycaemia by baseline glucose metabolism status in Study GPHK, which targeted patients with overweight or obesity without type 2 diabetes mellitus. Severe hypoglycaemia was observed in only 1 subject in the tirzepatide 5 mg group.[14)] The incidence and rate of hypoglycaemia with blood glucose levels <54 mg/dL and <70 mg/dL were higher in the tirzepatide group than in the placebo group in both the population with normal glucose metabolism at baseline and the population with prediabetes at baseline. Most cases of hypoglycaemia with blood glucose levels <54 mg/dL were asymptomatic and observed during the OGTT, while symptomatic hypoglycaemia with blood glucose levels <54 mg/dL was observed in 1 subject in the tirzepatide 5 mg group, 3 subjects in the tirzepatide 10 mg group, and 1 subject in the tirzepatide 15 mg group.

Table 49. Incidence of hypoglycaemia by baseline glucose metabolism status (Study GPHK, safety analysis population)

Event	Glucose metabolism[a)]	Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)
Hypoglycaemia (blood glucose <54 mg/dL) or severe hypoglycaemia	Normal	0.3 (1/371)	1.1 (4/379)	1.9 (7/370)	2.4 (9/376)
		0.2 [1]	0.7 [4]	1.3 [7]	1.9 [10]
	Prediabetes	0 (0/266)	2.0 (5/245)	1.2 (3/258)	0.4 (1/252)
		0 [0]	1.8 [6]	1.7 [6]	0.3 [1]
Hypoglycaemia (blood glucose <70 mg/dL) or severe hypoglycaemia	Normal	2.2 (8/371)	4.5 (17/379)	7.0 (26/370)	6.6 (25/376)
		2.6 [13]	3.6 [19]	5.5 [29]	5.6 [30]
	Prediabetes	0.4 (1/266)	2.9 (7/245)	4.3 (11/258)	3.2 (8/252)
		0.3 [1]	2.7 [9]	7.0 [24]	2.6 [9]

Upper row: Incidence % (number of subjects with events/number of subjects evaluated)
Lower row: Rate of events (number of events/100 person-years) [number of events]
a) Classified according to the ADA definition.

Table 50 shows the incidence of hypoglycaemia in Study GPHL, which targeted patients with overweight or obesity with type 2 diabetes mellitus. No severe hypoglycaemia was observed. The incidence of hypoglycaemia with blood glucose levels <54 mg/dL and <70 mg/dL was higher in the tirzepatide group than in the placebo group. The rate showed no difference between the tirzepatide and placebo groups.

Table 50. Incidence of hypoglycaemia (Study GPHL, safety analysis population)

Event	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
Hypoglycaemia (blood glucose <54 mg/dL) or severe hypoglycaemia	1.3 (4) 9.1 [31]	3.6 (11) 4.0 [17]	5.0 (15) 5.7 [24]
Hypoglycaemia (blood glucose <70 mg/dL) or severe hypoglycaemia	4.9 (15) 45.1 [153]	19.9 (60) 42.3 [179]	16.2 (49) 45.4 [191]

Upper row: Incidence % (number of subjects with events)
Lower row: Rate of events (number of events/100 person-years) [number of events]

The effect of concomitant use of other hypoglycemic drugs on the occurrence of hypoglycaemia was examined based on the results of Study GPHL, focusing on the effect of sulfonylurea (SU) drugs, which are associated with a high risk of hypoglycaemia. The incidence of hypoglycaemia with blood glucose levels <54 mg/dL in subjects receiving concomitant SU therapy was 3.2% (3 of 94 subjects) in the placebo group, 9.2% (7 of 76 subjects) in the tirzepatide 10 mg group, and 11.5% (9 of 78 subjects) in the tirzepatide 15 mg group. In subjects not receiving SU therapy, the incidence was 0.5% (1 of 213 subjects) in the placebo group, 1.8% (4 of 226 subjects) in the tirzepatide 10 mg group, and 2.7% (6 of 225 subjects) in the tirzepatide 15 mg group. In all treatment groups, the incidence was higher in subjects receiving concomitant SU therapy than in those not receiving SU therapy. This trend was consistent with the findings from existing tirzepatide formulations for type 2 diabetes mellitus.

As shown in the above clinical study results, most cases of hypoglycaemia observed in subjects with overweight or obesity without type 2 diabetes mellitus were asymptomatic. The risk of clinically significant hypoglycaemia in subjects with overweight or obesity with type 2 diabetes mellitus treated with tirzepatide was similar to the safety profile of existing tirzepatide formulations for type 2 diabetes mellitus.

PMDA's view:
Although the incidence of hypoglycaemia with blood glucose levels <54 mg/dL and <70 mg/dL tended to be higher in the tirzepatide groups than in the placebo group in clinical studies, severe hypoglycaemia was observed in only 1 subject in the tirzepatide group in Study GPHK. Furthermore, considering the applicant's explanation about the safety profile of tirzepatide in comparison with existing tirzepatide formulations for type 2 diabetes mellitus, the safety profile concerning hypoglycaemia can be regarded as similar. Therefore, as with existing tirzepatide formulations, appropriate warnings about hypoglycaemia should be included in the package insert to ensure that the risk of hypoglycaemia in clinical use is manageable. Continued attention is necessary concerning the increased incidence of hypoglycaemia observed when tirzepatide is used concomitantly with SU drugs. As with existing tirzepatide formulations, appropriate precautions about concomitant use with hypoglycemic drugs, including SU drugs, should be provided.

7.R.2.3 Pancreatitis and gallbladder-related events

The applicant's explanation:
In the phase III studies (Studies GPHZ, GPHK, and GPHL), no cases confirmed as acute pancreatitis by the Clinical Events Committee were observed in Study GPHZ. In Study GPHK, acute pancreatitis was observed in 0.2% (1 of 637) of subjects in the placebo group, 0.2% (1 of 624) of subjects in the tirzepatide 5 mg group, 0.2% (1 of 628) of subjects in the tirzepatide 10 mg group, and 0.2% (1 of 628)

of subjects in the tirzepatide 15 mg group. All cases were of mild or moderate severity. In Study GPHL, acute pancreatitis was observed in 0.3% (1 of 307) of subjects in the placebo group, 0% (0 of 302) of subjects in the tirzepatide 10 mg group, and 0.7% (2 of 303) of subjects in the tirzepatide 15 mg group. All cases were of mild severity.

In none of the studies were any adverse events identified as pancreatitis-related[20)] according to the reported adverse event terms.

With respect to pancreatic enzyme levels, Tables 51 and 52 show the maximum levels of serum lipase and amylase from baseline to the end of treatment in Studies GPHZ, GPHK, and GPHL. The proportion of subjects whose serum lipase and amylase exceeded the upper limit of normal (ULN) tended to be higher in the tirzepatide groups than in the placebo group; in contrast, there was no trend towards dose-dependent increase observed in the tirzepatide groups.

Table 51. Maximum lipase levels from baseline to end of treatment (safety analysis population)

Parameter		Placebo		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Study GPHZ	Above ULN	0 (0/75)		-	9.6 (7/73)	10.4 (8/77)
	>3 × ULN	0 (0/75)		-	0 (0/73)	0 (0/77)
Study GPHK	Above ULN	2.0 (13/637)		7.9 (49/624)	7.3 (46/628)	6.5 (41/628)
	>3 × ULN	0.2 (1/637)		1.1 (7/624)	1.1 (7/628)	1.0 (6/628)
Study GPHL	Above ULN	11.4 (35/307)		-	19.5 (59/302)	19.8 (60/303)
	>3 × ULN	2.6 (8/307)		-	4.0 (12/302)	2.0 (6/303)

Incidence % (number of subjects with events/number of subjects evaluated); -, not applicable
ULN: Upper limit of normal (lipase 100 IU/L for ages ≥18 and <60 years, 120 IU/L for ages ≥60 and <70 years, 130 IU/L for ages ≥70 years

Table 52. Maximum amylase levels from baseline to end of treatment (safety analysis population)

Parameter		Placebo	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Study GPHZ	Above ULN	2.7 (2/75)	-	12.3 (9/73)	18.2 (14/77)
	>3 × ULN	0 (0/75)	-	0 (0/73)	1.3 (1/77)
Study GPHK	Above ULN	7.7 (49/637)	16.7 (104/624)	19.3 (121/628)	17.5 (110/628)
	>3 × ULN	0 (0/637)	1.0 (6/624)	0.5 (3/628)	1.0 (6/628)
Study GPHL	Above ULN	19.2 (59/307)	-	34.8 (105/302)	32.0 (97/303)
	>3 × ULN	2.6 (8/307)	-	3.6 (11/302)	2.6 (8/303)

Incidence % (number of subjects with events/number of subjects evaluated); -, not applicable
ULN: Upper limit of normal (amylase 46 IU/L)

Table 53 shows the incidence of gallbladder-related events.[21)] The number of subjects with events was low across all studies, and no distinct differences were seen between treatment groups, including the placebo group. Cholelithiasis was the most commonly observed event across all studies.

[20)] Events meeting the criteria for acute pancreatitis (narrow) in SMQ or pancreatitis chronic in the preferred term (PT).
[21)] Events in SMQ for gallbladder-related disorders (narrow), gallstone-related disorders (narrow), or biliary tract disorders (narrow).

Table 53. Incidence of gallbladder-related events (safety analysis population)

Event	Study GPHZ		
	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
All gallbladder-related events	0 (0)	0 (0)	1.3 (1)
Severe or serious gallbladder-related events	0 (0)	0 (0)	0 (0)

Event	Study GPHK				Study GPHL		
	Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
All gallbladder-related events	1.3 (8)	1.9 (12)	2.7 (17)	1.3 (8)	2.6 (8)	1.3 (4)	2.6 (8)
Severe or serious gallbladder-related events	0.8 (5)	0.8 (5)	1.8 (11)	1.0 (6)	1.0 (3)	0.7 (2)	1.3 (4)

Incidence % (number of subjects with events)

As shown in the above clinical study results, while the proportion of subjects with elevated pancreatic enzyme levels was higher in the tirzepatide groups compared to the placebo group, no trend suggesting an increased risk of pancreatitis with tirzepatide administration was observed. The incidence of gallbladder-related events was low in all treatment groups, with no substantial difference in incidence between the tirzepatide and placebo groups. The results were consistent with the safety profile of existing tirzepatide formulations for type 2 diabetes mellitus.

PMDA's view:

Since acute pancreatitis, elevated pancreatic enzyme levels, and gallbladder-related events have been observed with tirzepatide administration in clinical studies targeting patients with obesity disease or patients with overweight or obesity, appropriate cautionary statements are necessary. Considering the applicant's explanation about the comparison of these clinical study results with the incidence of pancreatitis and gallbladder-related events in those treated with existing tirzepatide formulations for type 2 diabetes mellitus, the safety profile is considered to be similar. Precautionary statements about pancreatitis and gallbladder-related events should be provided in the package insert, as with those for existing tirzepatide formulations.

7.R.2.4 Hypersensitivity

The applicant's explanation:

Tables 41, 42, and 43 show the incidence of hypersensitivity reactions[22)] in the phase III studies (Studies GPHZ, GPHK, and GPHL). The incidence of both immediate-type[23)] and non-immediate-type[24)] hypersensitivity reactions tended to be higher in the tirzepatide groups than in the placebo group in Studies GPHZ and GPHK, whereas no significant differences among treatment groups, including the placebo group, were observed in Study GPHL. In Study GPHZ, severe or serious immediate-type hypersensitivity reactions were not observed. Severe or serious non-immediate-type hypersensitivity reaction was observed in 1 subject in the tirzepatide 15 mg group (anaphylactic shock). This event was

22) Events in SMQ for anaphylactic reaction (narrow), angioedema (narrow), severe cutaneous adverse reactions (narrow), hypersensitivity (narrow), and vasculitis (narrow) (except for SMQ vasculitis [narrow] in Study GPHK). Events potentially indicative of immediate-type hypersensitivity reactions included all terms encompassed in the algorithm for anaphylactic reactions in SMQ.
23) Events of hypersensitivity reactions occurring within 24 hours after administration of the study drug.
24) Events of hypersensitivity reactions occurring between 24 hours post-dose and the next dose of the study drug.

considered to be food-related and was not classified as an adverse drug reaction. In Studies GPHK and GPHL, no serious immediate-type or non-immediate-type hypersensitivity reactions were observed. Severe immediate-type and non-immediate-type hypersensitivity reactions were observed in 2 subjects in the tirzepatide 10 mg group (hypersensitivity [immediate-type], rash [non-immediate-type]) and 1 subject in the tirzepatide 15 mg group (dermatitis [non-immediate-type]) in Study GPHK. The 2 cases in the tirzepatide 10 mg group were determined to be adverse drug reactions.

As shown in the above results, while the incidence of hypersensitivity tended to be higher in the tirzepatide groups than in the placebo group in Studies GPHZ and GPHK, the occurrence of severe or serious events was low across all studies, and no clinically significant concerns were identified.

PMDA's view:
In clinical studies, the incidence of hypersensitivity reactions tended to be higher in the tirzepatide groups than in the placebo group in some studies. The occurrence of severe or serious events was low across all studies, and judging from the currently available data, the risk of hypersensitivity due to tirzepatide administration does not raise significant concerns that would outweigh its benefits. Nevertheless, given that hypersensitivity, including anaphylaxis, has been reported with existing tirzepatide formulations for type 2 diabetes mellitus, appropriate cautionary statements should be included in the package insert, consistent with those for existing tirzepatide formulations.

7.R.2.5 Antibody production

The applicant's explanation:
Table 54 shows the proportion of subjects who tested positive[25)] for anti-tirzepatide antibodies in phase III studies (Studies GPHZ, GPHK, and GPHL). In all studies, the proportion of subjects who tested positive for anti-tirzepatide antibodies after administration of the study drug was higher in the tirzepatide group compared to the placebo group; however, there were no significant differences across the dose levels within the tirzepatide group.

Table 54. Proportion of subjects tested positive for anti-tirzepatide antibodies (safety analysis population)

Study	Measuring time point	Placebo	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
GPHZ	Baseline	8.0 (6/75)	-	12.9 (9/70)	3.9 (3/76)
	After treatment start	0 (0/75)	-	75.7 (53/70)	75.0 (57/76)
GPHK	Baseline	7.4 (46/625)	7.5 (46/613)	5.5 (34/616)	8.2 (50/613)
	After treatment start	3.4 (21/625)	64.1 (393/613)	65.3 (402/616)	68.7 (421/613)
GPHL	Baseline	8.9 (27/302)	-	11.4 (34/297)	10.5 (31/294)
	After treatment start	1.3 (4/302)	-	58.6 (174/297)	61.2 (180/294)

Incidence % (number of subjects with positive result/number of subjects evaluated); -, not applicable
Subjects who had anti-tirzepatide antibody test results at baseline and at least 1 test result after the start of administration were included in the evaluation.

[25)] The criteria for defining positivity for anti-tirzepatide antibodies were as follows: (a) Subjects who tested negative for anti-tirzepatide antibodies at baseline and subsequently tested positive at least once after the start of administration of the study drug, with an antibody titer at least twice the minimum dilution factor of the anti-tirzepatide antibody assay, or (b) Subjects who tested positive for anti-tirzepatide antibodies at baseline and after the start of administration of the study drug, with an antibody titer at least 4 times higher than at baseline.

Table 55 shows the status of anti-tirzepatide antibody production, including neutralizing antibodies in the pooled analysis of tirzepatide[26] (a pooled analysis of the global phase III studies [Studies GPHK and GPHL] and foreign phase III studies [Studies GPHM[27] and GPHN[28]]). No differences were observed among doses of tirzepatide in the production of anti-tirzepatide antibodies, including neutralizing antibodies.

Table 55. Status of anti-tirzepatide antibody production in the pooled analysis of tirzepatide

Parameter	Measuring time point	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Anti-tirzepatide antibody	At baseline	7.5 (46/613)	7.4 (68/913)	8.9 (81/907)
	After treatment start	64.1 (393/613)	63.1 (576/913)	66.3 (601/907)
Neutralizing antibodies against GIP receptor activation[a)]	At baseline	0.2 (1/604)	0 (0/906)	0 (0/900)
	After treatment start	2.3 (14/604)	2.6 (24/906)	3.2 (29/900)
Neutralizing antibodies against GLP-1 receptor activation[a)]	At baseline	0 (0/604)	0 (0/906)	0 (0/900)
	After treatment start	3.0 (18/604)	3.0 (27/906)	2.1 (19/900)
Neutralizing antibodies against endogenous GIP[a)]	At baseline	0 (0/604)	0 (0/906)	0 (0/900)
	After treatment start	1.0 (6/604)	0.9 (8/906)	0.6 (5/900)
Neutralizing antibodies against endogenous GLP-1[a)]	At baseline	0 (0/604)	0 (0/906)	0 (0/900)
	After treatment start	0 (0/604)	0.2 (2/906)	0 (0/900)

Incidence % (number of subjects with positive result/number of subjects evaluated)
Subjects who had anti-tirzepatide antibody test results at baseline and at least 1 test result after the start of administration were included in the evaluation.
a) The evaluation of neutralizing antibodies in samples from subjects participating in studies conducted in China was not performed.

Table 56 shows the incidence of hypersensitivity reactions and injection site reactions stratified by the status of anti-tirzepatide antibodies in the pooled analysis of tirzepatide. The incidence of hypersensitivity reactions and injection site reactions was higher in subjects who tested positive for anti-tirzepatide antibodies than in those who tested negative. Most hypersensitivity reactions observed in subjects positive for anti-tirzepatide antibodies were mild or moderate. Severe or serious hypersensitivity reactions were reported in 3 subjects (1 in a subject positive for anti-tirzepatide antibodies and 2 in subjects negative for anti-tirzepatide antibodies). No severe or serious injection site reactions were observed.

Table 56. Incidence of adverse events by status of anti-tirzepatide antibodies in the pooled analysis of tirzepatide

Parameter	Tirzepatide 5 mg		Tirzepatide 10 mg		Tirzepatide 15 mg	
Anti-tirzepatide antibodies	Positive	Negative	Positive	Negative	Positive	Negative
Hypersensitivity reactions[a)]	6.4 (25/393)	1.4 (3/219)	5.6 (32/576)	3.9 (13/337)	6.5 (39/601)	2.9 (9/306)
Injection site reactions[b)]	8.4 (33/393)	0.9 (2/219)	12.8 (74/576)	1.2 (4/337)	12.1 (73/601)	1.0 (3/306)

Incidence % (number of subjects with positive or negative result/number of subjects evaluated)
Subjects who had anti-tirzepatide antibody test results at baseline and at least 1 test result after the start of administration were included in the evaluation.
a) Events in SMQ for anaphylactic reaction (narrow), angioedema (narrow), severe cutaneous adverse reactions (narrow), hypersensitivity (narrow), and vasculitis (narrow) (except SMQ for vasculitis [narrow] in Study GPHK).
b) Events in HLT of injection site reactions, administration site reactions, and infusion site reactions.

[26] Data from all tirzepatide groups, including data of the lead-in period of Study GPHN, in which tirzepatide was administered in an open-label manner, were pooled.
[27] A randomized, double-blind, parallel-group study evaluating the efficacy of subcutaneous administration of tirzepatide (10 mg or 15 mg) or placebo once weekly for 72 weeks on weight management in (1) subjects with obesity (BMI ≥30 kg/m²) without type 2 diabetes mellitus or (2) subjects with overweight (BMI ≥27 kg/m²) with at least one weight-related comorbidity (obstructive sleep apnoea, hypertension, dyslipidaemia, or cardiovascular disease), who achieved a weight loss of ≥5.0% after a 12-week lead-in period of an intensive lifestyle intervention program.
[28] An 88-week randomized, double-blind, parallel-group study evaluating the efficacy of subcutaneous administration of tirzepatide (10 mg or 15 mg) or placebo once weekly for 52 weeks on maintenance of weight loss, after a 36-week lead-in period of unblind administration of tirzepatide (10 mg or 15 mg) in (1) subjects with obesity (BMI ≥30 kg/m²) without type 2 diabetes mellitus or (2) subjects with overweight (BMI ≥27 kg/m²) with at least one weight-related comorbidity (obstructive sleep apnoea, hypertension, dyslipidaemia, or cardiovascular disease.)

Concerning the impact of antibody production on efficacy, Table 57 shows the rate of body weight change from randomization[29)] to each evaluation time point, stratified by the status of anti-tirzepatide antibodies in each study included in the pooled analysis of tirzepatide. No significant differences were observed depending on the status of anti-tirzepatide antibodies or neutralizing antibodies.

Table 57. Rate of body weight change from randomization to each evaluation time point by status of anti-tirzepatide antibodies and neutralizing antibodies against GIP or GLP-1 receptor activation

Parameter		Study GPHK (Week 72)	Study GPHL (Week 72)	Study GPHM (Week 72)	Study GPHN (Week 88)
Anti-tirzepatide antibody	Positive	−20.5 ± 10.09 (N = 1084)	−15.2 ± 9.14 (N = 324)	−20.7 ± 10.50 (N = 158)	−18.0 ± 11.72 (N = 395)
	Negative	−20.2 ± 10.41 (N = 489)	−13.8 ± 9.01 (N = 197)	−22.0 ± 8.98 (60)	−18.4 ± 13.77 (N = 153)
Neutralizing antibodies against GIP receptor activation[a)]	Positive	−20.6 ± 10.65 (N = 51)	−12.2 ± 6.40 (N = 12)	−23.4 ± 5.82 (N = 3)	−18.7 ± 14.97 (N = 11)
	Negative	−20.5 ± 10.13 (N = 1505)	−14.7 ± 9.16 (N = 509)	−21.0 ± 10.15 (N = 215)	−18.1 ± 12.27 (N = 537)
Neutralizing antibodies against GLP-1 receptor activation[a)]	Positive	−21.1 ± 12.15 (N = 54)	−5.7 ± 8.06 (N = 3)	−8.9 ± 16.39 (N = 2)	−18.1 ± 13.30 (N = 13)
	Negative	−20.5 ± 10.07 (N = 1502)	−14.7 ± 9.09 (N = 518)	−21.2 ± 10.02 (N = 216)	−18.1 ± 12.30 (N = 535)

Unit, %; mean ± SD (number of subjects evaluated)
Subjects who had anti-tirzepatide antibody test results at baseline and at least 1 test result after the start of administration were included in the evaluation.
a) The evaluation of neutralizing antibodies in samples from subjects participating in studies conducted in China was not performed.

As shown in the above clinical study results, antibody production was observed following the administration of tirzepatide; however, no significant concerns were identified regarding the impact of anti-tirzepatide antibodies or neutralizing antibodies against GIP receptor or GLP-1 receptor activation on the efficacy and safety of tirzepatide. The above results were consistent with the safety profile of existing tirzepatide formulations for type 2 diabetes mellitus. Information on anti-tirzepatide antibody production in the present studies will be provided in the package insert.

PMDA's view:
In clinical studies, antibody production was observed following administration of tirzepatide, but the incidence of neutralizing antibodies was low. Subjects positive for anti-tirzepatide antibodies showed a trend toward a higher incidence of hypersensitivity and injection site reactions compared to those who were negative, but most reported events were mild or moderate. No impact on efficacy due to antibody production was observed. Considering the above clinical study results and the applicant's explanation about antibody production and its impact on efficacy in existing tirzepatide formulations for type 2 diabetes mellitus, information on anti-tirzepatide antibody production should be included in the package insert, as with existing tirzepatide formulations for type 2 diabetes mellitus.

[29)] Studies GPHK, GPHL, and GPHM used baseline as the reference point, while Study GPHN used Week 36 of the lead-in period as the reference point.

7.R.2.6 Diabetic retinopathy

The applicant's explanation:

In Study GPHL, which involved patients with overweight or obesity with type 2 diabetes mellitus, the incidence of potential diabetic retinopathy events[30)] was 0.7% (2 of 307 subjects, 3 events; diabetic retinopathy, vision blurred, and macular oedema [1 event each]) in the placebo group, 1.7% (5 of 302 subjects, 5 event; diabetic retinopathy [3 events] and vision blurred [2 events]) in the tirzepatide 10 mg group, and 0.7% (2 of 303 subjects, 2 events; vision blurred and diabetic retinal oedema [1 event each]) in the tirzepatide 15 mg group. No serious events were observed.

The above results demonstrated that the incidence of potential diabetic retinopathy events with tirzepatide was low, and no clear differences in incidence were observed among the treatment groups, including the placebo group. The findings were consistent with the known safety profile of existing tirzepatide formulations for type 2 diabetes mellitus.

PMDA's view:

In Study GPHL, patients with a history of proliferative diabetic retinopathy, diabetic macular oedema, or non-proliferative diabetic retinopathy requiring acute treatment were excluded, and the safety of tirzepatide in such patients remains unknown. Judging from the incidence of diabetic retinopathy-related events, the applicant explanation that the safety profile of tirzepatide with respect to diabetic retinopathy is consistent with that of existing tirzepatide formulations for type 2 diabetes mellitus is reasonable. As with existing tirzepatide formulations, appropriate precautions should be included in the package insert, and continued monitoring of relevant safety signals in the post-marketing setting is necessary.

7.R.2.7 Cardiovascular events

The applicant's explanation:

In phase III studies (Studies GPHZ, GPHK, and GPHL), the incidence of major adverse cardiovascular events[31)] confirmed by the Clinical Events Committee was as follows:

In Study GPHZ, 1.3% (1 of 75 subjects, 2 events; acute myocardial infarction and catheterisation cardiac [1 event each]) in the placebo group, 2.7% (2 of 73 subjects, 2 events; brain stem infarction and cerebral infarction [1 event each]) in the tirzepatide 10 mg group, and 0% (0 of 77 subjects) in the tirzepatide 15 mg group

In Study GPHK, 0.8% (5 of 637 subjects, 6 events; ischaemic stroke, cardiac failure acute, coronary artery disease, coronary revascularisation, pulmonary embolism, and transient ischaemic attack [1 event each]) in the placebo group, 0.6% (4 of 624 subjects, 4 events; angina unstable, COVID-19 pneumonia,

30) Events classified in the following PTs: Amaurosis, amaurosis fugax, arteriosclerotic retinopathy, blindness, blindness transient, blindness unilateral, choroidal neovascularisation, cystoid macular oedema, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, diabetic blindness, diabetic eye disease, diabetic retinal oedema, diabetic retinopathy, diabetic uveitis, diplopia, exudative retinopathy, eye laser surgery, fundoscopy, fundoscopy abnormal, intra-ocular injection, macular detachment, macular oedema, maculopathy, noninfective chorioretinitis, noninfective retinitis, phacotrabeculectomy, retinal aneurysm, retinal arteriovenous malformation, retinal artery embolism, retinal artery occlusion, retinal artery stenosis, retinal collateral vessels, retinal cryoablation, retinal detachment, retinal exudates, retinal haemorrhage, retinal laser coagulation, retinal neovascularisation, retinal oedema, retinal operation, retinal thickening, retinal vascular disorder, retinal vascular occlusion, retinal vein occlusion, retinitis, retinopathy, retinopathy haemorrhagic, retinopathy hypertensive, retinopathy hyperviscosity, retinopathy proliferative, scintillating scotoma, sudden vision loss, venous stasis retinopathy, vision blurred, visual impairment, vision acuity reduced, vision acuity reduced transient, and vitrectomy.

31) Defined as all-cause mortality, myocardial infarction, hospitalization due to angina unstable, hospitalization due to heart failure, coronary artery intervention, or cardiovascular events (stroke and transient ischaemic attack).

thalamus haemorrhage, and vertebrobasilar stroke [1 event each]) in the tirzepatide 5 mg group, 0.5% (3 of 628 subjects, 4 events; ischaemic stroke, acute coronary syndrome, coronary arterial stent insertion, and myocardial infarction [1 event each]) in the tirzepatide 10 mg group, and 0% (0 of 628 subjects) in the tirzepatide 15 mg group

In Study GPHL, 1.3% (4 of 307 subjects, 4 events; transient ischaemic attack, acute myocardial infarction, cardiac failure congestive, and coronary artery disease [1 event each]) in the placebo group, 1.3% (4 of 302 subjects, 6 events; angina unstable, transient ischaemic attack, cardio-respiratory arrest, coronary angioplasty, haemorrhagic stroke, and revascularisation procedure [1 event each]) in the tirzepatide 10 mg group, and 1.0% (3 of 303 subjects, 4 events; angina unstable, cardiac ventricular thrombosis, coronary artery occlusion, and ischaemic stroke [1 event each]) in the tirzepatide 15 mg group

In all studies, the incidence was low, and no significant differences in incidence were observed among treatment groups.

Table 58 shows the incidence of events related to arrhythmias or cardiac conduction disorders[32)] in phase III studies (Studies GPHZ, GPHK, and GPHL), with no significant differences among treatment groups. Severe or serious cases observed were as follows:
In Study GPHK, 1 subject (atrial fibrillation [serious, moderate]) in the placebo group, 1 subject (syncope [non-serious, severe]) in the tirzepatide 10 mg group, and 2 subjects (loss of consciousness [non-serious, severe] and atrial fibrillation [non-serious, severe] in 1 subject each) in the tirzepatide 15 mg group

In Study GPHL, 1 subject (syncope [non-serious, severe]) in the placebo group, 4 subjects (syncope [non-serious, severe], cardio-respiratory arrest [serious, severe], ventricular extrasystoles [serious, moderate], and atrial fibrillation/atrial flutter [serious, severe] in 1 subject each) in the tirzepatide 10 mg group, and 1 subject (ventricular arrhythmia [serious, moderate]) in the tirzepatide 15 mg group

Atrial fibrillation in 1 subject in the tirzepatide 15 mg group in Study GPHK was unresolved, and cardio-respiratory arrest in 1 subject in the tirzepatide 10 mg group in Study GPHL resulted in death. Neither was determined to be an adverse drug reaction. All other events resolved.

Table 58. Incidence of adverse events related to arrhythmia or cardiac conduction disorders in phase III studies (safety analysis population)

Study	Placebo	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
GPHZ	0 (0/75)	-	4.1 (3/73)	0 (0/77)
GPHK	3.6 (23/637)	3.7 (23/624)	3.0 (19/628)	3.3 (21/628)
GPHL	5.2 (16/307)	-	6.0 (18/302)	4.0 (12/303)

Incidence % (number of subjects with events/number of subjects evaluated); -, not applicable

As for electrocardiograms, the proportion of subjects who exhibited QT interval using Fridericia's correction (QTcF) prolongation (male, >450 ms; female, >470 ms) after administration of the study drug

[32)] Events in SMQ for arrhythmia related investigations, signs and symptoms (broad and narrow), supraventricular tachyarrhythmias (broad and narrow), tachyarrhythmia terms, nonspecific (narrow), ventricular tachyarrhythmias (narrow), conduction defects (narrow); and HLT for cardiac conduction disorders.

was 6.7% (5 of 75 subjects) in the placebo group, 6.9% (5 of 72 subjects) in the tirzepatide 10 mg group, and 1.3% (1 of 77 subjects) in the tirzepatide 15 mg group in Study GPHZ; 2.1% (13 of 624 subjects) in the placebo group, 1.8% (11 of 615 subjects) in the tirzepatide 5 mg group, 1.5% (9 of 618 subjects) in the tirzepatide 10 mg group, and 1.5% (9 of 619 subjects) in the tirzepatide 15 mg group in Study GPHK; and 2.7% (8 of 296 subjects) in the placebo group, 0.3% (1 of 292 subjects) in the tirzepatide 10 mg group, and 1.4% (4 of 294 subjects) in the tirzepatide 15 mg group in Study GPHL. No significant differences were observed among the treatment groups.

Table 59 shows the changes in vital signs from baseline to Week 72 in phase III studies (Studies GPHZ, GPHK, and GPHL). An increase in pulse rate was observed in the tirzepatide groups compared with the placebo group in all studies, with a trend of dose-dependent increase. For systolic and diastolic blood pressure, a greater decrease was observed in the tirzepatide groups compared with the placebo group in all studies. The findings were consistent with trends observed with existing tirzepatide formulations for type 2 diabetes mellitus.

Table 59. Changes in vital signs from baseline to Week 72 (safety analysis population)

Parameter	Study GPHZ		
	Placebo	Tirzepatide 10 mg	Tirzepatide 15 mg
Pulse rate (beats per minute)	−1.1 ± 7.11 (N = 66)	2.7 ± 10.07 (N =66)	5.0 ± 8.92 (N = 74)
Systolic blood pressure (mmHg)	1.7 ± 9.08 (N = 66)	−10.5 ± 13.30 (N = 66)	−11.3 ± 13.17 (N = 74)
Diastolic blood pressure (mmHg)	0.3 ± 8.25 (N = 66)	−5.6 ± 10.31 (N = 66)	−6.1 ± 8.54 (N = 74)

Parameter	Study GPHK				Study GPHL		
	Placebo	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo	Tirzepatide 10 mg	Tirzepatide 15 mg
Pulse rate (beats per minute)	−0.3 ± 8.66 (N = 491)	0.6 ± 9.58 (N = 557)	2.6 ± 9.66 (N = 554)	2.5 ± 10.59 (N = 569)	−0.5 ± 8.87 (N = 269)	0.4 ± 9.93 (N = 286)	0.8 ± 8.81 (N = 276)
Systolic blood pressure (mmHg)	−1.0 ± 11.93 (N = 491)	−7.3 ± 12.72 (N = 557)	−8.7 ± 13.11 (N = 554)	−7.7 ± 13.01 (N = 569)	−1.4 ± 13.64 (N = 269)	−5.9 ± 14.33 (N = 286)	−7.4 ± 13.17 (N = 276)
Diastolic blood pressure (mmHg)	−1.1 ± 8.25 (N = 491)	−5.1 ± 8.72 (N = 557)	−5.7 ± 9.01 (N = 554)	−4.6 ± 9.20 (N = 569)	−0.3 ± 7.77 (N = 269)	−2.4 ± 8.62 (N = 286)	−3.0 ± 9.63 (N = 276)

Mean ± SD (number of subjects evaluated)

Table 60 shows the incidence of abnormal low values of systolic or diastolic blood pressure (systolic blood pressure, ≤90 mmHg with a decrease of ≥20 mmHg from baseline; diastolic blood pressure, ≤50 mmHg with a decrease of ≥10 mmHg from baseline) after administration of the study drug. The incidence was higher in the tirzepatide groups than in the placebo group, but no trend of dose-dependent increase was observed.

Table 60. Incidence of abnormal low values of systolic or diastolic blood pressure[a)] after administration of the study drug (safety analysis population)

Parameter	Study GPHZ		
	Placebo (N = 75)	Tirzepatide 10 mg (N = 73)	Tirzepatide 15 mg (N = 77)
Systolic blood pressure	0 (0/75)	8.3 (6/72)	9.1 (7/77)
Diastolic blood pressure	0 (0/75)	2.8 (2/72)	1.3 (1/77)

Parameter	Study GPHK				Study GPHL		
	Placebo (N = 637)	Tirzepatide 5 mg (N = 624)	Tirzepatide 10 mg (N = 628)	Tirzepatide 15 mg (N = 628)	Placebo (N = 307)	Tirzepatide 10 mg (N = 302)	Tirzepatide 15 mg (N = 303)
Systolic blood pressure	0 (0/634)	2.9 (18/621)	3.4 (21/623)	3.0 (19/625)	0.7 (2/306)	1.3 (4/302)	1.7 (5/301)
Diastolic blood pressure	0.2 (1/634)	0.6 (4/621)	0.6 (4/623)	0.6 (4/625)	0 (0/306)	0 (0/302)	0 (0/301)

Incidence % (number of subjects with events/number of subjects evaluated)

a) Systolic blood pressure, ≤90 mmHg with a decrease of ≥20 mmHg from baseline; diastolic blood pressure, ≤50 mmHg with a decrease of ≥10 mmHg from baseline.

As summarized in the clinical study results, the incidence of major cardiovascular events confirmed by the Clinical Event Committee and events related to arrhythmia or cardiac conduction disorders of severe or serious intensity was low. No results suggesting an increased cardiovascular risk with tirzepatide administration were observed. Reductions in blood pressure and increases in pulse rate were more frequently observed in the tirzepatide groups compared with the placebo group. The above findings were consistent with those observed in clinical studies of existing tirzepatide formulations for type 2 diabetes mellitus. The cardiovascular risk associated with tirzepatide administration is considered similar to that of existing tirzepatide formulations.

PMDA's view:

In clinical studies, increases in pulse rate and abnormal low values of blood pressure were observed with tirzepatide administration. However, comparisons between the tirzepatide and placebo groups regarding the incidence of major cardiovascular events confirmed by the Clinical Event Committee, as well as events related to arrhythmias or cardiac conduction disorders, have not revealed any significant clinical concerns. Thus, according to the currently available information, no results suggesting an increased cardiovascular risk have been observed. The applicant's explanation that the safety profile is consistent with that of existing tirzepatide formulations for type 2 diabetes mellitus is considered appropriate. Adequate cautionary statements should be included in the package insert concerning increases in pulse rate and decreases in blood pressure, similar to existing tirzepatide formulations.

7.R.2.8 Relationship with tumor development

The applicant's explanation:

Tables 41, 42, and 43 show the incidence of malignant neoplasm-related events[33)] in the phase III studies (Studies GPHZ, GPHK, and GPHL). In all studies, there was no significant difference in incidence among treatment groups, including the placebo group. In addition, there were no specific trends in the organs and tissues where malignant neoplasm-related events occurred in the tirzepatide group, and no

33) Events in SMQ for malignant tumours (narrow) and tumours of unspecified malignancy (narrow).

particular type of malignant neoplasm was notably prevalent. Medullary thyroid cancer, C-cell hyperplasia, and pancreatic carcinoma were not observed in the tirzepatide group.

In Study GPHZ, no subject had a maximum serum calcitonin level exceeding 20 ng/L after administration of the study drug. In Studies GPHK and GPHL, subjects whose calcitonin levels increased by ≥50% from baseline and reached or exceeded 35 ng/L after the initiation of study drug administration included 4 subjects in the placebo group and 5 subjects in the tirzepatide group (2 in the tirzepatide 10 mg group in Study GPHK, 2 in the tirzepatide 15 mg group in Study GPHK, and 1 in the tirzepatide 15 mg group in Study GPHL). Among the 5 subjects in the tirzepatide group, 4 subjects had elevated baseline calcitonin levels, and except for 1 subject, calcitonin levels recovered by the follow-up period or the final clinical examination. One subject with a normal baseline calcitonin level experienced a ≥50% increase in calcitonin levels from baseline and a calcitonin level ≥35 ng/L, but a reassessment 9 days later showed a return to the normal range.

As shown in the above study results, no trend suggesting an increased incidence of thyroid cancer, pancreatic carcinoma, or other malignant tumours associated with the administration of tirzepatide was observed. The safety profile was consistent with that of existing tirzepatide formulations for type 2 diabetes mellitus.

PMDA's view:
The clinical study data do not indicate any increased risk of tumor-related events at this time. Additional precautions concerning this risk are unnecessary.

7.R.2.9 Depression and suicide-related events

The applicant's explanation:
Considering that population with obesity, particularly those experiencing weight loss, have been reported to be at risk for depression and suicide (*Psychiatry Investig.* 2020;17:715-24, *Obes Surg*. 2019;29:322-33), patients with a history of psychiatric disorders such as depression and suicide attempts were excluded from the phase III studies (Studies GPHZ, GPHK, and GPHL). Tables 41, 42, and 43 show the incidence of depression and suicide-related events[34)] in Studies GPHZ, GPHK, and GPHL, with no significant differences observed among the treatment groups, including the placebo group. Severe or serious depression and suicide-related events were observed in 1 subject (major depression [serious, severe]) in the tirzepatide 5 mg group, 2 subjects (suicide attempt [serious, moderate], adjustment disorder with mixed anxiety and depressed mood [serious, severe]) in the tirzepatide 10 mg group, 2 subjects (suicide attempt [serious, severe], clinical depression [non-serious, severe]) in the tirzepatide 15 mg group in Study GPHK, and 1 subject (depression [non-serious, severe]) in the placebo group in Study GPHL. Among the severe or serious events observed in the tirzepatide groups, only 1 case in the tirzepatide 10 mg group in Study GPHK (suicide attempt) was determined to be an adverse drug reaction. All subjects who experienced such events, including individuals who had the adverse drug reaction, had pre-existing mental health issues before receiving tirzepatide.

34) Events in SMQ for depression (excl suicide and self-injury) (narrow) and suicide/self-injury (narrow).

Thus, the clinical study results did not indicate any association between tirzepatide administration and depression or suicide-related events.

PMDA's view:
Since patients with a history of psychiatric disorders (such as depression) and suicide attempts were excluded from the clinical studies, the risk in such patients remains unknown. Given the fact that no clear increase in the incidence of depression or suicide-related events was observed following administration of tirzepatide, no definitive risk associated with depression or suicide has been demonstrated at this time. Therefore, the applicant's explanation for not including precautions about suicide attempts and suicidal ideation in the package insert is appropriate. Nevertheless, attention should be paid to signals related to depression and suicide risks in the post-marketing setting for obesity treatment.

7.R.3 Indication and clinical positioning

7.R.3.1 Indication

The applicant's explanation about the clinical development history and the proposed indication of tirzepatide:
According to the World Health Organization (WHO), a BMI of ≥25 kg/m^2 and <30 kg/m^2 is classified as overweight, while a BMI of ≥30 kg/m^2 is classified as obesity. WHO and other major international organizations define obesity as a disease (*Obesity.* 2019;27:7-9). The Guidelines for the Management of Obesity Disease 2022, edited by the Japan Society for the Study of Obesity (Japanese Guidelines for the Management of Obesity Disease) define obesity disease as "a disease requiring medical weight loss due to the presence of or the anticipated risk of health disorders caused by or associated with obesity." Among individuals with obesity (BMI ≥25 kg/m^2), if they have at least 1 of the health disorders[35)] necessary for the diagnosis or if they are suspected of having visceral fat accumulation from waist circumference screening and confirmed to have visceral obesity by abdominal computed tomography (CT), they are diagnosed with obesity disease. The guidelines stated weight loss targets for preventing and improving health disorders as follows: A 3% weight reduction for patients with obesity disease and a 5% to 10% reduction for patients with severe obesity disease (BMI ≥35 kg/m^2). If effective weight loss is not achieved through diet, exercise, and behavioral therapy for 3 to 6 months, or if the seriousness of comorbid health disorders necessitates rapid weight loss, therapy in combination with pharmacotherapy should be considered.

For clinical development of tirzepatide in weight management for obesity and overweight, Study GPHK was designed according to the Food and Drug Administration (FDA)[36)] and European Medicines Agency (EMA)[37)] guidance. This study targeted subjects with a BMI ≥30 kg/m^2 without type 2 diabetes mellitus

35) Based on accumulated evidence demonstrating that weight reduction can contribute to the prevention and improvement of these conditions, the following 11 health disorders are considered necessary for the diagnosis of obesity disease:
(a) Impaired glucose tolerance (type 2 diabetes mellitus, IGT, etc.), (b) dyslipidaemia, (c) hypertension, (d) hyperuricaemia/gout, (e) coronary artery disease, (f) cerebral infarction/transient ischaemic attack, (g) NAFLD, (h) menstrual abnormalities/female infertility, (i) obstructive sleep apnoea syndrome/obesity hypoventilation syndrome, (j) musculoskeletal disorders (osteoarthritis; knee joint/hip joint/finger joints, degenerative spondylosis), (k) obesity-related kidney disease.

36) United States Food and Drug Administration. Guidance for industry. Developing products for weight management. Draft guidance. Rev.1. Published February 2007. https://www.fda.gov/media/71252/download (last accessed on September 13, 2024).

37) European Medicines Agency. Guideline on clinical evaluation of medicinal products used in weight management. 2016. Published June 23, 2016. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-medicinal-products-used-weight-management-revision-1_en.pdf (last accessed on September 13, 2024).

or subjects with a BMI ≥27 kg/m^2 with weight-related comorbidities.[38)] Additionally, the following studies were planned: A study targeting subjects with BMI ≥27 kg/m^2 with type 2 diabetes mellitus (Study GPHL), along with 2 foreign phase III studies (Studies GPHM[27)] and GPHN[28)]) targeting subjects with BMI ≥30 kg/m^2 without type 2 diabetes mellitus or subjects with BMI ≥27 kg/m^2 with weight-related comorbidities.[38)] Japan participated in Studies GPHK and GPHL. Considering that the Japanese Guidelines for the Management of Obesity Disease require weight loss rate as the primary endpoint for evaluation of anti-obesity disease agents and emphasize secondary endpoints such as improvements in comorbid health disorders, the applicant designed and conducted a Japanese phase III study (Study GPHZ).

Study GPHZ aimed to evaluate the therapeutic effect of tirzepatide for obesity disease through improvements in health disorders associated with weight reduction. It targeted patients for whom lifestyle modifications alone were insufficient to achieve weight loss goals. Inclusion criteria were patients with BMI ≥27 kg/m^2 with at least 2 obesity-related health disorders or patients with BMI ≥35 kg/m^2 with at least 1 obesity-related health disorder. Obesity-related health disorders defined in the inclusion criteria were IGT, hypertriglyceridaemia, and NAFLD, which were expected to improve given tirzepatide's mechanism of action and could be evaluated using laboratory parameters.

In Study GPHZ, the percentage change in body weight from baseline to Week 72 (mean ± standard deviation [SD]) was −18.4% ± 7.61% in the tirzepatide 10 mg group and −22.6% ± 8.90% in the tirzepatide 15 mg group. The proportion of subjects achieving a weight reduction of ≥5% at Week 72 was 94.9% (56 of 59) of subjects in the tirzepatide 10 mg group and 96.9% (63 of 65) of subjects in the tirzepatide 15 mg group, demonstrating clinically meaningful weight reduction (Table 9). Improvement trends in glucose levels, blood pressure, and lipid parameters, including LDL cholesterol, were observed (Table 11). The proportion of subjects with improvements in obesity-related health disorders (IGT, hypertriglyceridaemia, and NAFLD) was higher in the tirzepatide groups than in the placebo group (Table 12). Furthermore, the safety profile was consistent with existing tirzepatide formulations for type 2 diabetes mellitus. The results were supported by findings from Studies GPHK and GPHL.

Taking account of the above evaluations, the indication of tirzepatide was based primarily on the population in Study GPHZ. The indication was for patients with obesity disease, with impaired glucose tolerance (such as type 2 diabetes mellitus and IGT), dyslipidaemia, or NAFLD, provided that (a) they have BMI ≥27 kg/m^2 and at least 2 obesity-related health disorders,[35)] or (b) they have BMI ≥35 kg/m^2 and at least 1 obesity-related health disorder. Table 61 summarizes the proportion of subjects with obesity-related health disorders enrolled in Studies GPHZ, GPHK, and GPHL.

[38)] Hypertension, dyslipidaemia, obstructive sleep apnoea syndrome, or cardiovascular disease.

Table 61. Proportion of subjects with obesity-related health disorders (mITT population)

Obesity-related health disorders	Study GPHZ (N = 225)	Study GPHK (N = 2517)	Study GPHL (N = 912)
Glucose tolerance impaired[a)]	65.8 (148)	40.6 (1021)	100 (912)
Dyslipidaemia[b)]	89.3 (201)	29.5 (743)	61.2 (558)
Hypertriglyceridaemia[c)]	55.6 (125)	34.6 (870)	53.6 (489)
Hyper LDL cholesterolaemia[d)]	38.7 (87)	19.3 (484)	9.4 (86)
Hypertension[e)]	53.3 (120)	32.0 (805)	66.6 (607)
Hyperuricaemia/Gout[f)]	35.6 (80)	5.0 (126)	5.4 (49)
Coronary artery disease[g)]	2.2 (5)	3.0 (76)	10.3 (94)
Cerebral infarction/Transient ischaemic attack[h)]	0 (0)	0.3 (8)	1.1 (10)
NAFLD[i)]	98.2 (221)	7.0 (177)	17.1 (156)
Menstrual abnormalities/Female infertility[j)]	2.2 (5)	1.5 (39)	0.7 (6)
Obstructive sleep apnoea syndrome/Obesity hypoventilation syndrome[k)]	8.9 (20)	7.7 (195)	8.3 (76)
Locomotive disorder[l)]	8.0 (18)	12.8 (323)	15.6 (142)
Obesity-related kidney disease[m)]	4.0 (9)	1.0 (26)	3.6 (33)

Percentage (number of applicable subjects)

a) In Study GPHZ, IGT as defined in the inclusion criteria was counted; in Study GPHK, prediabetes as defined in the inclusion criteria was counted; and in Study GPHL, type 2 diabetes mellitus as defined in the inclusion criteria was counted.
b) In Study GPHZ, hypertriglyceridaemia as defined in the inclusion criteria or dyslipidaemia reported as a medical history at baseline was counted; in Study GPHK, dyslipidaemia as defined in the inclusion criteria was counted; and in Study GPHL, dyslipidaemia reported as a medical history at baseline was counted.
c) In Study GPHZ, hypertriglyceridaemia as defined in the inclusion criteria was counted; in Studies GPHK and GPHL, fasting triglyceride ≥150 mg/dL at baseline was counted.
d) Subjects with LDL cholesterol ≥140 mg/dL at baseline were counted.
e) In Study GPHK, hypertension as defined in the inclusion criteria was counted.
f) In Studies GPHK and GPHL, gout was counted.
g) In Studies GPHK and GPHL, atherosclerotic cardiovascular disease was counted.
h) In Study GPHZ, cerebral infarction was counted; in Studies GPHK and GPHL, transient ischaemic attack, cerebral ischaemia, and ischaemic stroke were counted.
i) In Study GPHZ, NAFLD as defined in the inclusion criteria or reported as a medical history at baseline was counted.
j) In Studies GPHK and GPHL, polycystic ovary syndrome was counted.
k) Obstructive sleep apnoea syndrome was counted.
l) In Studies GPHK and GPHL, osteoarthritis was counted.
m) In Study GPHZ, kidney disease was counted; in Studies GPHK and GPHL, nephropathy and chronic kidney disease were counted.

PMDA's view:

The patient population for tirzepatide should be specified as those requiring pharmacotherapy for obesity disease. The indication should clearly describe that the disease or condition necessitates pharmacotherapy, and it should specify Japanese patients with obesity disease with health disorders who are expected to improve their conditions with weight loss, based on clinical study results. PMDA requested the applicant to evaluate the appropriateness of the target patient population, considering the following:

- IGT: In the current diagnostic system for type 2 diabetes mellitus in Japan, pharmacotherapy is not uniformly required for IGT (Japanese Clinical Practice Guideline for Diabetes 2024, edited by Japan Diabetes Society). There is no broad consensus on the significance of pharmacotherapy intervention for IGT.
- NAFLD: A diagnosis of NAFLD alone is not sufficient to warrant pharmacotherapy. No established criteria exist to differentiate patients requiring pharmacotherapy. The Japanese guidelines for NAFLD treatment (Evidence-based Clinical Guidelines for Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis 2020, 2nd Edition, edited by Japanese Society of Gastroenterology and Japan Society of Hepatology) state that liver fibrosis is the most prognostically relevant factor for NAFLD, and hepatic fat fraction (HFF) evaluated in Study GPHZ has less impact on prognosis compared to liver fibrosis.

- Hypertension: A certain proportion of patients with hypertension were included in Studies GPHZ, GPHK, and GPHL, showing improvements in systolic and diastolic blood pressure in the tirzepatide groups. Hypertension is a major cardiovascular risk factor.

The applicant's explanation:
Obesity lies upstream in the metabolic domino and serves as a contributing factor in the onset and progression of obesity-related health disorders, including metabolic diseases such as diabetes mellitus and dyslipidaemia, as well as coronary artery disease and cerebrovascular disorders that develop on the basis of such underlying conditions. The health conditions specified in the indications should be selected according to the efficacy and safety profile of the drug. On the other hand, the clinical significance of pharmacological intervention in obesity disease itself should be clarified. While the applicant considers that pharmacological intervention in IGT and NAFLD has certain scientific and clinical significance, they will not be included in the health disorders specified in the indications, taking into account that, at present, the significance of such intervention has not been established in clinical practice guidelines.

For hypertension, proportions of subjects with hypertension enrolled in Study GPHZ, Study GPHK, and Study GPHL were 53.3% (120 of 225 subjects), 32.0% (805 of 2517 subjects), and 66.6% (607 of 912 subjects), respectively. All studies showed reductions in systolic and diastolic blood pressure in the tirzepatide groups compared to the placebo group. Hypertension is a representative risk factor for cardiovascular diseases, and the treatment and management of hypertension associated with obesity disease are crucial for maintaining life prognosis and healthy lifespan. Also, weight reduction is a primary treatment for lowering blood pressure. Hypertension should be included as a health disorder specified in the indications.

As for dyslipidaemia, a certain proportion of patients with dyslipidaemia were included in Studies GPHZ, GPHK, and GPHL. The results of the studies demonstrated an improving trend in each lipid parameter. Therefore, dyslipidaemia should be included as a health disorder specified in the indications.

Based on the above, the health disorders specified in the indications as the target for tirzepatide administration are type 2 diabetes mellitus, dyslipidaemia, or hypertension.

PMDA's view:
In Studies GPHZ, GPHK, and GPHL, the weight reduction effect of tirzepatide administration was observed, along with an improving trend in blood glucose levels, blood pressure, and lipid parameters (including LDL cholesterol). Given the above results, tirzepatide is expected to improve comorbid type 2 diabetes mellitus, hypertension, and dyslipidaemia, in association with weight reduction after tirzepatide administration. Taking into account that pharmacotherapy is evidently necessary for these 3 health disorders, the indication of tirzepatide should be "obesity" combined with any of type 2 diabetes mellitus, dyslipidaemia, or hypertension. In addition, taking the inclusion criteria in Study GPHZ into account, the indication should include obesity-related health disorders as those requiring at least 2 such disorders when BMI is $\geq$27 kg/m^2 or at least 1 when BMI is $\geq$35 kg/m^2. Furthermore, the applicant's opinion to exclude IGT and NAFLD from the health disorders specified in the indications is appropriate.

PMDA will finalize the target population for tirzepatide administration, taking account of comments raised in the Expert Discussion.

7.R.3.2 Clinical positioning

The applicant's explanation:

In Japan, mazindol and semaglutide formulations have been approved as therapeutic drugs for obesity disease. Mazindol formulation (Sanorex Tablets 0.5 mg) is subject to restrictions, including a maximum prescription period of 3 months and an indication limited to patients with severe obesity disease (BMI ≥35 kg/m^2). In March 2023, semaglutide formulation (Wegovy Subcutaneous Injection 0.25, 0.5, 1.0, 1.7, and 2.4 mg SD [Wegovy Subcutaneous Injection]), a once-weekly subcutaneous injection with GLP-1 receptor agonist activity, was approved for the treatment of obesity. In Japan, in contrast, therapeutic options for the pharmacological management of obesity, including the improvement of obesity-related health disorders through weight reduction, remain limited. Consequently, in addition to lifestyle modifications through diet and exercise interventions, it is still necessary to treat various obesity-related health disorders on a disease-by-disease basis.

Tirzepatide is a once-weekly subcutaneous injection, similar to the approved semaglutide formulation (Wegovy Subcutaneous Injection). Clinical studies of tirzepatide have demonstrated meaningful weight reduction, as well as improvements in blood glucose, blood pressure, lipid parameters, etc. The safety profile of tirzepatide was similar to that of the existing tirzepatide formulations and GLP-1 receptor agonists used for type 2 diabetes mellitus. The above results indicate that tirzepatide can be a new option for pharmacotherapy for patients with obesity disease.

PMDA's view:

In Japan, a mazindol formulation and, more recently, a semaglutide formulation have been approved for obesity, but the available pharmacotherapy options are still limited. The weight reduction effect of tirzepatide has been demonstrated in Studies GPHZ, GPHK, and GPHL, along with improvements in parameters related to the respective comorbidities [see Section "7.R.1 Efficacy"]. Considering the demonstrated efficacy, the safety profile of tirzepatide is acceptable if appropriate precautions are provided [see Section "7.R.2 Safety"]. Taking the above findings and the mechanism of action of tirzepatide into account, tirzepatide can be a pharmacotherapy option for obesity disease, with a clinical positioning similar to that of the approved semaglutide formulation.

7.R.4 Dosage and administration

The applicant's explanation:

In the foreign phase II study of tirzepatide targeting patients with type 2 diabetes mellitus (Study GPGB[39]), body weight loss was observed in the tirzepatide 5 mg, 10 mg, and 15 mg groups compared to the placebo group. The proportions of subjects achieving ≥5% body weight loss at Week 26 were

[39] A 26-week randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of tirzepatide in non-Japanese patients with type 2 diabetes mellitus who had inadequate glycemic control with diet and exercise therapy or metformin monotherapy (target sample size, 300 subjects, 50 per group). Subjects received once-weekly subcutaneous injections of either placebo, tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg), or dulaglutide (genetical recombination) 1.5 mg. Regarding the dosage regimen of tirzepatide, subjects in the 1 mg and 5 mg groups received 1 mg and 5 mg, respectively, for 26 weeks. In the 10 mg group, subjects received 5 mg for the first 2 weeks, followed by 10 mg for the remaining 24 weeks. In the 15 mg group, subjects received 5 mg for the first 2 weeks, followed by 10 mg for 4 weeks, and then 15 mg for the remaining 20 weeks. For patients receiving metformin, the dosage regimen was generally maintained without modification.

approximately 50%, 77%, and 86% in the tirzepatide 5 mg, 10 mg, and 15 mg groups (the same order applies hereinafter), respectively. The proportions achieving ≥10% body weight loss were approximately 17%, 46%, and 54%, respectively. Improvements in blood glucose and lipid parameters were observed in the tirzepatide 10 mg and 15 mg groups compared to the placebo group. On the basis of the above findings, in clinical development for weight management in obesity or overweight, the maintenance doses in the phase III studies, except for Study GPHK, were 10 mg and 15 mg. In Study GPHK, the maintenance doses were 5 mg, 10 mg, and 15 mg to evaluate the dose-response relationship of heart rate increase in patients with overweight or obese without type 2 diabetes mellitus. The superiority over placebo was evaluated at only 2 doses, 10 mg and 15 mg. With regard to the administration method of tirzepatide, clinical development of tirzepatide for type 2 diabetes mellitus suggested that smaller stepwise dose increases and a longer escalation period tended to reduce the incidence of gastrointestinal disorders. Therefore, in all phase III studies (Studies GPHZ, GPHK, and GPHL), the initial dose of tirzepatide was 2.5 mg once weekly, with an increase of 2.5 mg every 4 weeks.

In Studies GPHZ, GPHK, and GPHL, which were conducted taking the above considerations into account, the superiority of tirzepatide 10 mg and 15 mg over placebo was demonstrated for the co-primary endpoints. The percentage change in body weight from baseline to Week 72 in Study GPHK (mean ± SD) was −16.5% ± 9.13% in the tirzepatide 5 mg group, −21.9% ± 10.16% in the tirzepatide 10 mg group, and −22.9% ± 10.16% in the tirzepatide 15 mg group. A dose-dependent weight reduction trend was observed. Compared to the tirzepatide 5 mg group, the degree of reduced body weight gain was greater in the tirzepatide 10 mg and 15 mg groups (Table 14). The proportion of subjects achieving weight loss and the change in BMI, which were secondary endpoints, were also greater in the tirzepatide 10 mg and 15 mg groups than in the tirzepatide 5 mg group (Table 15).

Regarding the safety of tirzepatide administration, results obtained from Studies GPHK, GPHL, and GPHZ showed a safety profile similar to that of existing tirzepatide formulations for type 2 diabetes mellitus. When initiated at 2.5 mg once weekly with a stepwise increase every 4 weeks and with appropriate safety precautions, maintaining a dose of 10 mg with a maximum dose of 15 mg was deemed acceptable, with no particular concerns identified.

Thus, the efficacy and safety of tirzepatide 10 mg and 15 mg for obesity disease have been demonstrated, and a favorable benefit-risk profile has been recognized. The maintenance dose of tirzepatide should be 10 mg, and a dose increase to 15 mg was allowed in patients with an inadequate response to 10 mg once weekly. For the dose escalation method, it is considered appropriate to start at 2.5 mg and increase in 2.5 mg increments every 4 weeks, consistent with the phase III study.

With respect to the continuation of tirzepatide administration, an analysis of the time course of body weight and associated health disorder parameters following treatment discontinuation was conducted in the foreign phase III study (Study GPHN[28)]). In this study, all subjects received the maximum tolerated dose of tirzepatide (10 mg or 15 mg) in an open-label manner for 36 weeks. They were then randomized into either the placebo group or the continued tirzepatide group, receiving either placebo or tirzepatide in a double-blind manner for an additional 52 weeks while undergoing diet and exercise therapy. The percentage change in body weight from the time of randomization to Week 52 of placebo or tirzepatide

treatment (mean ± SD [number of subjects evaluated]) was 14.5% ± 9.63% (273 subjects) in the placebo group and −6.6% ± 8.56% (299 subjects) in the tirzepatide group. Weight gain was observed in the placebo group, whereas weight maintenance was observed in the tirzepatide group. Changes in blood glucose, blood pressure, and lipid parameters from randomization to Week 52 indicated a worsening trend in the placebo group compared to the tirzepatide group. Based on these findings, continuous administration of tirzepatide is considered to prevent weight regain and the worsening of obesity-related comorbidities.

PMDA requested the applicant to explain whether it is necessary to establish the continuation of tirzepatide 5 mg as a treatment option for obesity disease in Japan, considering the findings from Study GPHK. In this study, although the analysis was conducted as a secondary endpoint, the mean percentage change in body weight from baseline to Week 72 in the tirzepatide 5 mg group was −16.5%, and the proportion of subjects achieving ≥5% weight reduction at Week 72 was 90.3%, demonstrating a consistent weight loss effect.

The applicant's explanation:
A published article has reported that a weight reduction of ≥3% was associated with statistically significant improvements in glucose and lipid metabolism, blood pressure, and liver function markers, and greater weight loss led to greater degrees of improvement (*Obes Res Clin Pract.* 2014;8:e466-75). Given the above findings, the Japanese Guidelines for the Management of Obesity Disease state that the weight loss targets for patients with obesity disease and severe obesity disease are ≥3% and ≥5% to ≥10% of their initial body weight, respectively. In patients undergoing laparoscopic sleeve gastrectomy, those who achieved a weight reduction rate exceeding 15% tended to have a higher remission rate of dyslipidaemia, while those with a reduction rate exceeding 20% exhibited a higher remission rate of diabetes mellitus (*Ann Gastroenterol Surg.* 2019;3:638-47). The FDA guidance suggests that a weight loss of ≥5% is associated with improvements in weight-related comorbidities.[36)] Specifically, in patients with obesity, approximately 5% weight loss improves insulin sensitivity and pancreatic β-cell function, whereas an 11% to 16% weight loss results in further improvements (*Cell Metab.* 2016;23:591-601). Moreover, a weight reduction of ≥15% in patients with obesity or overweight is associated with a lower risk of worsening health conditions and progression to more serious diseases compared to a weight reduction of ≤10% (*Diabetes Care.* 2011;34:1481-6).

Considering the above findings, the applicant considers that an anti-obesity disease agent should have a weight loss rate of at least 10% to 15%.

In Study GPHK, the mean percentage change in body weight at Week 72 in the tirzepatide 5 mg group was −16.5% in the entire population and −12.3% in the Japanese subpopulation (Table 14). Although clinically meaningful efficacy was demonstrated, the proportion of subjects achieving ≥10% and ≥15% weight reduction in the tirzepatide 5 mg group was 75.0% and 53.5%, respectively, in the entire population, and 65.2% and 30.4%, respectively, in the Japanese subpopulation (Table 15). Given that patients with obesity disease using tirzepatide in clinical settings may have diverse disease characteristics, tirzepatide 5 mg may not be adequate to achieve the desired weight loss rate of at least 10% to 15%.

Rather than continuing treatment indefinitely with tirzepatide 5 mg, increasing the dose to 10 mg and continuing treatment at this dose is expected to achieve the target weight reduction more rapidly, providing benefits in treatment for obesity disease. Therefore, the applicant considers it appropriate to recommend dose reduction to 5 mg for patients unable to tolerate 10 mg and dose escalation to 15 mg for those with an inadequate response to 10 mg.

PMDA's view:
Regarding the efficacy of tirzepatide, the superiority of tirzepatide 10 mg and 15 mg over placebo in terms of weight loss effects has been demonstrated in Studies GPHZ, GPHK, and GPHL, along with improvements in blood glucose, blood pressure, and lipid parameters. In comparisons between different doses of tirzepatide, including 5 mg, both tirzepatide 10 mg and 15 mg demonstrated greater improvement in weight and obesity-related health disorders compared to tirzepatide 5 mg. As for the effect on weight loss and health disorders, Study GPHK did not show a significant difference between tirzepatide 15 mg and 10 mg groups, whereas the other 2 studies indicated greater improvement in the tirzepatide 15 mg group compared to the tirzepatide 10 mg group.

As for the safety of tirzepatide, analysis across different doses, including 5 mg, showed that the incidence of serious adverse events was similar across doses. However, in Study GPHK, the incidence of adverse events leading to treatment discontinuation was higher in the tirzepatide 10 mg and 15 mg groups than in the tirzepatide 5 mg group. In Studies GPHZ and GPHK, the incidence was similar between the tirzepatide 10 mg and 15 mg groups, while in Study GPHL, it tended to be higher in the tirzepatide 15 mg group than in the tirzepatide 10 mg group. Hypoglycaemia and gastrointestinal disorders, which were the main adverse events observed in clinical studies of tirzepatide, were reported at similar frequencies across dose groups.

Considering the efficacy and safety results from dose comparisons in clinical studies of tirzepatide, the applicant's proposal to start with a weekly dose of 2.5 mg and escalate up to 10 mg, with the option to further increase to 15 mg for patients with an inadequate response to 10 mg, is appropriate. In Study GPHK, the tirzepatide 5 mg group still demonstrated steady weight loss effects and trends toward improvement in blood glucose, blood pressure, and lipid parameters. The incidence of adverse drug reactions and adverse events leading to treatment discontinuation was higher in the tirzepatide 10 mg and 15 mg groups than in the 5 mg group. Given these results, including tirzepatide 5 mg as a treatment option for obesity disease could increase the number of patients who may benefit from tirzepatide. For patients unable to tolerate tirzepatide 10 mg, dose reduction to 5 mg should be an option. Continuing treatment at 5 mg without increasing to 10 mg should also be possible depending on the patient's condition.

As for the initial dose and dose escalation method, in light of concerns about gastrointestinal disorders at the beginning of treatment with tirzepatide, it is appropriate to adopt the same regimen as that used in clinical studies that demonstrated good tolerability, i.e., starting at 2.5 mg once weekly and increasing the dose in 2.5 mg increments every 4 weeks.

Concerning treatment continuation, clinical studies have demonstrated sustained efficacy of tirzepatide on weight and comorbid health disorders during the treatment period. In foreign studies, weight and parameters related to comorbid health disorders tended to worsen upon discontinuation of tirzepatide despite diet and exercise therapy. Thus, careful consideration is required when determining the timing of discontinuation. Given the variability in the obesity status, and types and degree of comorbid health disorders in patients with obesity disease, the decision to continue tirzepatide treatment should be made according to weight loss effect and degree of improvement in comorbid conditions in each patient. If patients have an inadequate response to tirzepatide, other treatment options may need to be considered, and treatment discontinuation might be an option. The following cautionary statement should be included in the package insert: weight and parameters related to comorbid health disorders should be periodically monitored and treatment discontinuation should be considered if efficacy is inadequate.

PMDA will finalize the specific Dosage and Administration and Precautions Concerning Dosage and Administration, taking account of comments raised in the Expert Discussion.

7.R.5 Proper use

The applicant's explanation:

To prevent the off-label use of tirzepatide solely for weight loss purposes in individuals other than eligible patients with obesity disease, the applicant will include references to the package insert in materials for healthcare professionals. These materials will specify the criteria for patient eligibility and provide precautions. The applicant is also considering collaborating with relevant academic societies to promote the proper use of tirzepatide. When improper use is identified, the applicant intends to promote proper use by utilizing the package insert, materials for healthcare professionals, and materials jointly developed with relevant academic societies.

To prevent the duplicate administration of tirzepatide and existing tirzepatide formulations, the package insert will include information stating that concomitant use with other tirzepatide formulations should be avoided. Furthermore, materials for both healthcare professionals and patients will include a cautionary statement that tirzepatide should not be used in combination with Mounjaro Subcutaneous Injection, which contains the same active ingredient, or with other GLP-1 receptor agonists.

PMDA's view:

The applicant's policy that precautions should be included not only in the package insert but also in materials for healthcare professionals and patients to specify the criteria for patient eligibility and to warn against duplicate administration with existing tirzepatide formulations is acceptable. Nevertheless, measures to prevent improper use, particularly for purposes such as weight loss, should continue to be evaluated while closely monitoring the situation in clinical practice.

7.R.6 Post-marketing investigations

The applicant's explanation:

The adverse events observed in the phase III studies of tirzepatide (Studies GPHZ, GPHK, and GPHL) were already known from existing tirzepatide formulations for type 2 diabetes mellitus, and no new safety concerns have been identified at this time. Therefore, apart from the early post-marketing phase

vigilance, additional pharmacovigilance activities will not be conducted. Instead, routine pharmacovigilance activities will be implemented, which are considered sufficient for the safety monitoring of tirzepatide in patients with obesity disease. For existing tirzepatide formulations, a specific use-results survey targeting patients with type 2 diabetes mellitus is currently being conducted as an additional pharmacovigilance activity. The safety profile of tirzepatide will continue to be evaluated from the results of this specific use-results survey and other relevant findings.

PMDA's view:
Concerning existing tirzepatide formulations for type 2 diabetes mellitus, use experience in clinical studies and post-marketing has been accumulating in both Japan and foreign countries. The adverse events observed in the phase III studies of tirzepatide (Studies GPHZ, GPHK, and GPHL) were similar to those observed with existing tirzepatide formulations, and no new safety concerns have been identified. The range of dosage regimen of existing tirzepatide formulations and tirzepatide are identical. The target population for tirzepatide (patients with obesity disease) has a similar characteristics to that of patients with type 2 diabetes mellitus, which is an approved indication for existing tirzepatide formulations. The safety of existing tirzepatide formulations continues to be evaluated in post-marketing surveillance, including the results of the specified use-results survey and other data. Given the above mentioned information, the applicant's explanation that post-marketing safety information of tirzepatide is initially collected through routine pharmacovigilance activities is appropriate. The final decision on this assessment by PMDA will be made, taking account of comments raised in the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tirzepatide has efficacy in the treatment of obesity disease with type 2 diabetes mellitus, dyslipidaemia, or hypertension, and that tirzepatide has acceptable safety in view of its benefits. Tirzepatide offers a new treatment option for patients with obesity disease and is clinically meaningful.

PMDA has concluded that tirzepatide may be approved if tirzepatide is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 13, 2024

Product Submitted for Approval

Brand Name	Zepbound Subcutaneous Injection 2.5 mg Ateos Zepbound Subcutaneous Injection 5 mg Ateos Zepbound Subcutaneous Injection 7.5 mg Ateos Zepbound Subcutaneous Injection 10 mg Ateos Zepbound Subcutaneous Injection 12.5 mg Ateos Zepbound Subcutaneous Injection 15 mg Ateos
Non-proprietary Name	Tirzepatide
Applicant	Eli Lilly Japan K.K.
Date of Application	February 9, 2024

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on efficacy, clinical positioning, and proper use described in the Review Report (1).

1.1 Safety

PMDA's conclusion described in Section "7.R.2 Safety" of the Review Report (1) was supported by expert advisors. The following opinions were expressed:

- In an early post-marketing phase vigilance of existing tirzepatide formulations for type 2 diabetes mellitus, 2 fatal cases involving elderly patients were reported. In the Japanese phase III study (Study GPHZ), the proportion of patients aged ≥65 years was 6.8% (5 of 73 subjects) in the tirzepatide 10 mg group and 9.1% (7 of 77 subjects) in the tirzepatide 15 mg group, which was low. Furthermore, the number of patients aged ≥75 years was extremely limited. It is therefore considered important to place precautions in elderly patients treated with tirzepatide.

PMDA's explanation about the safety of elderly patients:
In the phase III studies of tirzepatide, no trend was observed indicating an increase in adverse events or an increased incidence of specific adverse events with advancing age. However, the number of patients aged ≥75 years included in the studies was extremely limited, with only 1 subject in the tirzepatide 10 mg group in Study GPHZ, 1 to 6 subjects in the entire population of Studies GPHK and GPHL, and no subjects in the Japanese subpopulation. Considering that elderly patients generally experience a decline in physiological functions, a precaution should be included in the package insert stating that tirzepatide should be carefully administered to elderly patients with monitoring of their condition.

The above conclusions of PMDA were supported by the expert advisors.

1.2 Indication

The expert advisors generally supported the PMDA's conclusion described in Section "7.R.3.1 Indication" of the Review Report (1), together with the following opinions:

- On the basis of the results of 3 phase III studies (Studies GPHZ, GPHK, and GPHL), it is appropriate to establish type 2 diabetes mellitus, dyslipidaemia, and hypertension as health disorders specified under the indication. While there is currently no consensus on the significance of pharmacotherapy for IGT, it is considered that there is a consensus that weight loss suppresses the progression from IGT to type 2 diabetes mellitus. Additionally, weight loss has been reported to lead to histological improvement in the liver for NAFLD. Considering the above, it may also be possible to include IGT and NAFLD as health disorders specified under the indications of tirzepatide.

PMDA's explanation about the health disorders specified under the indication:
Taking into account the medical environment in Japan, the health disorders specified under the indication of tirzepatide should be those for which the need for pharmacotherapy is clear and for which improvement has been evidently demonstrated in clinical studies. Among the health disorders examined in the clinical studies of tirzepatide, hypertension, dyslipidaemia, and type 2 diabetes mellitus can be considered as meeting the above criteria. In addition to the fact that the clinical significance of pharmacological intervention of IGT and NAFLD has not been established in clinical practice guidelines, it cannot be concluded from Study GPHZ that the improvements in IGT and NAFLD were clearly demonstrated. Therefore, IGT and NAFLD cannot be positioned as health disorders specified under the indication on the same level as hypertension, dyslipidaemia, or type 2 diabetes mellitus.

The above conclusions of PMDA were supported by the expert advisors. Considering the review in Section "7.R.3.1 Indication" and taking account of comments from the Expert Discussion, PMDA determined that the following indications were appropriate, and the applicant responded accordingly.

Indication

Obesity

Zepbound should be used only in patients with any of hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not responded sufficiently to diet therapy and exercise therapy, and meet the following conditions:

- BMI of ≥ 27 kg/m^2 in the presence of at least 2 obesity-related health disorders
- BMI of ≥35 kg/m^2

1.3 Dosage and administration

Concerning the dosage regimen of tirzepatide, the PMDA's conclusion described in Section "7.R.4 Dosage and administration" in the Review Report (1) was supported by the expert advisors. Additionally, the following comments were raised from the expert advisors:

- Diet and exercise therapy constitute the fundamental treatment for obesity disease, and treatment discontinuation should be considered if patients have an inadequate response to tirzepatide. The following precautions should be included in the package insert: Diet and exercise therapy should be continued during tirzepatide administration, and treatment discontinuation should be considered if patients have an inadequate response to tirzepatide.

Based on the review of Section "7.R.4 Dosage and administration" and comments from the Expert Discussion, PMDA concluded that the Dosage and Administration should be specified as shown below and the following Precautions Concerning Dosage and Administration should be provided. The applicant has appropriately addressed these matters.

Dosage and Administration

The usual starting dosage for adults is 2.5 mg of tirzepatide injected subcutaneously once weekly. The dose should be increased in 2.5 mg increments every 4 weeks, up to 10 mg once weekly.

The dose may be adjusted depending on the patient's condition. It may be reduced to 5 mg once weekly or increased in 2.5 mg increments at intervals of at least 4 weeks, up to 15 mg once weekly.

Precautions Concerning Dosage and Administration (relevant text only)

When adjusting the dosage of tirzepatide, the following points should be considered:

- If patients do not tolerate a dose due to gastrointestinal disorders etc., dose reduction or postponement of dose escalation should be considered.
- Depending on the degree of weight loss and the tolerability of tirzepatide, continuing treatment with tirzepatide 5 mg once weekly should also be considered.

Important Precautions (relevant text only)

Tirzepatide should be used as an adjunct to continuous diet and exercise therapy. Body weight, blood glucose, blood pressure, lipid parameters, etc. should be periodically measured. If there is no trend towards improvement after 3 to 4 months of treatment, treatment with tirzepatide should be discontinued. If a trend towards improvement is observed after 3 to 4 months of treatment with tirzepatide, body weight, blood glucose, blood pressure, and lipid parameters, etc. should be periodically measured to

closely monitor the patients' conditions. If patients have an inadequate response to tirzepatide, discontinuation of tirzepatide should be considered.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1). PMDA has concluded that the risk management plan (draft) for tirzepatide should include the safety specifications presented in Table 62, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 63.

Table 62. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypoglycaemia • Gastrointestinal disorders	• Pancreatitis acute • Thyroid C-cell tumor • Pancreatic carcinoma • Safety related to weight loss (Mounjaro Subcutaneous Injection) • Impact on cardiovascular risk • Diabetic retinopathy • Acute biliary disease • Hyperglycaemia (including diabetic ketoacidosis) resulting from insulin discontinuation • Intestinal obstruction • Anaphylaxis, angioedema	None
Efficacy specifications		
None		

Table 63. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients • Disseminate data gathered during early post-marketing phase vigilance

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and dosage and administration, with the approval condition shown below. Although the product is a drug with a new indication and a new dosage, the re-examination period for the present application is the remainder of re-examination period for the initial approval of Mounjaro Subcutaneous Injection, the formulation containing the same active ingredient (until September 25, 2030) because it has more than 4 years left. The product is not classified as a biological product or a specified biological product. The drug product is classified as a powerful drug.

Indication

Obesity

Zepbound should be used only in patients with any of hypertension, dyslipidaemia, or type 2 diabetes mellitus who have not responded sufficiently to diet therapy and exercise therapy, and meet the following conditions:

- BMI of ≥ 27 kg/m^2 in the presence of at least 2 obesity-related health disorders
- BMI of ≥35 kg/m^2

Dosage and Administration

The usual starting dosage for adults is 2.5 mg of tirzepatide injected subcutaneously once weekly. The dose should be increased in 2.5 mg increments every 4 weeks, up to 10 mg once weekly.

The dose may be adjusted depending on the patient's condition. It may be reduced to 5 mg once weekly or increased in 2.5 mg increments at intervals of at least 4 weeks, up to 15 mg once weekly.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ACE-ECL	Affinity capture elution-electrochemiluminescence
ADA	American Diabetes Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
C_{max}	Maximum observed drug plasma concentration
COVID-19	Coronavirus Disease 2019
CT	Computed tomography
DIO	Diet-induced obesity
DPP-4	Dipeptidyl peptidase-4
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good clinical practice
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HFF	Hepatic fat fraction
HLT	High level term
IC_{50}	Half maximal inhibitory concentration
IGT	Impaired glucose tolerance
LC/MS	Liquid chromatography-mass spectrometry
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
LPL	Lipoprotein lipase
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mITT	Modified intent-to-treat
MMRM	Mixed-effects model for repeated measures
Mounjaro Subcutaneous Injection	Mounjaro Subcutaneous Injection 2.5 mg Ateos, Mounjaro Subcutaneous Injection 5 mg Ateos, Mounjaro Subcutaneous Injection 7.5 mg Ateos, Mounjaro Subcutaneous Injection 10 mg Ateos, Mounjaro Subcutaneous Injection 12.5 mg Ateos, and Mounjaro Subcutaneous Injection 15 mg Ateos
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
OGTT	Oral glucose tolerance test
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
QTcF	QT interval using Fridericia's correction
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus 2
SMQ	Standardized MedDRA queries
SOC	System organ class
SU	Sulfonylurea
The Japanese Guidelines for the Management of Obesity Disease	Guidelines for the Management of Obesity Disease 2022 Edited by the Japan Society for the Study of Obesity
Tirzepatide	Tirzepatide

Wegovy Subcutaneous Injection	Wegovy Subcutaneous Injection 0.25 mg SD, Wegovy Subcutaneous Injection 0.5 mg SD, Wegovy Subcutaneous Injection 1.0 mg SD, Wegovy Subcutaneous Injection 1.7 mg SD, and Wegovy Subcutaneous Injection 2.4 mg SD
WHO	World Health Organization
Zepbound	Zepbound Subcutaneous Injection